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Principles and Practice of Gynecologic Oncology

SIXTH EDITION



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AND PRACTICE
OF GYNECOLOGIC
ONCOLOGY**
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PRINCIPLES AND PRACTICE OF GYNECOLOGIC ONCOLOGY

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DEDICATION

This book is dedicated to our families—Catherine Barakat and children Joanna, Richard Jr., and Christian Barakat; Brabham Morgan Randall and children Ken, Morgan, and Marycobb Randall; Tomes Markman and children Margaret, Jonathan, Timothy, and Elisabeth Markman; and Amy Berchuck and children Samuel, Jacob, and Benjamin Berchuck. Their patience, good humor, encouragement, and love have inspired us throughout our careers. In this regard, they have each made significant contributions to this book.

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PREFACE

The landscape of cancer care is changing rapidly and dramatically, with truly exciting developments in our understanding of cancer biology and the resulting explosion in translational research at the fore. In their preface to the third edition of *Principles and Practice of Gynecologic Oncology*, published in 2000, our predecessors, the founding editors of the PPGO textbook, William J. Hoskins, MD, Carlos A. Perez, MD, and Robert C. Young, MD, anticipated the further growth of multidisciplinary therapy for the treatment of gynecologic cancers, and predicted that “over the next decade it will involve the active partnership of the laboratory scientist.” Now, 13 years later, as we publish the sixth edition of PPGO, multidisciplinary approaches are at the heart of cancer care, multimodal strategies offer improved clinical outcomes in a wide variety of settings and new possibilities in patient quality of life, and targeted therapies now enable the development of truly innovative approaches to individualized treatment.

For the current, sixth edition of PPGO, we have sought to create a text reflective of the changes in the field of gynecologic oncology, and, in so doing, to continue to build on the important contribution to the medical literature of the textbook’s founding editors. To do this most effectively, we have brought on as editor Dr. Andrew Berchuck, Chief of Gynecologic Oncology and Director of Gynecologic Cancer Research at the Duke University Cancer Institute, a practicing oncologist and distinguished researcher who has made significant contributions to the understanding of the molecular pathogenesis of ovarian and endometrial cancer. We are pleased to be able to incorporate his expertise and thoughtful editorial contributions in the current edition.

This textbook has been designed for specialists who care for women afflicted with gynecologic cancer, including surgeons, medical oncologists, radiation oncologists, pathologists, and nurses. It will also serve as a valuable resource for residents and fellows in training for a career in cancer care. As in past editions, we are certain that this new edition contains the most up-to-date information available about the treatment of gynecologic cancers. Returning readers will see changes within—including an attractive and effective new four-color layout—as well as much that is familiar. The textbook’s first section is now “Etiology, Prevention, and Molecular Biology” and includes new chapters on “Molecular Pathogenesis of Gynecologic Cancers” and “Hereditary Gynecologic Cancers”; Section II, now “Diagnostic and Therapeutic Modalities,” features new chapters on “Minimally Invasive Surgery,” “Diagnostic Imaging,” and “Comparative Effectiveness Research in Gynecologic Oncology.” In Section III, “Disease Sites,” we remain committed to the multidisciplinary theme of the textbook, with chapters authored by teams consisting of a surgeon, a medical oncologist, a radiation oncologist, and a pathologist. The textbook’s final section, “Special Management Topics,” focuses on all of the auxiliary concerns so important in the care of all cancer patients, tailored for the GYN oncology setting. As in previous editions, we have rotated approximately 30% of the authors, and all chapters have been either completely rewritten or extensively updated, including the chapters on the three major diseases—ovarian, uterine, and cervical cancer.

With this new edition we are very pleased to be able to offer readers a dynamic online full-color companion to the printed textbook. Viewable through a browser or as a download to your tablet or smartphone, this unique digital version offers the textbook content in a searchable, interactive format with ongoing updates that reflect new developments in the field. Additionally, the entire text plus up to date content has been incorporated into LWWOncology.com, a comprehensive database of the most authoritative content in oncology today, available to individuals and institutions. Readers can now use the digital version of the book in the context of clinic and conferences, and as an authoritative source of knowledge available in real time.

Finally, we wish to thank the readers for their ongoing support, and we look forward to their feedback on the current edition. We will continue to strive to improve the content and quality of this comprehensive textbook, and we hope that *Principles and Practice of Gynecologic Oncology, Sixth Edition* will contribute to the knowledge and wisdom of all those entrusted with the care of women afflicted with gynecologic cancer.

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SECTION I

ETIOLOGY, PREVENTION, AND MOLECULAR BIOLOGY

CHAPTER

1

Epidemiology of Gynecologic Cancers

LOUISE A. BRINTON ■ VIKRANT V. SAHASRABUDDHE ■ BRITTON TRABERT

Disease-oriented texts often include a chapter on epidemiology or etiology, which is considered perfunctory if the book is used by therapists whose daily practice is rarely influenced by these considerations. This is not the case for physicians who treat patients with gynecologic cancers, because these clinicians have frequent opportunities to interpret epidemiologic findings and make observations of etiologic importance. Moreover, public health measures based on epidemiologic findings influence gynecologic practice perhaps more than any other clinical discipline. In particular, epidemiologic data are critical for the prevention and early diagnosis of cervical and uterine cancers.

From the observation 150 years ago of the rarity of cervical cancer in nuns to the most recent follow-up studies of type-specific human papillomavirus infection, determining the cause, natural history, and prevention of this disease has focused on sexual practices and suspect infectious agents. Screening interventions based on natural history studies have fundamentally altered the usual presentation of this disease, and as more information about preceding infectious processes becomes available, even more radical changes in presentation and management are likely.

The probable estrogenic cause of endometrial cancer was proposed by etiologically oriented gynecologists decades before its demonstration by epidemiologists. Unfortunately, this did not prevent the largest epidemic of iatrogenic cancer in recorded history (i.e., endometrial cancer caused by unopposed estrogen therapy). The resurgent interest in menopausal hormone therapy, effects of progestins added to this regimen, and associated risk-benefit questions are certain to link the epidemiologist and the gynecologist for the foreseeable future. The iatrogenic chemoprevention of endometrial and ovarian cancers through oral contraception has similarly thrust the two disciplines together around issues ranging from basic biology to risk-benefit assessments.

The rich tradition of the mingling of epidemiology and gynecologic oncology has led to better opportunities for prevention, screening, and gaining insights into basic mechanisms of disease than for any other subspecialty concerned with cancer. This chapter is written with the aim of clarifying how epidemiology is an integral part of the effort to reduce the morbidity and mortality from gynecologic cancers in women.

In this chapter, we review results from a number of epidemiologic investigations, mainly observational studies, including cohort and case-control studies. There have been a number

of large cohort studies focused on women, such as the Nurses' Health Study and the Million Women Study, and these have provided much useful information regarding etiologic factors for gynecologic cancers. However, these investigations, which collect baseline information and then follow subjects forward in time to capture information on incident cancers, are often limited in terms of the exposure information that is captured. They also are not usually useful for exploring risk factors for rare malignancies, and thus, we also depend on results from case-control investigations to clarify risks. Although these studies more often raise concerns regarding the possible role of selection and recall biases because of the retrospective nature of the information gathered from women with certain cancers and nondiseased comparison subjects, they oftentimes collect more exposure information that can be informative in terms of controlling for the influence of confounding factors and assessing interactions between risk factors (effect modification). The issue of control for confounding (i.e., disentangling effects of correlated variables in terms of identifying the independence of effects) is an important issue for both case-control and cohort studies.

In the studies reviewed below, various measures of risk are discussed, including relative risks (RR) from cohort studies and odds ratios (OR) from case-control studies. The RR from a cohort study represents the incidence of disease in women exposed to a factor compared to the incidence in unexposed women. The OR from a case-control study is an approximation of the RR determined by comparing the odds of developing the disease based on an exposure compared to the odds based on lack of the exposure. There are uncertainties with both these measures, which are influenced by the prevalence of the exposure, the incidence of the disease, the numbers of cases included in a study, and the amount of random variability inherent in the data-collection process. In an attempt to quantify the random error that underlies the risk estimate, the RRs or ORs are usually accompanied by derived 95% confidence intervals (CI). The 95% CI means that if the data collection and analysis were replicated an infinite number of times, the CI would include the true risk estimate 95% of the time. Significantly elevated or decreased risks are indicated, respectively, if the lower confidence limit exceeds 1.0 or the upper confidence limit is less than 1.0. Thus significance levels are comparable, although not precisely equivalent, to $p < 0.05$, which is commonly used as a standard level of acceptance of a risk that is interpreted as importantly elevated or decreased.

UTERINE CORPUS CANCER

Demographic Patterns

Cancer of the uterine corpus (hereafter referred to as uterine cancer) is the most common invasive gynecologic cancer and the fourth most frequently diagnosed cancer among U.S. women today. One in 40 U.S. women will develop uterine cancer during her lifetime, and it is estimated that there were approximately 46,470 diagnoses during 2011 (1). The average annual age-adjusted (2000 U.S. standard) incidence from the Surveillance, Epidemiology and End Results (SEER) program, a cancer reporting system involving approximately 28% of U.S. residents, was 23.9 per 100,000 women for 2004–2008; the corresponding age-adjusted mortality rate was 4.2 per 100,000 women, reflecting the relatively good prognosis for this cancer (2). The 5-year survival rate is approximately 81.8%. It is estimated that approximately 8,010 women will die from uterine cancer during 2012 (1).

Uterine cancer rates are generally highest in North America and Northern Europe, intermediate in Southern Europe, temperate in South America, and low in Southern and Eastern Asia (including Japan) and in most of Africa (except southern Africa) (3) (Fig. 1.1). The disease is rare before the age of 45 years, but the risk rises sharply among women in their late 40s to middle 60s (Fig. 1.2). The age-adjusted incidence for Whites is approximately twice the incidence for non-Whites (Fig. 1.3). Reasons for the discrepancy remain largely undefined. Within the last several decades in the U.S., a dramatic change in the incidence pattern for uterine cancer has occurred, characterized by a marked increase that peaked around 1975 (4). Considerable evidence has linked this rise and fall with the widespread use of unopposed estrogen therapy in the late 1960s and early 1970s. Mortality rates, albeit considerably lower, have generally mirrored incidence rates (Fig. 1.3).

Reproductive Risk Factors

Nulliparity is a recognized risk factor for uterine cancer. Most studies demonstrate a two- to threefold higher risk for nulliparous women than for parous women. The association of uterine cancer with nulliparity has been suggested to reflect prolonged periods of infertility. The hypothesis that infertility is a risk factor for uterine cancer is supported by studies showing higher risks for married nulliparous women than for unmarried women. Several studies have found that infertile women experience a three- to eightfold increase in risk (5,6). Mechanisms that may mediate the risk associated with infertility include anovulatory menstrual cycles (i.e., prolonged exposure to estrogens without sufficient progesterone), high serum levels of androstenedione (i.e., excess androstenedione is available for conversion to estrone), and the absence of monthly sloughing of the endometrial lining (i.e., residual tissue may become hyperplastic). In addition, nulliparity has been associated with lower levels of serum sex-hormone-binding globulin (SHBG), leading to increased bioavailable estrogen (7).

It has been established for many years that the risk of uterine cancer decreases with increasing parity, especially among premenopausal women (8,9). More recent attention has focused on characteristics of ages at which these births occurred. Several investigators have found decreased risks with either older ages at or shorter intervals since a last birth, and have suggested that this might reflect a protective effect of mechanical clearance of initiated cells (10,11).

An understanding of the effects of infertility on cancer risk must also consider relationships according to different methods of birth control, including oral contraceptives (discussed later in this chapter). However, it is also of interest that a number of investigations have noted reductions in risk among users of intra-uterine devices, as discussed in a recent meta-analysis (12). The mechanisms involved with this apparent protective effect have not been elaborated, although it is possible that the devices may

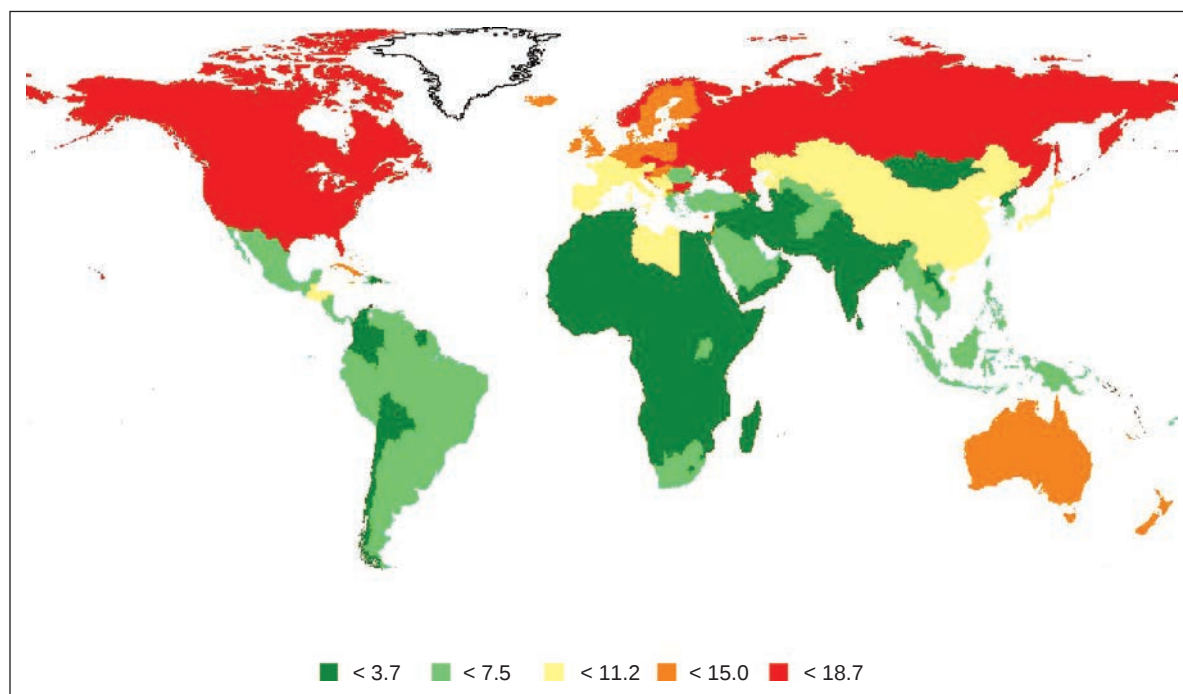


FIGURE 1.1. International incidence for uterine cancer (per 100,000 woman years) age-standardized to the world population, 2008.

Source: Ferlay J, Shin JR, Bray F, et al. GLOBOCON 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010; Available from: <http://globocan.iarc.fr>; accessed on 23 March 2012.

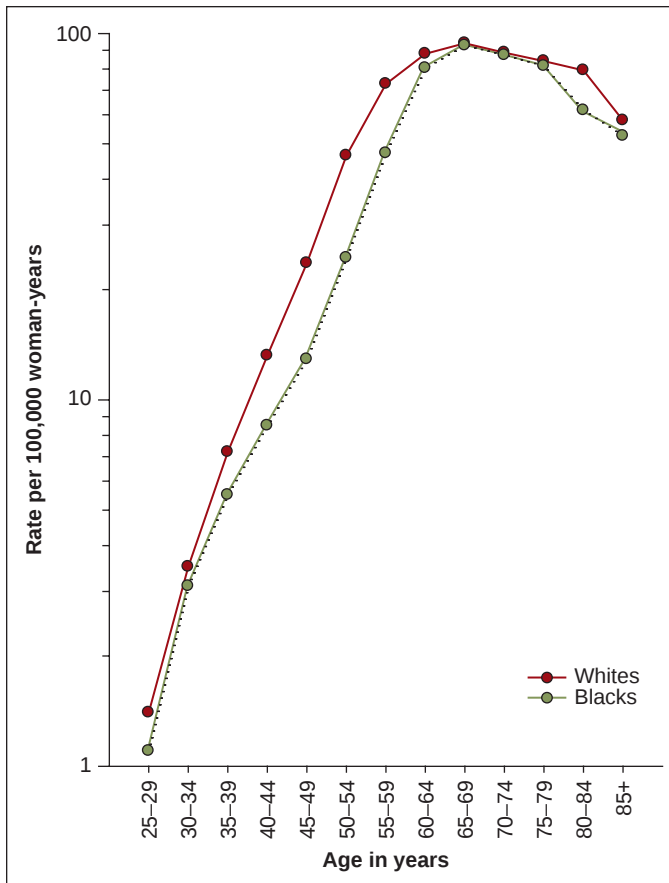


FIGURE 1.2. Age-specific uterine cancer incidence rates by race, U.S. SEER-17, 2000–2008.

affect risk by causing structural or biochemical changes that alter the sensitivity of the endometrium to circulating hormones.

An additional area of interest is the effect of exposure to fertility drugs, given several studies that have shown that users of ovulation-inducing drugs are at an increased risk of developing uterine cancers (13,14). Although this observation requires replication, it is of interest given the structural similarity of clomiphene and tamoxifen, which has been extensively linked with the occurrence of uterine cancers (discussed in more detail below).

The relationship of risk to breast-feeding remains controversial. Although some studies suggest that prolonged lactation may offer protection (15), this has not been noted in all investigations (11).

Menstrual Risk Factors

Early ages at menarche have generally been related to an elevated risk for uterine cancer in many studies. A recent report from a large multicenter prospective cohort reported a 30% reduction in risk with late age at menarche and an inverse dose-response trend (11). Stronger effects of ages at menarche may prevail for younger women (11). The extent to which these relationships reflect increased exposure to ovarian hormones or other correlates of early menarche (e.g., increased body weight) is unresolved.

Most studies have indicated that age at menopause is directly related to the risk of developing uterine cancer. Approximately 70% of all women diagnosed with uterine cancer are postmenopausal. Most studies support the estimate that there is about

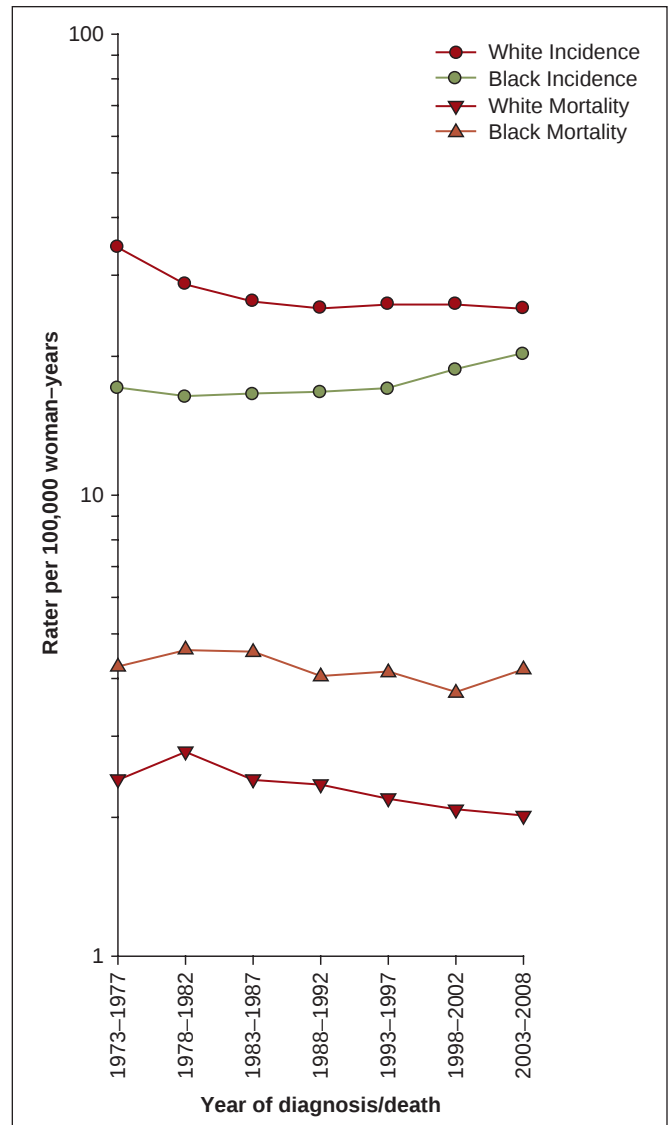


FIGURE 1.3. Uterine cancer incidence and mortality trends among US women, SEER-17, 1973–2008.

a twofold risk associated with natural menopause after the age of 52 years compared to before the age of 49 years (16). It has been hypothesized that the effect of late age at menopause on risk may reflect prolonged exposure of the uterus to estrogen stimulation in the presence of anovulatory (progesterone-deficient) cycles. The interrelationships among menstrual factors, age, and weight are complex, and the biologic mechanisms of these variables operating in the pathogenesis of uterine cancer are subject to substantial speculation.

Exogenous Hormones

Oral Contraceptives

The use of combination oral contraceptives may reduce the risk of uterine cancer by 40% to 60%, and long-term use may decrease the risk further (11,17). One meta-analysis noted that the decreased risk persisted more than 20 years after ceasing use (18). In several studies, the greatest reduction in risk was associated with high-progestin-dose pills, although recent findings indicate that this may be true only among obese women (19).

Menopausal Hormones

It is well established that unopposed estrogens are associated with a 2- to 12-fold elevation in uterine cancer risk (20). In most investigations, the increased risk does not become apparent until the drugs have been used for at least 2 to 3 years, and longer use of estrogens is generally associated with higher risk. The highest RRs have been observed after 10 years of use (up to 20-fold), although it is unclear whether risk increases after 15 years. Most but not all studies have found that cessation of use is associated with a relatively rapid decrease in risk, although a number of studies have found significantly elevated risks to persist 10 or more years after last usage. Although higher doses of estrogen are associated with the greatest elevations in risk, one study showed that even 0.3 mg of unopposed equine estrogen can result in a significant increase in risk (21).

This large body of evidence linking estrogen use to increases in the risk of uterine cancers has led to estrogens being prescribed in conjunction with progestins among women who have not had a hysterectomy. Progesterone has been shown to cause regression of endometrial hyperplasia, the presumed precursor of uterine cancers (22). The large Women's Health Initiative (WHI) clinical trial showed that women assigned to 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate daily had a lower hazard ratio (0.81, 95% CI: 0.48–1.36) than those assigned to placebo, but this risk was based on relatively small numbers of endometrial cancers and short follow-up (23). Similar observational results derive from the Million Women Study in the United Kingdom, where usage of continuous combined therapy resulted in a relative risk of 0.71 (95% CI: 0.56–0.90) (20).

Although a number of studies indicate that the excess risk of uterine cancer associated with estrogens can be significantly reduced if progestins are given for at least 10 days each month (24,25), some studies have shown that subjects prescribed progestins for less than 10 days per month (sequential users) experience some increase in risk, with only a slight reduction compared to estrogen-only users (26,27). The sharp contrast between the effects of <10 and ≥10 days of progestin use has led to the suggestion that the extent of uterine sloughing or of “terminal” differentiation at the completion of the progestin phase may play a critical role in determining risk. It remains questionable whether 10 days of progestin administration per month is sufficient for complete protection, particularly for long-term users (24). Few studies have had large numbers of long-term sequential users, but there is some evidence that this pattern of usage may result in some persistence of risk (28).

Studies have shown that the effects of hormonal therapy (both unopposed estrogens as well as combination therapy) may vary by user characteristics, most notably by a woman's body mass. A number of studies have shown that the adverse effects of unopposed estrogens were greatest in nonobese women and that the beneficial effects of combined therapy were greatest in obese women (20,28,29).

Most data regarding effects of hormones derive from studies on users of pills. Unresolved is whether the use of estrogen patches, creams, or injections can affect risk; given relationships of risk with even low-dose estrogens, it is plausible that these regimens may confer some increase in risk.

Tamoxifen

A number of clinical trials and one population-based case-control study have demonstrated an increased risk of uterine cancer among tamoxifen-treated breast cancer patients (30,32). This is consistent with tamoxifen's estrogenic effects on the endometrium. Elevated risks have been observed primarily among women receiving high cumulative doses of therapy, usually in

the range of 15 g or greater. The risk for more high-risk endometrial cancer histologies may be especially elevated (33).

Anthropometry and Physical Activity

Obesity

Obesity is a well-recognized risk factor for uterine cancer and may account for up to 25% of cases (34). Very heavy women appear to have exceptionally high risks (29). Although studies have demonstrated significant positive trends of uterine cancer with both weight and various measures of obesity, including BMI (weight / height²), height has not been consistently associated with risk. Obesity appears to affect both premenopausal and postmenopausal uterine cancer.

Although initial studies hypothesized that adolescent and long-standing obesity may be more important than adult weight, recent studies support that contemporary weight and weight gain during adulthood are the most important predictors of uterine cancer risk (29,35). Relationships with obesity may be stronger for postmenopausal disease and among women not exposed to exogenous hormones (29,36).

Recent interest has focused on determining whether the distribution of body fat predicts uterine cancer risk. A number of studies have shown that central obesity may have an effect independent of overall body size (29), although not all studies confirm this relationship.

Physical Activity

Recent investigations have focused on the role of physical activity in the etiology of uterine cancer. A potential relationship is biologically appealing given that physical activity can result in changes in the menstrual cycle, body fat distribution, and levels of endogenous hormones. Accumulating evidence suggests a protective effect of physical activity on uterine cancer risk independent of relationships with body weight. A recent meta-analysis of prospective studies demonstrated a decreased risk of uterine cancer with moderate-to-vigorous physical activity independent of relationships with known potential confounders, namely obesity, menopausal hormone therapy use, and parity (37). Generally, studies that have evaluated occupational and recreational physical activity have reported decreased risks.

Inadequate physical activity has been evaluated as a potential risk factor for uterine cancer; specifically sedentary behavior, often measured as sitting time, has been associated with increased risk of uterine cancer (37,38). It is still not clear, however, from the existing studies if the association is independent of moderate-to-vigorous physical activity or body weight (37). Indirect support for a link between sedentary behavior and uterine cancer risk comes from occupational studies, in which the increased risk among women with sedentary jobs is very clear.

Cigarette Smoking

A reduced risk of uterine cancer among smokers has been reported, with current smokers having approximately half the risk of nonsmokers (39–41). Cigarette smoking has been linked to an earlier age at natural menopause in some populations and to reduced levels of endogenous estrogens. Reduced risks may be more pronounced in parous or obese patients (42).

At present, biologic mechanisms underlying the inverse relationship of smoking to uterine cancer risk remain elusive. Alterations in endogenous hormones or metabolites are likely involved. In one report (43), the inverse association of smoking with uterine cancer risk appeared to be more strongly related to higher serum androstenedione levels than to lower serum estrogen levels, except perhaps among overweight women.

Dietary Factors

Despite the fact that obesity has been consistently related to uterine cancer, the role of dietary factors remains controversial. Geographic differences in disease rates (i.e., high rates in Western and low rates in Eastern societies) suggest that nutrition has a role, especially the high content of animal fat in Western diets. Armstrong and Doll (44) demonstrated a strong correlation between a country's total fat intake and uterine cancer incidence.

Dietary Fat

Although early studies speculated that dietary fat intake (particularly animal fat) might play a role in the etiology of uterine cancers, results from more recent studies have provided inconsistent results (45–47). The Women's Health Initiative Dietary Modification Randomized Control Trial, which evaluated chronic disease risks related to a low-fat diet, revealed no effects on the incidence of uterine cancers (48).

Fruits, Vegetables, and Associated Micronutrients

Some studies suggest a reduction in the risk of uterine cancer related to high intakes of fruits and vegetables (49,50). Various micronutrients have been implicated as responsible for this association, although their independence from each other and from other risk factors has not been fully resolved (51). Further, not all studies support relationships with fruits and vegetables, including several large cohort studies (52,53).

Other Dietary Factors

Given the recognized role of diabetes in the etiology of uterine cancers, a number of studies have assessed risk in relation to carbohydrate intake, glycemic intake and glycemic load, which are known to increase insulin and estrogen levels. There are suggestions that all three factors may relate to risk (54–56), although further studies are needed to sort out their independence from other risk factors, including obesity, diabetes, and physical activity levels. Acrylamides, a probable human carcinogen detected in various heat-treated carbohydrate-rich foods, have recently been linked to possible increases in endometrial cancer risk in several studies (57,58). Several studies have found that consumption of phytoestrogens and omega-3 fatty acids (found in fatty fish) may be protective (59,60).

Alcohol and Caffeine

Although early studies suggested that alcohol consumption might lead to reductions in endometrial cancer risk, the findings may have reflected residual confounding by cigarette smoking. More recent studies suggest either no association or one that is increased modestly (61,62).

A recent meta-analysis of coffee consumption and uterine cancer reported a decreased risk of cancer with one cup of coffee per day or more, with consistent findings across case-control and cohort studies (63). In a meta-analysis of green and black tea, green tea was associated with a decreased risk of uterine cancer, whereas black tea was associated with an increased risk of uterine cancer (64); however, the summary measures were based on a small number of studies and should be considered preliminary.

Medical Conditions

Numerous clinical reports link polycystic ovary syndrome (PCOS) with an increase in the risk of uterine cancer, particularly among younger women; however, it is uncertain whether

this risk is independent of obesity. In a recent systematic review and meta-analysis of case-control studies, women with PCOS were found to be at an almost threefold increased risk of uterine cancer (65). Assessing histories of PCOS is challenging in case-control studies, but it is of interest that uterine cancer has been associated with histories of either hirsutism or acne (5,66), which are conditions often associated with hyperandrogenism.

A number of studies have noted a high risk of uterine cancer among diabetic patients, but questions arise as to the extent to which the association is independent of weight. Some studies (67–69) suggest that the relationship persists when analyses are restricted to nonobese women or are adjusted for weight. However, a stronger relationship between diabetes and endometrial cancer risk among obese women in some studies has prompted interest in the etiologic role of selected metabolic abnormalities, including hyperinsulinemia. Thus, more recent studies have focused on effects of metabolic syndrome, with findings that this may predict risk better than merely a history of diabetes (70,71).

A variety of other diseases, including hypertension, arthritis, thyroid conditions, anemia, and cholecystectomy, have been suggested to predispose to uterine cancers, although without consistent findings (72,73). In a number of studies, positive findings may be partially explained by the correlation of the diseases with other factors. Similar to breast cancer, patients with previous fractures have been found to have a reduced risk of uterine cancer (74), presumably reflecting the association of lowered bone density with altered endogenous hormone levels.

Recent studies have also focused on the effects of use of non-hormonal medications on the risk of developing uterine cancer. Given speculation that inflammatory processes might play an important role in the development of uterine cancers (75), a number of studies have assessed relationships with use of nonsteroidal anti-inflammatory drugs, with inconsistent results (72,76,77).

Host Factors

Although studies have shown that a family history of uterine cancer is a risk factor for the disease, particularly among younger subjects (78), this appears to explain less than 5% of disease occurrence (79). In addition, subjects with a family history of colon cancer are at increased risk (78), an association that is now recognized as reflective of hereditary non-polyposis colorectal cancer (HNPCC), a dominantly inherited syndrome associated with mutations in the DNA mismatch repair genes *MSH2*, *MLH1*, *MSH6*, *PMS1*, *PMS2*, and *TGFBR2*. Lifetime risk of uterine cancer is 44% in HNPCC mutation carriers (*MSH2* and *MLH1*), with a median age at onset in the mid-40s (80).

A number of studies have focused on relationships of uterine cancer risk with common single nucleotide polymorphisms (SNPs), including those involved with obesity (81), hormone biosynthesis, metabolism or receptors (82,83), DNA repair (84), and folate metabolism (85). More recent studies have used more robust genome-wide association approaches to identify genetic variants of importance. In a recent study, a susceptibility locus close to *HNF1B* (rs4430796), which has also been positively associated with prostate cancer risk and inversely with type 2 diabetes, emerged as a significant predictor of endometrial cancer risk (86). Genome-Wide Association Studies (GWAS) have also identified that the SNP rs1202524, near the *CAPN9* gene on chromosome 1q42.2, may host an endometrial cancer susceptibility locus (87).

Environmental and Occupational Risk Factors

Geographic variation in rates of uterine cancer, with high rates in certain industrial areas, has led to the suggestion that

certain environmental agents may affect risk. Given the well-recognized influence of hormones on the disease, there has been particular concern about a potential role for certain endocrine disruptors, including dichlorodiphenyltrichloroethane (DDT). Several studies have addressed this issue by comparing dichlorodiphenyldichloroethylene (DDE) levels (the active metabolite of DDT) in the sera of cases and controls, finding no significant differences (88–90). Several studies have focused on effects of electromagnetic radiation as a risk factor, but findings regarding electric blanket or mattress covers have produced mixed results (91,92).

Data for occupational exposures are limited. Elevated endometrial cancer rates have been found among teachers in California (93) and individuals exposed to animal dust and sedentary work in Finland (94). The extent to which these relationships reflect the influence of social class is unknown.

Etiologic Heterogeneity

In 1983, Bokhman (95) proposed that endometrial cancers could be divided into two broad types: Type I, the predominant form, which has a hormonally driven etiology, and Type II, which is unrelated to typical endometrial cancer risk factors, not associated with endometrial hyperplasia, and generally clinically aggressive. Subsequent clinicopathologic studies led to the view that most Type I cancers correspond histologically to endometrioid adenocarcinomas, whereas Type II cancers encompass most nonendometrioid histologic types, with serous carcinoma representing the prototype (96). Differences in molecular markers according to histology support the notion of at least two broad classes of endometrial carcinoma (97,98).

Although it is generally now embraced that there are at least two main biological types of endometrial cancer (and possibly more), most epidemiologic studies have assessed risk factors for endometrial cancer overall—which essentially represent the risks for the predominant Type I tumors, especially in largely Caucasian populations. Registry data consistently have shown that Type II cancers occur at older ages and more often affect non-White women compared with Type I tumors. Some epidemiologic investigations have found that Type II cancers are less strongly linked to classic Type I risk factors, such as obesity, nulliparity, and hormones (99,100), but these have involved relatively limited numbers of nonendometrioid cancers, incomplete collection of relevant risk factors, and unstandardized pathologic classification of tumors.

Biologic Mechanisms Underlying Risk Factor Associations

Many of the identified risk factors are thought to operate through alterations in various endogenous hormones. The majority of studies have found increased risks associated with higher levels of circulating estrogens among postmenopausal women that persisted after adjustment for the effects of body mass (27,101). Although based on relatively small numbers, several studies have shown that estrogens appear less predictive of premenopausal disease (27,102), suggesting that anovulation or progesterone deficiency might be more influential.

Less well investigated is whether other endogenous hormones are related to uterine cancer risk. Key and Pike (103) suggested that uterine carcinogenesis is dependent on uterine mitosis, which is increased by estrogens and reduced by progesterone, but risk associated with progesterone levels has not been well explored. Several studies have shown positive associations of uterine cancer risk with serum androstenedione and

testosterone levels (27,102,104). It has been hypothesized that this may reflect a role of chronic anovulation and progesterone deficiency in premenopausal women, whereas after menopause, aromatase and local conversion of estrone from androstenedione may be involved (105).

Obesity, which is hypothesized to reflect elevated estrogen levels, seems to represent a key risk factor for both uterine carcinoma and endometrial hyperplasia, but the mechanisms mediating this are unclear. A case-control analysis of serum estrogen levels (102) reported that the risk associated with obesity was not entirely mediated by estrogens, especially among premenopausal women, whereas a cohort study of postmenopausal women showed that elevated serum estrogen levels appeared to account for the majority of the risk associated with obesity (106). A potential role for insulin and insulin-like growth (IGF) factors has been suggested, although studies generally have not found support for a role of either c-peptide (107) or IGF (108) levels.

Conclusions

A unified theory of how risk factors for uterine cancer might operate through one common hormonal pathway has been suggested. Estrogen promotes proliferation in the endometrium, which is opposed by progesterone. Therefore, exposure to estrogen, particularly bioavailable estrogen that is weakly bound or unbound to plasma protein, is viewed as a critical carcinogen. Functional ovarian tumors, PCOS, late menopause, and administration of exogenous estrogens and sequential oral contraceptives and menopausal hormone therapies produce higher levels of estrogen exposure without the antiproliferative effects of progesterone. Obesity could also contribute in a variety of ways (109). Adipose tissue is the primary site for conversion of androstenedione to estrone, which is the primary source for estrogen after menopause. Obesity is associated with higher conversion rates and/or elevated plasma levels of estrogen in postmenopausal women. In addition, obesity is related to lower levels of SHBG and more frequent anovulatory menstrual cycles (i.e., less progesterone). Vegetarianism is associated with lower plasma estrogen levels, presumably on the basis of the relationship of diet composition to estrogen metabolism. The beneficial effects of combination oral contraceptives and continuous progestins added to menopausal hormone therapy presumably operate through the antiestrogenic effects of progesterone. The peculiar age incidence patterns for uterine cancer (i.e., extremely rare under age 45 years, followed by a rapid and progressive rise from ages 45 to 60 years) could also reflect the waning influence of progesterone. Nulliparity, hypertension, diabetes, the absence of smoking, and race may yet be added to the unifying scheme as knowledge of endocrinologic mechanisms in endometrial tissue increases.

Although there are several identified risk factors for uterine cancer (Table 1.1), important gaps in knowledge currently limit a full understanding of the proposed carcinogenic process. We need to understand when in a woman's life obesity matters most and how risk is influenced by weight loss; whether the number of adipocytes, their fat composition, or other factors determine peripheral conversion of androstenedione; and the precise hormonal mechanisms associated with vegetarianism. Perhaps the most important gap is in understanding the basic mechanism of estrogen carcinogenesis. It is unclear whether estrogens are complete carcinogens, classic “promoters” that affect initiated cells, or growth stimulants for abnormal cells or carcinogens that act on vulnerable genetic material. The epidemiologic data are consistent with estrogens acting at a relatively late stage of carcinogenesis, emphasizing the need for further investigations to identify tumor initiators.

Table 1.1 Risk Factors for Uterine Cancer

Factors Influencing Risk	Estimated Relative Risk ^a
Demographic factors	
Older age	2.0–3.0
Residency in North America, Northern Europe	3.0–18.0
Higher levels of education or income	1.5–2.0
White race	2.0
Exposures that increase risk	
Obesity	2.0–5.0
Long-term use of menopausal estrogens	10.0–20.0
Nulliparity	3.0
History of infertility	2.0–3.0
Menstrual irregularities	1.5
Early age at menarche	1.5–2.0
Late age at natural menopause	2.0–3.0
Polycystic ovary disease or estrogen-producing tumors	>5.0
Histories of diabetes, hypertension, gall-bladder disease, or thyroid disease	1.3–3.0
Exposures that decrease risk	
Use of oral contraceptives	0.3–0.5
Moderate-to-vigorous physical activity	0.5–0.8
Cigarette smoking	0.5

^aRelative risks depend on the study and referent group employed.

OVARIAN CANCER

Demographic Patterns

Ovarian cancer accounts for 3% of all incident cancers in U.S. women (1). Approximately 1 in 71 U.S. women will develop ovarian cancer during her lifetime. The average annual age-adjusted incidence for all SEER areas, between 2004 and 2008, was 12.8 per 100,000 women (2). An estimated 22,280 new cases were diagnosed in the U.S. in 2012 (1).

Diagnosis usually occurs at advanced stages; the overall 5-year survival between 2001 and 2007 was only 43.8%. The average annual age-adjusted mortality rate is 8.4 per 100,000 women (2). The estimated 15,500 deaths due to ovarian cancer in 2012 will make it the fifth leading cause of cancer death among U.S. women (1). After rising during the mid-twentieth century, age-adjusted mortality rates have been declining by 1.9% per year since 2002 (1). Incidence rates have also slowly declined over the past 2 decades—ovarian cancer incidence rates decreased by 0.7% per year from 1985 to 2001 and by 1.8% per year from 2001 to 2008 (2). In the U.S., Blacks and Whites have nearly identical mortality rates, but the incidence rates remain higher for White women (110) (Fig. 1.4). Although incidence rate increases with age, at all ages rates are higher for Whites than Blacks (Fig. 1.5).

The highest incidence generally occurs in European, Scandinavian, and North American countries, whereas the lowest rates

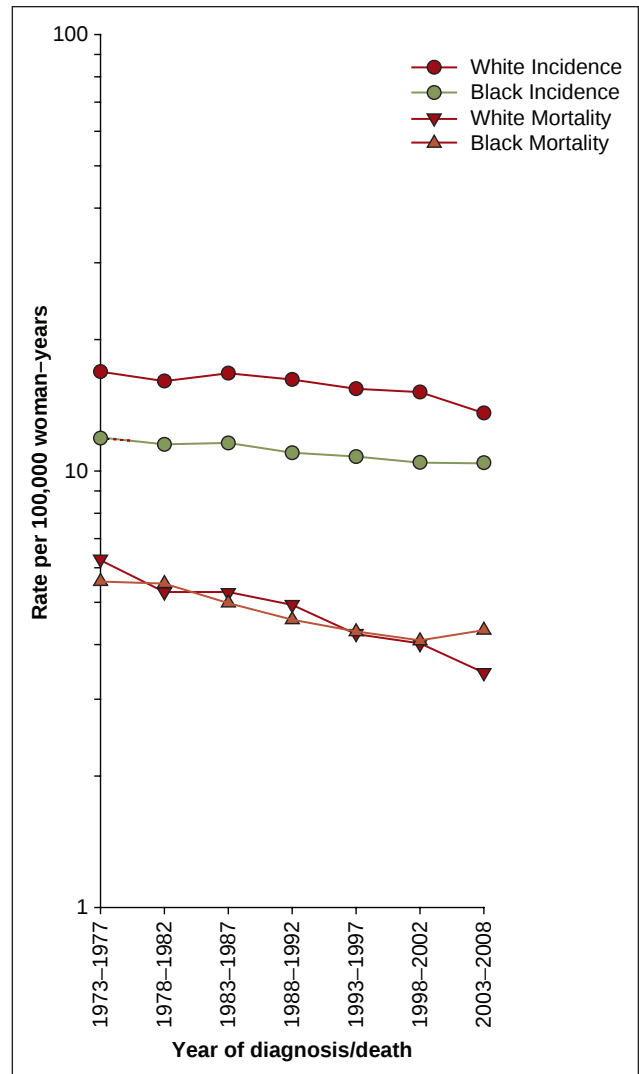


FIGURE 1.4. Ovarian cancer incidence and mortality trends among US women, SEER-17, 1973–2008.

occur in African nations and some eastern countries, such as China (3) (Fig. 1.6). Age-standardized rates vary 3.4-fold across countries. Mortality data show a similar but slightly less dramatic pattern (Fig. 1.6). The estimated age-standardized mortality rates are 5.1 in more developed regions and 3.1 in less developed regions (111).

Reproductive Risk Factors

Gravidity is consistently associated with decreased ovarian cancer risk. Compared with nulligravid women, women with a single pregnancy have a relative risk of 0.6 to 0.8. Each additional pregnancy decreases risk another 10% to 15%. The number of full-term births seems most influential, but several studies have also found decreased risks associated with an increasing number of incomplete pregnancies (112). Most studies that adjusted for parity report no residual association with age at first or last birth (113), but some investigators argue that both number of births and timing matter (114,115).

Whether identified reproductive relationships reflect a hazardous role for infertility or merely the protective role of pregnancy is unclear. Studies with higher risks among infertile women support some role for abnormal endocrine factors. In one study (116), sexually active women who were not using contraceptives and had not conceived for 10 or more years were

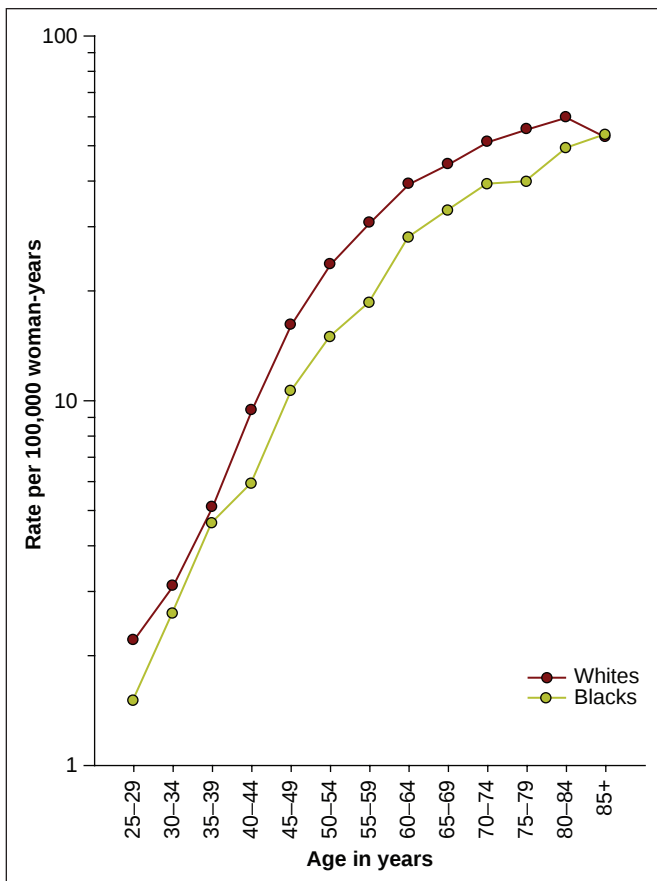


FIGURE 1.5. Age-specific ovarian cancer incidence rates by race, U.S. SEER-17, 2000–2008.

at a six-fold excess risk compared with other women. Another large study similarly found a high risk associated with nulliparity despite unprotected intercourse, especially in women with long periods of ovulatory experience (117).

Although several early studies showed substantial increases in ovarian cancer risk linked to use of fertility drugs (118,119), subsequent studies have generally not confirmed an association, at least for invasive cancers (120). There are, however, lingering concerns regarding whether fertility medications might increase the risk of borderline ovarian cancers, especially given the results from a recent large Dutch cohort study (121). Whether this reflects a biologic relationship or merely increased medical surveillance among infertility patients is yet to be determined.

A number of studies have found a reduced risk of ovarian cancer associated with breast-feeding, although the association has not always been shown to be independent of parity or to relate to risk in a dose-response relation (122,123). A pooling of two large cohort studies reported inverse trends in risk with extended breast-feeding that were independent of parity effects (124). Notably, each month of breast-feeding decreased the relative risk of ovarian cancer by 2%. A subsequent, large, case-control study in Australia reported consistent risks of ovarian cancer with breast-feeding independent of parity and suggested that the risks of invasive serous tumors were most influenced by breast-feeding (125). Suppression of ovulation and decreased gonadotropin levels were proposed as explanatory of the reduced risks, but further studies are needed to confirm this hypothesis.

Menstrual Factors and Gynecologic Surgery

Numerous studies have noted reduced risks among women who have had a simple hysterectomy or tubal ligation. These patients' risks were 30% to 40% lower than the risks among

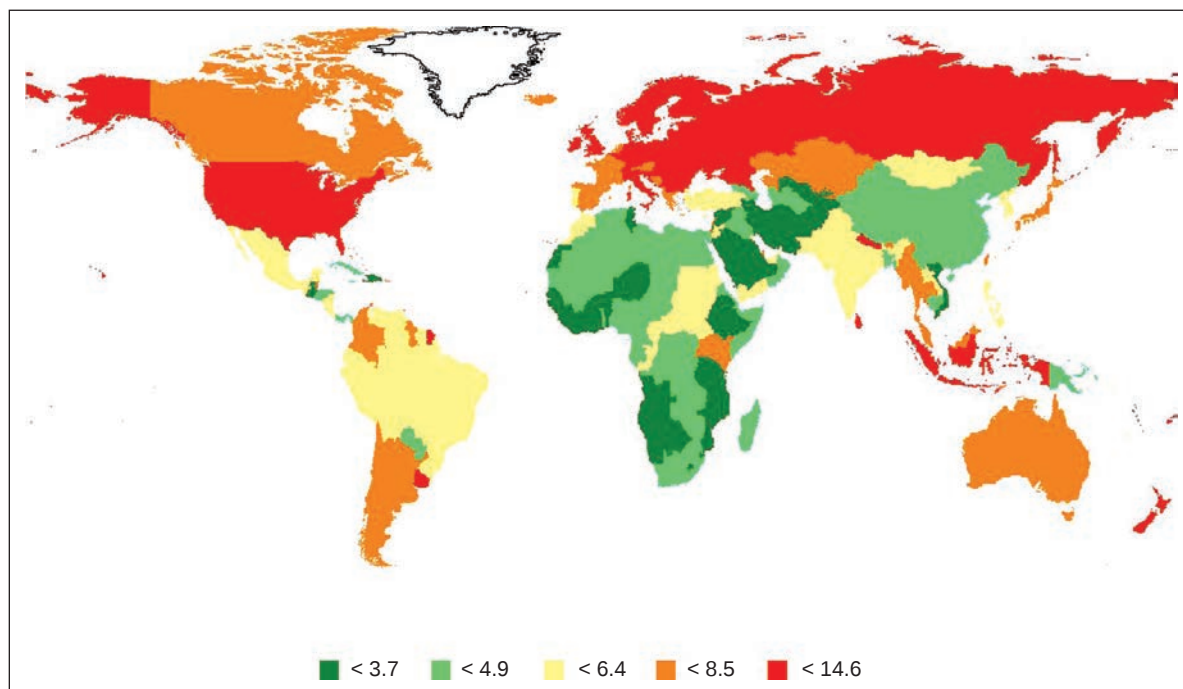


FIGURE 1.6. International incidence rates for ovarian cancer (per 100,000 woman-years) age-standardized to the world population, 2008. Source: Ferlay J, Shin JR, Bray F, et al. GLOBOCON 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010; Available from: <http://globocan.iarc.fr>; accessed on 23 March 2012.

women who had not undergone surgery. A subsequent meta-analysis reported a 37% reduced risk of ovarian cancer with tubal ligation and evidence that the reduced risk persists 10 to 14 years after the procedure (126). This meta-analysis showed the association with tubal ligations to be specific for endometrioid and serous malignancies (126), while another showed stronger reduced risks related to endometrioid than serous cancers (127). It has been suggested that surgery offers an opportunity to remove abnormal-appearing ovaries, but this alone is unlikely to explain the protective effect. Partial devascularization or partial removal of tubes that decreases the risk of tubal carcinogenesis, a precursor to serous ovarian cancer, represents a possible alternative; however, reduced exposure to potential environmental causes of inflammation resulting from tubal ligation or hysterectomy blocking the route of exposure from the outside of the body to the fallopian tube fimbria and ovaries has also been proposed (128).

A number of studies have linked late age at natural menopause with an increased risk of ovarian cancer (113,129,130), although not all studies have confirmed this relationship (131). Most studies have not found earlier ages at menarche to increase risk, but some have reported weak positive associations (116,129,130,132).

Hormonal Risk Factors

Oral Contraceptives

Oral contraceptive use has been consistently associated with a lower risk of ovarian cancer. A pooled analysis of 45 studies reported reduced ovarian cancer risk with long-duration oral contraceptive use (133). The overall estimated protection is approximately 40% for ever use of oral contraceptives and increases to more than 50% with 5 years of use or longer, with the reduction in risk persisting for 30 years beyond last use. The lower-dose formulations, now in use, seem to reduce risk at least as effectively as their higher dose predecessors (134–136). In addition, the androgenicity of the progestins used does not appear to differentiate risks (137).

Menopausal Hormones

Unopposed estrogen menopausal hormone therapy has been consistently associated with an increased risk of ovarian cancer (138). Associations between estrogen plus progestin use and ovarian cancer risk have been less consistent. In the WHI clinical trial, women exposed to estrogen plus progestin therapy had an increased, albeit not significant, risk of ovarian cancer compared to those receiving a placebo (RR 2.42; 95% CI: 0.64–9.12) (23). A meta-analysis of population-based case-control, cohort, and clinical trial data reported an increased risk of ovarian cancer per 5 years of estrogen plus progestin use (139). Further, the recently published Danish Sex Hormone Register study reported increased risk for both sequential and continuous estrogen plus progestin use (140), suggesting that progestins do not mitigate the increased risk associated with estrogen menopausal hormone therapy.

Endogenous Hormones

Recent interest has focused on the role of endogenous hormones in the etiology of ovarian cancer. Although one nested case-control study found higher levels of androgens and lower levels of gonadotropins among cases than among controls (141), the association with androgens was not confirmed in more recent investigations (142–144), whereas the inverse association with FSH was confirmed in an additional nested case-control study

(145). One study, however, found some suggestion that free testosterone might play a role in early onset ovarian cancers (142). Another investigation, which pooled data from three studies, reported null associations with estrogens, androgens, SHBG, IGF-1, and associated binding proteins (IGFBPs) (143,146). Despite these initial null results, there remains interest in further exploring the role of endogenous hormones in the etiology of ovarian cancers, especially given that they may interact with immunologic factors, which have been suggested to play an important role in ovarian carcinogenesis (see below).

Medical Conditions and Medications

Several studies surveyed whether certain medical conditions predispose to ovarian cancer. Diabetes, hypertension, and thyroid diseases seem unrelated to risk (67,147). In line with a number of clinical studies showing simultaneous occurrences of endometriosis and ovarian cancer, a number of epidemiologic studies have found that women with a diagnosis of endometriosis have elevated risks for developing ovarian cancer (148–151). In several of these studies, the relationship was shown to preferentially affect clear cell and endometrioid ovarian cancers (149,150) and more recently also low-grade serous malignancies (151). As reviewed by Ness (152), the two conditions share a number of pathophysiologic processes, including estrogen excesses and progesterone deficits, immunologic responses, and inflammatory reactions. Pelvic inflammatory disease has also been found in several studies to be a possible risk factor for ovarian cancer (128,153,154), supporting the notion of a role for inflammation in ovarian carcinogenesis.

Medications recently surfaced both as potential risk and protective factors. Several studies showed increased risks among users of psychotropic medications, particularly those operating through dopaminergic mechanisms (155). However, subsequent studies that employed cohort designs or improved exposure assessment reported null associations (156–159). Findings also have suggested a reduced risk among women who used anti-inflammatory or other analgesic medications (160–162), and a meta-analysis reported a weak inverse association between acetaminophen use and ovarian cancer risk (163). However, as with the psychotropic medication data, subsequent studies showed, at most, a weak and inconsistent association. Chemoprevention via the use of these medications remains a premature concept.

Anthropometry and Physical Activity

Obesity has recently received increased scrutiny as a possible risk factor. Most individual studies fail to show an association, but pooling projects and meta-analyses are beginning to indicate increased risks associated with higher BMIs (164–166). An increased risk with obesity in premenopausal women was reported in a pooled analysis of 12 cohort studies, but they did not observe an association among postmenopausal women (166). The European Prospective Investigation into Cancer and Nutrition (EPIC), however, reported an excess ovarian cancer risk primarily among postmenopausal women (167). Some investigations have shown stronger relationships restricted to certain subgroups, including those who have never had children (168), nonusers of menopausal estrogens (165,169), women without a family history of ovarian cancer (169), and physically inactive women (170). Further, some studies have suggested that obesity is a risk factor only for certain types of tumors. However, the histologic subgroups identified as being increased among obese women have varied across studies (167,171).

Height has also recently emerged as a risk factor independent of obesity (165,166). Studies have also examined effects of

physical activity levels on ovarian cancer risk, although results are inconclusive, with some studies showing inverse relations, others showing positive associations, and still others noting no association. The most recent meta-analysis reported a 19% risk reduction associated with recreational activity, although the association was not statistically significant when only cohort investigations were considered (164).

Cigarette Smoking

In general, cigarette smoking is not considered a major risk factor for ovarian cancer. However, a number of studies have found evidence that there may be an increased risk of mucinous tumors associated with smoking (172). In a systematic review, smoking was found to lead to a significant doubling in risk for mucinous tumors but not an increased risk for endometrioid or clear cell tumors (173). The risk of mucinous cancers increased with amount smoked but returned to that of never smokers within 20 to 30 years of stopping smoking. Fewer studies have evaluated effects of passive smoking on ovarian cancer risk, with no consensus as to whether this might alter risk or have histologic specificity (174,175).

Dietary Factors

Ecologic studies of dietary factors and ovarian cancer risk led to the hypothesis that high intake of fat, milk, and eggs may be related to an increased risk of ovarian cancer while high intake of fruits and vegetables may be related to a decreased risk (44). However, the majority of the observational studies targeting food classes, lactose and dairy foods, fats, vitamins/nutrients, fiber, fruits, and vegetables, provide conflicting results.

Lactose Consumption

Findings linking higher consumption of yogurt, cottage cheese, and other lactose-rich dairy products with an increased risk of ovarian cancer (176) were viewed with interest given that galactose-related enzymes can influence gonadotropin levels, which are hypothesized to be crucial ovarian cancer risk determinants. The majority of subsequent studies failed to show increases in risk with lactose consumption or galactose metabolism (177;178), although a few studies have provided some support for the hypothesis (179,180). Results from the Nurses' Health Study suggest that further attention may be warranted regarding effects for serous tumors (181).

Fat Intake

The Women's Health Initiative Dietary Modification Randomized Control Trial evaluated the effects of a low-fat dietary pattern on chronic disease incidence, and reported a decreased risk of ovarian cancer associated with the intervention (a 20% reduction in total fat intake) (48). Although some case-control studies have reported higher risks of ovarian cancer associated with intake of fatty foods (e.g., butter and meats) as well as types of fat, the observational data are not entirely consistent. Cohort studies have also been inconsistent, with earlier studies reporting no relationship with dietary fat consumption and recent studies reporting a small, albeit increased, risk with total fat, fat from animal sources, polyunsaturated fats, and trans fat. A meta-analysis of 12 cohort studies found no overall association with fat, cholesterol, or egg intake, but suggested that very high levels of saturated fat intake may increase risk (182). Additional meta-analyses reported no association between red meat and inconsistent results for high intake of processed meat (183,184).

Fruits and Vegetables and Micronutrient Intake

Although some studies have suggested that ovarian cancer risk might be reduced by higher consumption of fruits and vegetables (177,185) or fiber (186,187), while others, including a pooling project of 12 cohort studies, fail to support these relationships (188). Some studies showed inverse associations with particular nutrients, such as vitamins A, C, E, beta-carotene, folate, or methionine (189–192), although results have not been consistent across studies. A meta-analysis evaluating vitamin D and ovarian cancer risk reported no association (193). Further clarification of effects may require evaluating associations according to other risk factors and within histologic subgroups.

Alcohol and Caffeine

A number of studies have examined the effects on ovarian cancer risk related to alcohol consumption. Most have not found any convincing relationships, including a pooled analysis of 10 cohort studies (194).

Caffeine and ovarian cancer risk has been evaluated in studies of coffee consumption, tea consumption, and both combined. Coffee consumption was linked to an elevated risk of ovarian cancer in several early studies and a recent cohort study (195); however, additional studies have not replicated the association (196,197). One study on coffee and tea consumption suggested an inverse association with coffee consumption, but concluded that this was not due to caffeine intake since no relationship was observed with tea consumption (198). A systematic review of tea consumption reported no association with ovarian cancer risk (199); however, a subsequent meta-analysis reported reduced ovarian cancer risk with green tea consumption and no association with black tea consumption (64). Finally, a cohort study reported a modest inverse association of caffeine consumption with ovarian cancer; however, this association was specific to nonhormone users (200). Overall, there are no consistent patterns between caffeine consumption and ovarian cancer; it may be that more detailed information on source of caffeine, frequency, and duration need to be evaluated.

Host Factors

A family history of ovarian cancer is the strongest risk factor identified to date. Which family member was affected is less important than the total number of affected relatives or their age at diagnosis. Women with two or more affected relatives or whose relative was diagnosed before 50 years of age experience the highest risks (201). Approximately 5% to 10% of ovarian cancer patients have a first-degree relative with ovarian cancer (202). Family histories of breast and colon cancer are also associated with increased ovarian cancer risk but slightly less strongly than a family history of ovarian cancer.

Inherited mutations in two autosomal dominant genes—*BRCA1* and *BRCA2*—are strongly linked to familial ovarian cancer (and breast and other cancers) (203). Whereas the lifetime probability of developing ovarian cancer in most women is 2%, the probabilities in women with a family history or women with a *BRCA1/2* mutation are 9.4% (204) and 15% to 40% (205), respectively. Despite these increases, *BRCA1/2* mutations explain less than one third of the elevated risk in women with familial ovarian cancer (201). Lynch syndrome, or hereditary non-polyposis colorectal cancer (HNPCC), is related to mutations in mismatch repair genes and reported to be associated with a 12% lifetime risk of ovarian cancer (206). Disease heterogeneity is influenced by high-penetrance genetic variation, whereby mutations in *BRCA1/2* lead to the development of serous cancers and mutations of DNA mismatch repair genes are

more frequently associated with mucinous and endometrioid tumors (207).

Common genetic variation and ovarian cancer risk in moderate- or low-penetrance susceptibility genes have been evaluated using candidate gene studies of SNPs and through GWAS. Candidate genes/SNPs have generally been selected from biologic pathways based on relevant hypotheses, and several candidate genes have been identified to date, including *PGR*, *TP53*, and *CDKN2A*. GWAS have further identified susceptibility loci for ovarian cancer at 9p22.2, 8q24, 19p13, 2q31, 3q25, and 17q21 (207). Identifying common genetic susceptibility alleles will lead to a greater understanding of disease etiology, potentially leading to the development of preventive approaches targeted toward women who have these genetic variants.

Talc

Like asbestos, over-the-counter talc such as asbestos, is a silicate that has been studied in relation to ovarian cancer risk. The published case-control studies generally report positive associations between ovarian cancer and perineal talc exposure; summary estimates suggest a 30% increase in risk (208,209). However, a lack of consistent statistical significance and inconsistent associations with different patterns of talc use raise questions about the validity of this association.

Environmental and Occupational Risk Factors

Certain occupations came under scrutiny when studies linked hair dyes and triazine herbicides to ovarian cancer (210,211). Record linkage studies in Finland (212), Norway (213), Sweden (214), Canada (215), and the U.S. (93,216) suggested a pattern of increased risks among certain professions (e.g., teachers, health care workers) or with particular occupational exposures (e.g., solvents, asbestos). It was recently concluded in a Monographs Working Group of the International Agency for Research on Cancer (IARC) that asbestos exposure is associated with ovarian cancer; a subsequent meta-analysis of occupational cohorts reported increased ovarian cancer mortality among women occupationally exposed to asbestos (217). Until additional data address the potential for inconsistent or chance findings and the challenge of finding large populations with sufficient data on other potential confounding variables, occupational exposures beyond asbestos will likely not be considered major risk factors for ovarian cancer (218).

Etiologic Heterogeneity

A unified ovarian cancer progression model has not yet been established, and growing evidence demonstrates that subtypes of ovarian carcinomas have different molecular, pathological, and clinical characteristics, suggesting that there may be several distinct disease entities (219). Specifically, ovarian cancer subtypes have been described to molecularly and morphologically resemble cancers of other sites: fallopian tube (serous), endometrium (endometrioid), gastrointestinal tract (mucinous) and unspecified glycogenated epithelium (clear cell) (220).

As previously discussed, some risk factors have been shown to have distinctive effects for certain subtypes of ovarian cancer, but there have been inconsistent findings—most likely reflecting small numbers in the studies of some of the rarer subtypes. Probably one of the more consistent findings is the propensity of endometriosis to predispose to clear cell and endometrioid tumors (149–151), suggesting that a subset of disease does not

arise in the ovary but rather from transplanted endometriotic tissue. Tubal ligation also appears to be more strongly inversely related to endometrioid than to some of the other ovarian subtypes (127). There has also been some consistency regarding mucinous tumors being distinctive, showing increased risks related to cigarette smoking (173) and decreased risks with use of menopausal hormones (171,221,222). Obesity also is beginning to emerge as an especially strong predictor for endometrioid cancers (100,223).

It is clear that further leads regarding etiologic heterogeneity will depend on either large studies or more likely on consortial efforts that bring together data from multiple epidemiologic studies. Such efforts are currently underway by several groups and should provide further insights as to possibly distinct origins of some of these tumor subtypes.

Conclusions

Much of the clinical and epidemiologic evidence concerning risk factors for ovarian cancer implicates ovulatory activity (Table 1.2). Conditions associated with reduced ovulation, for example, pregnancy and oral contraceptives, consistently reduce risk. Combining these and other menstrual factors into single “ovulatory age” or “lifetime ovulatory cycles” indexes has generally produced the expected associations with ovarian cancer risk; that is, older ovulatory ages (224) or higher cycle counts (225) increase risk. However, the misclassification inherent in these indexes is sufficient to generate different risk estimates (226), and the magnitude of risk reduction for short-term oral contraceptive use or a single pregnancy exceeds the proportional decrease in ovulatory cycles that would be expected to be associated with these exposures.

Table 1.2 Risk Factors for Ovarian Cancer

Factors Influencing Risk	Estimated Relative Risk ^a
Demographic factors	
Older age	3.0
Residency in North America, Northern Europe	2.0–5.0
Higher levels of education or income	1.5–2.0
White ethnicity	1.5
Exposures that increase risk	
Nulligravida	2.0–3.0
History of infertility	2.0–5.0
Early age at menarche	1.5
Late age at natural menopause	1.5–2.0
Long-term use of menopausal estrogens	3.0–5.0
Perineal talc exposure	1.5–2.0
Female relative with ovarian cancer	3.0–4.0
Endometriosis	1.5–2.0
Pelvic Inflammatory Disease	1.5–2.0
Exposures that decrease risk	
History of hysterectomy or tubal ligation	0.5–0.7
Use of oral contraceptives	0.3–0.5

^aRelative risks depend on the study and referent group employed.

The putative mechanisms behind ovulatory inhibition and the risk associated with “increased ovulation” (227) raise additional questions. An early report suggested, based on the associations with parity and infertility, that an unidentified endocrine abnormality predisposed women to relative or absolute infertility and ovarian cancer. The protection associated with oral contraceptives seems unlikely to fit this hypothesis unless, in some improbable manner, their use induces an endocrine milieu similar to that underlying fertility.

A second popular unifying hypothesis is that ovarian cancer is the result of accumulated exposure to circulating pituitary gonadotropins (228). Although this is consistent with the parity, menopause, and oral contraceptive associations, a study that directly measured gonadotropin levels failed to find a relationship with subsequent development of ovarian cancer (141). This theory also fails to account for the risks associated with clinical infertility, and it predicts that menopausal hormone therapy would decrease risk, because both exposures are associated with reduced gonadotropin levels.

A third explanation points to a biologic effect of ovulation on ovarian surface epithelium. Ovulation prompts a cascade of epithelial events, including minor trauma, increased local concentrations of estrogen-rich follicular fluid, and increased epithelial proliferation. Such proliferation, particularly near the point of ovulation, can recruit inclusions into the ovarian parenchyma. Some or all of these “incessant ovulation” events may lie on the causal path to ovarian cancer (229,230). This is consistent with most of the endocrine-related risk factors except for the risks associated with clinical infertility.

Although it has been hypothesized that epithelial inclusion cysts give rise to ovarian tumors, cancer precursors of ovarian surface epithelium remain unclear and progress in understanding ovarian carcinogenesis, as previously mentioned, is partly limited by this lack of clarity on the tissue of origin of ovarian epithelial carcinomas. Nearly all other epithelial gynecologic cancers arise via a sequence of events whereby the normal epithelium undergoes conversion to a precursor lesion that can then become an invasive neoplasia. Cervical intraepithelial neoplasia, the precursor of cervical cancer, is probably the most well-known example. More recently, increasing evidence indicates that at least a subset of high-grade serous ovarian cancers arise from high-grade intraepithelial serous carcinomas in the fallopian tube fimbria and spread to the ovary (220). This could help explain the inconsistent reduced risks associated with tubal ligation and hysterectomy, given that the fallopian tubes would be removed only in a subset of these procedures.

No single theory adequately incorporates the available data. A unifying hypothesis may lie in a combination of ovulation, hormones, and local effects. Additional factors, such as genetic alterations; androgens, progestagens, and other hormones (227); inflammation (128); and endometriosis (152), also appear to be important.

Each hypothesis identifies testable possibilities. Discriminating between the roles of voluntary versus involuntary infertility could identify the mechanisms underlying the role of parity. Characterizing the specific reproductive abnormalities associated with clinical infertility could reveal new biologic mechanisms involved in ovarian carcinogenesis. Exploring the interactive contributions of the hormones along the hypothalamic–pituitary–gonadal axis could explain how specific hormones seem to influence risk at different time periods. In addition, verifying that inflammation or related conditions and pathways play an etiologic role in ovarian carcinogenesis could open new lines of inquiry.

Ovarian cancer epidemiology presents both simple and complex patterns. Rates have slowly declined over the last 40 years, and virtually all studies show consistent associations with some exposures, such as oral contraceptives, parity, and family history. But where some uncertainty exists, it is substantial. For example,

reproductive or lifestyle factors that are consistently associated with other reproductive cancers—smoking, obesity, menopausal hormone therapy—have been published with such diversity that traditional attempts to summarize quantitatively the divergent data likely will not prove to be useful. Although it is tempting to attribute the differences to histology-specific associations, such hypotheses will require substantially more epidemiologic, clinical, genetic, and transitional data before their acceptance is certain.

The highly penetrant genes account for only a small proportion (10%) of women who develop ovarian cancer, but a better understanding of the mechanisms behind those risks could introduce immediate benefits for high-risk women. A clear picture has emerged for some protective factors, such as oral contraceptives and parity, but risk associated with other important public health issues, such as smoking, obesity, and physical activity, remains uncertain. Continued attempts to account for the differences between studies should help delineate the spurious associations from the etiologically relevant risk factors. Doing so should help identify targets for improving detection, treatment, and prevention of this deadly tumor.

CERVICAL CANCER

Chronic persistent infection with carcinogenic genotypes of sexually transmitted human papillomavirus (HPV) is the causative agent of virtually all cases of cervical cancer (231). Of the more than 150 genotypes of HPV, several dozen can infect the anogenital epithelium and more than 15 (including HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82) can cause anogenital cancer. Individual genotypes differ greatly in carcinogenic risk, and HPV16 is by far the most carcinogenic type, accounting for half of cervical cancer cases globally (231,232). Reflective of the “necessary, but not sufficient” role of HPV in the causation of cervical cancer, several other etiologic cofactors are involved. The remarkable body of evidence developed over the past three decades in the understanding of HPV epidemiology has provided transformative clinical applications aimed at cervical cancer prevention and control. The pathogenesis, diagnosis, and prevention aspects of cervical cancer are detailed in Chapter 7. The current chapter will concentrate mainly on the descriptive epidemiology of invasive cervical cancer, the natural history of HPV infection, and the broad relationships with major etiologic risk factors.

Demographic Patterns: Global and United States

According to the latest global data compiled by the IARC, cervical cancer is the third most common cancer (after breast and colorectal cancers) among women worldwide (233,234). It is the first or the second most common (after breast cancer) in less-developed countries. There were more than 529,000 incident cases estimated in 2008 and a 5-year prevalence of more than 1.5 million cases (233). Cervical cancer accounted for approximately 275,000 deaths worldwide in 2008, or just under one tenth of the total number of female cancer deaths (233). The cancer burden (incidence and mortality) is disproportionately high (greater than 85%) in the developing world.

The incidence rate per 100,000 women-years for invasive cervical cancer in various geographic areas is highly variable, reflective of differences in HPV infection and access to screening services (234) (Figs. 1.7 and 1.8). The highest age-standardized rates were reported from sub-Saharan Africa (31.7 per 100,000), with some countries (Guinea, Zambia, Comoros, Tanzania, Malawi, Mozambique, and Swaziland) having rates

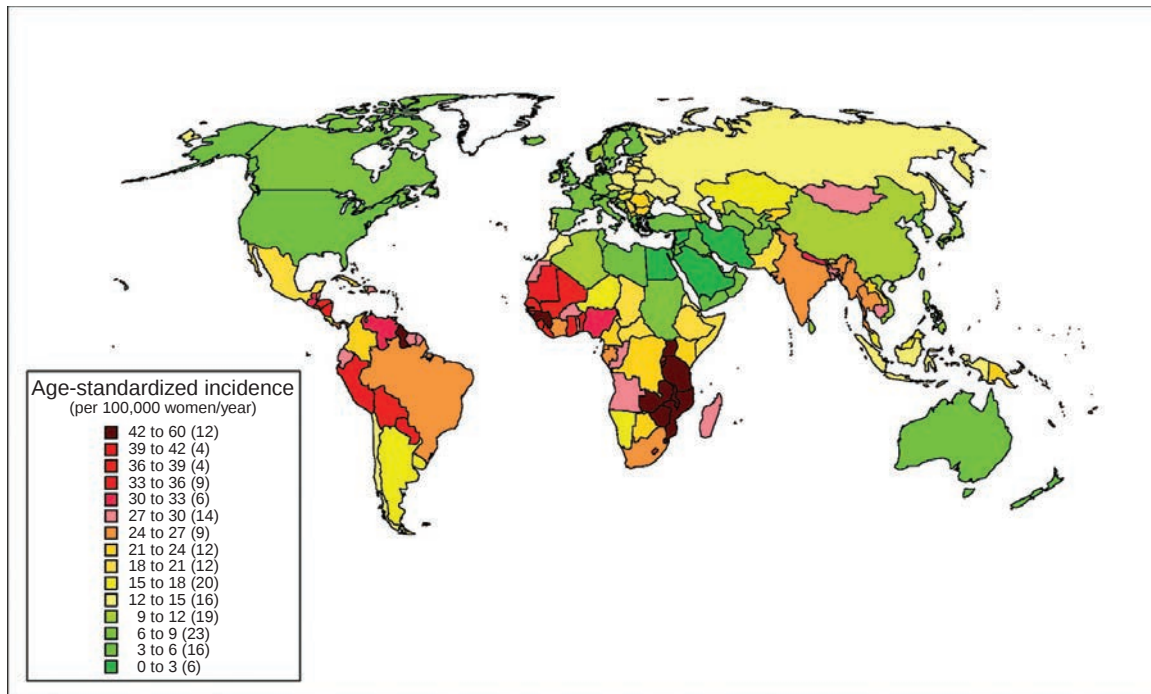


FIGURE 1.7. Global incidence of cervical cancer: Geographic distribution of the world age-standardized incidence rate of cervical cancer, by country, estimated for 2008 (per 100,000 women/year). The counts in parentheses in the legend correspond to the number of countries in each ASIR range.

Source: Data from Arbyn M, Castellsague X, de Sanjose S, et al. Worldwide burden of cervical cancer in 2008. *Ann Oncol*. 2011; with permission.

higher than 50 per 100,000. Other regions of the developing world, including South Central Asia (24.6), Latin America and the Caribbean (23.5), and the Pacific Islands (23.7), also have high burdens. The case burden of disease as reflected by annual new incident cases and deaths due to cervical cancer is highest in India (>134,000 cases and >72,000 deaths), followed by China, Brazil, Bangladesh, and Nigeria (233). An analysis of population-based surveys from 57 representative countries has indicated that the coverage of cervical cancer screening in developing countries is on average 19%, compared to 63% in developed countries, and there is a wide variation in coverage levels within developing countries (235) (Fig 1.8).

An examination of age-specific cervical cancer incidence, in countries prior to introduction of screening has demonstrated that the median age of cervical cancer diagnosis worldwide is between 40 and 60 years (mean ~50 years). Rates begin to increase around age 25, with an unusually early plateau or peak starting at age 40 to 50 (236). Incidence rates increase with age, and the age structure reflects that cervical cancers originate from HPV infections transmitted mainly in late adolescence and early adulthood.

It is reported that 12,710 women were diagnosed with and 4,290 died from cervical cancer during 2011 in the U.S. (237). The overall age-adjusted incidence rates for invasive cervical cancer based on SEER data suggest an incidence rate of 8.1 per 100,000 women for the period 2004 to 2008 (238). Regional differences in incidence, with excesses particularly in underserved regions in the Southeastern and Southwestern U.S. are apparent (239). Substantial racial/ethnic differences in incidence rates persist. Compared with Whites and Asian and Pacific Islanders, incidence rates were higher among Black, American Indian and Alaska Native, and Hispanic women (239) (Fig 1.9).

Cervical cancer rates began to fall during the early twentieth century, even before the advent of cytologic screening. Reduced parity may have contributed to this pattern, given that

multiparity appears to be a cofactor for progression of HPV infection to cervical neoplasia. In the latter half of the last century, effective screening contributed to a further reduction in cancer incidence and mortality, particularly among women aged between 30 and 74 years, because of targeting of this age group in many countries (Fig. 1.10).

In the U.S. and many other developed nations, rates of squamous cell carcinomas, accounting for approximately 80% of invasive cervical cancers, have declined steadily since the introduction of Pap smear screening, while adenocarcinomas (accounting for approximately 15%) have not (240,241). In fact, rates of cervical adenocarcinomas have risen in the past two to three decades in various countries, including the U.S., relative to both rates and absolute numbers of squamous cell carcinomas.

The 5-year survival rate for cervical cancer is 67.9% (238), with survival being highly dependent on stage at diagnosis. Younger women and White women are more likely than older women and Black and Hispanic women, respectively, to be diagnosed with localized cancer, which carries a good prognosis.

Human Papillomavirus

For more than a century, epidemiologic studies have suggested an association between sexual activity and cervical cancer, but proof that HPV is the sexually transmitted agent responsible for this association was not achieved until sensitive methods for detecting HPV DNA were developed. The recognition of the key etiologic role of HPV infection has profoundly altered the epidemiologic study of cervical cancer. The epidemiologic association between HPV infection and cervical cancer fulfills all of the established epidemiologic criteria for causality. As a result, HPV is now accepted to be the central, necessary causal factor for virtually all cases of cervical cancer in the world (231,242). It is increasingly clear which previously “established” epidemiologic

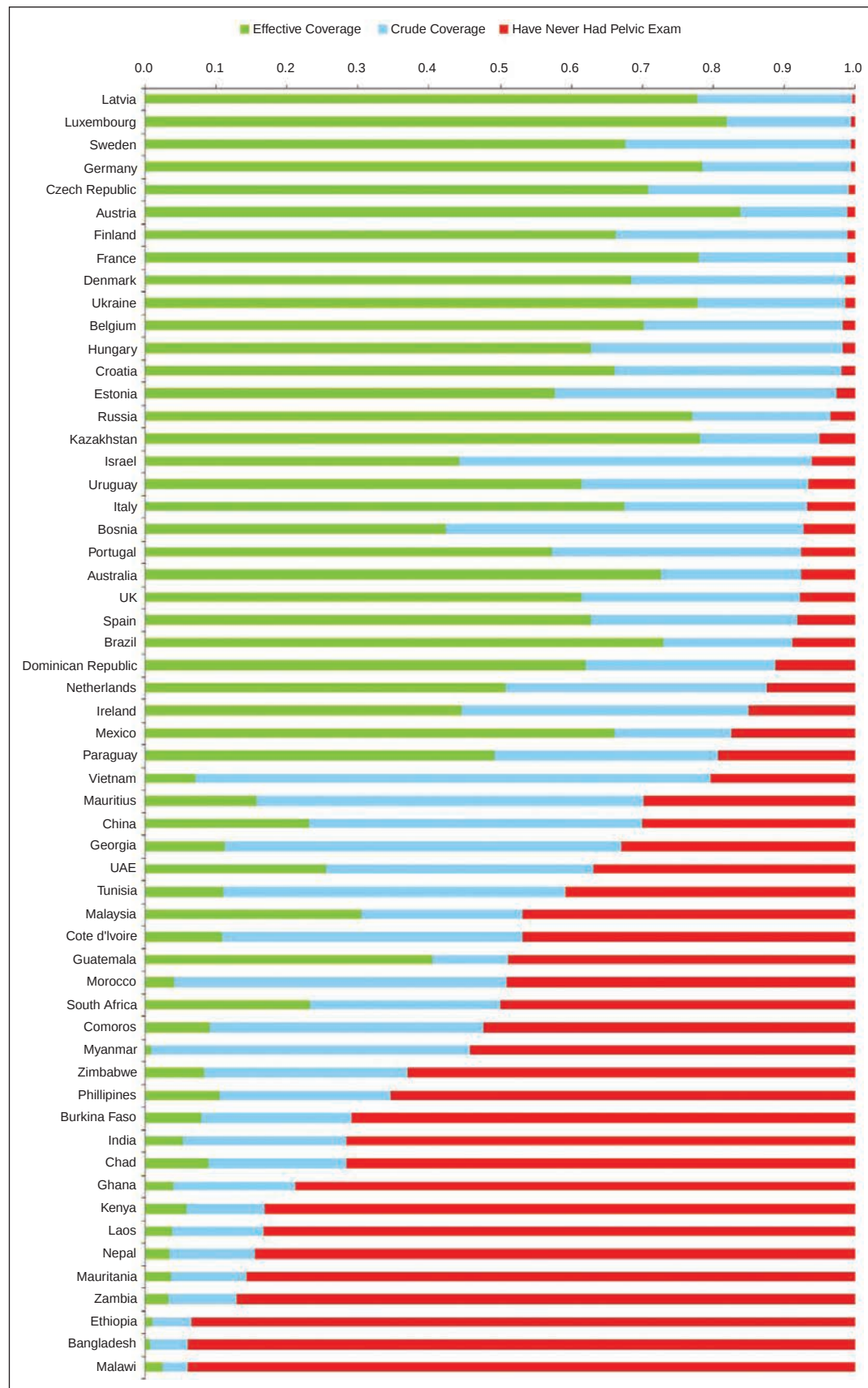


FIGURE 1.8 Cervical cancer screening coverage in 57 representative countries
 Source: From Gakidou et al. PLoS Medicine 2008, with permission.

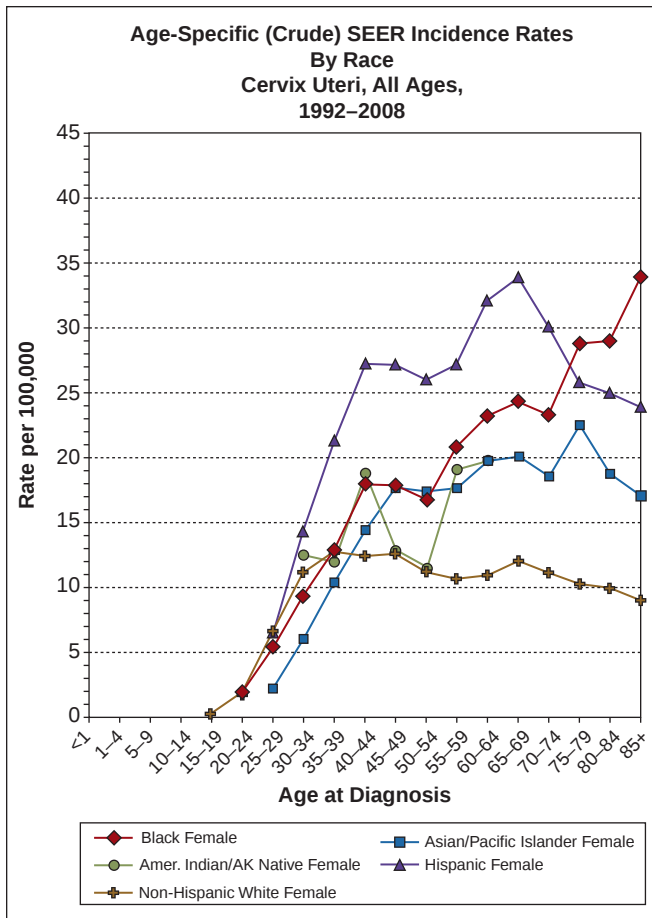


FIGURE 1.9. Age-specific incidence of invasive cancer of the cervix uteri by race.
Source: Data from the Surveillance, Epidemiology and End Results Program, 2000–2004, with permission.

risk factors for cervical cancer are correlates of HPV infection, which lead to infection, and which are cofactors operating only in the presence of HPV infection. An indirect proof for this is since HPV is transmitted by direct physical sexual contact, virgins (women without any sexual contact at all) almost invariably test negative for HPV, which explains their virtually negligible risk of cervical cancer regardless of other behaviors (243).

Cervical HPV transmission, which is primarily sexual, is studied best at the molecular level, primarily because genotypic heterogeneity informs risk stratification. Moreover, before development of precancerous stages, most infections are not microscopically or macroscopically evident. Each HPV type is a separate genetic species, and should be considered a separate sexually transmitted infection. Because all carcinogenic types are transmitted by the same sexual route, concurrent multiple-type infections are common. The available data, which are limited, seem to indicate that prevalent HPV types influence each other minimally (244).

The epidemiology of cervical cancer is most coherently understood in terms of the natural history of cervical carcinogenic HPV infection, which can be broadly categorized in the following stages: (a) exposure/acquisition of new HPV infection with clearance of a majority of the infection, (b) persistence of HPV infection and progression to precancerous lesions (cervical intraepithelial neoplasia 3 [CIN3]), and (c) development of invasion (Fig. 1.11) (236).

As the most common sexually transmitted infection, HPV infection is similar to other sexually transmitted infections, with a large peak following sexual initiation. Cervical HPV infections

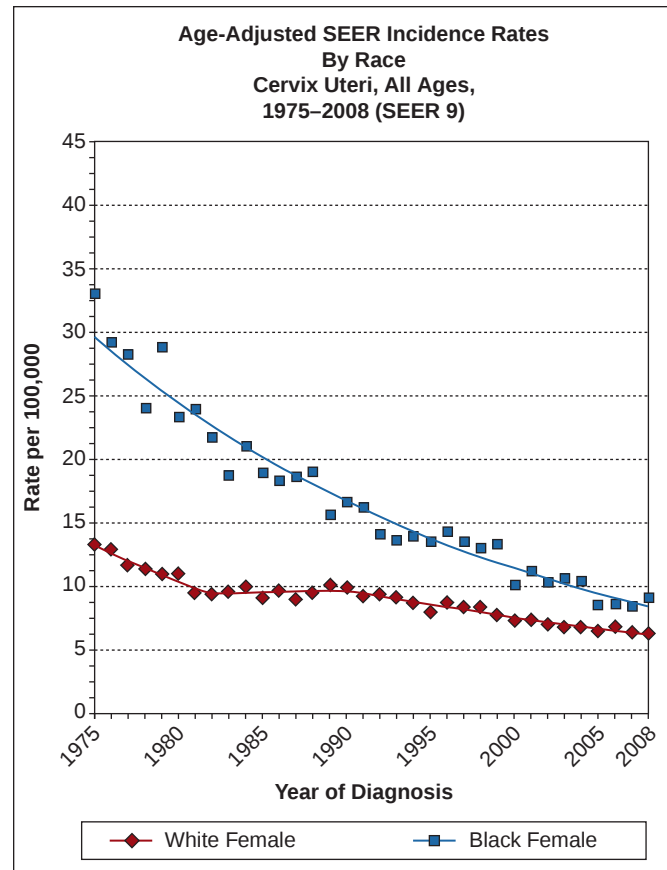


FIGURE 1.10. Incidence trends for cervical squamous cell carcinoma by race between 1975 and 2008.
Source: Data from the Surveillance, Epidemiology and End Results Program, with permission.

tend to clear after 6 to 24 months, as do warts anywhere on the body (244). Acquisition and clearance dynamically oppose each other in each cohort of women to produce the characteristic age distributions as infections are transmitted sexually when women have new partners and are then cleared (245). Transient HPV infections are ubiquitous among sexually active young women, but progression to a cervical cancer precursor requires persistence of carcinogenic types. It is the *overt persistence* of one of the carcinogenic types that is strongly linked to precancer, which histologically corresponds to CIN3, including carcinoma *in situ* (246). Persistence of carcinogenic types of HPV and development of precancer are not identical but, thus far, they are so closely linked that epidemiologists are only beginning to disentangle them. Part of the problem is that precancers begin as extremely small clonal lesions that may be below the limits of detection of microscopy (247).

The distribution of HPV types in cervical cancer has been extensively studied in the U.S. and international collaborative studies (248–251). The most common HPV types in descending order of frequency are HPV types 16, 18, 45, 31, 33, 52, 58 and 35, together responsible for approximately 90% of all cervical cancers worldwide. Persistent HPV16 infection is an extremely strong risk factor for subsequent diagnosis of CIN3 and invasive cancer and has been classified as a Class 1 human carcinogen by the IARC (231). HPV types are more predictive of risk than subtleties of minor and equivocal cytopathic effects, colposcopic findings, or behavioral cofactors like smoking. Furthermore, intratypic sequence variants of HPV 16 and possibly other types have been associated with altered risk, although these risk modifications are weaker than the intertypic variation (252). The role of elevated viral load (i.e., HPV content

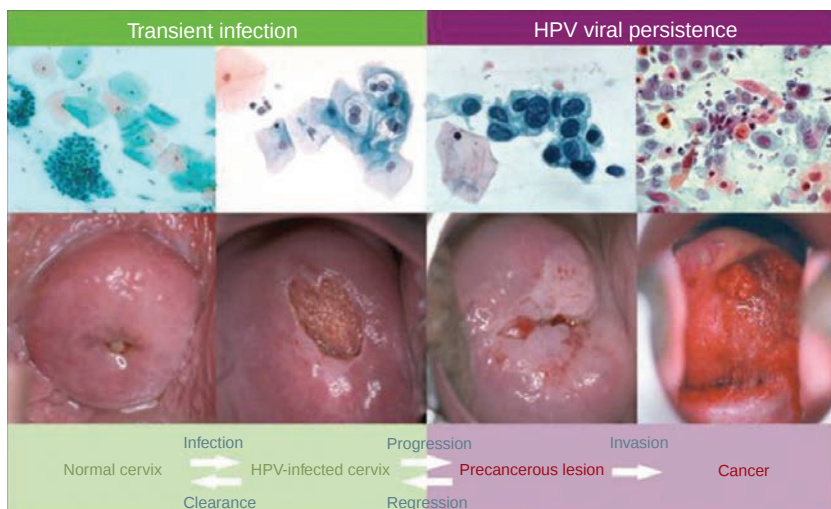


FIGURE 1.11. An epidemiologic model of the natural history of cervical carcinogenesis. The major steps in cervical carcinogenesis can be broadly categorized in the following stages: (I) exposure/acquisition of new human papillomavirus (HPV) infection that may cause transient cytological changes, a majority of which clear spontaneously; (II) persistence of few carcinogenic HPV infections and progression to precancerous lesions (cervical intraepithelial neoplasia 3 [CIN3]); and (III) development of invasion. The pictures in the top row show cytological changes and those in the bottom row show corresponding colposcopic impressions of the various stages of the natural history of cervical carcinogenesis.

Source: From Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. *Lancet*. 2007, with permission.

in samples obtained from infected women) in predicting persistence and progression of infection is complicated and varies by HPV type (253). A clear trend of increasing prospective risk with increasing viral load has been demonstrated only for HPV16. Viral load assessment is not useful clinically (254). Although studies suggest that women with prevalent infections may be more likely to acquire additional infections, infection with one HPV type does not seem to influence the risk of persistence and development of precancer from another concurrent infection (244).

HPV type greatly affects both the absolute risk of viral persistence and of progression to precancer associated with viral persistence (255,256). The most common carcinogenic type, HPV16, is also the most common type in the general population, linked to its greater propensity to persist (247,256). Although certain noncarcinogenic types (e.g., HPV61) can also be persistent and common, they do not cause malignant transformation (256,257). The average time of viral persistence that leads to diagnosable precancer is not clear. The average age at microscopic diagnosis of precancer is approximately 25 to 30 years (258), approximately 5 to 10 years after the average peak ages of carcinogenic HPV prevalence and associated minor cytologic abnormalities in screening populations. Biomarkers that predict persistence of cervical precancer and offer better discrimination of transforming versus transient HPV infections are increasingly available (259). Because the presence of HPV DNA is not specific enough to predict persistent HPV infection, other newer biomarkers such as the use of cellular correlates (e.g., p16^{INK4a} and ki-67) of increased expression of viral oncoproteins or increased expression of HPV viral oncogenic transcripts (e.g., E6/E7 mRNA) can allow triage for colposcopy after a mildly abnormal or borderline cytology or a positive HPV DNA test (259). The advances in cancer epigenetics have led to a strong focus on methylation-based biomarkers for many cancer sites, including the cervix. In addition, several recurring chromosomal imbalances have been observed for cervical precancer and are currently being explored as biomarkers along with other newer approaches such as micro-RNAs (miRNA) and proteomics (259).

Noncarcinogenic HPV infections are capable of producing lesions falsely diagnosed as precancer, especially CIN2, showing that this level of abnormality is not a perfect surrogate for cancer risk (260). Still, because of the U.S. emphasis on safety and concern over loss to follow-up, treating precancer (except as appropriate in very young women, etc.) is a valid clinical strategy to provide a margin of safety, given that it is not yet possible to know which lesions pose a threat. Eventually, better accuracy based on molecular profiling is the goal.

The immune response to HPV is an important determinant of viral clearance versus persistence and, by extension, a major determinant of cervical cancer risk (261). However, despite our growing understanding, many aspects of the interactions between HPV and the host immune system remain unknown (262). The key immune responses involved in the clearance of HPV infections are known to be cell-mediated, although neutralizing antibodies are highly protective after immunization with HPV virus-like-particle (VLP)-based vaccines (263). The immune response to naturally acquired HPV infection has not been quantified adequately and is difficult to study given the lack of site-specificity, challenges in serological assay development and validation, and the fact that seronegativity might not always reflect susceptibility. Responses to measure HPV vaccine responses, on the other hand, have been extensively developed and are currently being standardized for facilitating international epidemiology studies and future vaccine development and evaluation (264).

A major unresolved question of HPV natural history relates to the lack of understanding of viral latency (265). In long-term studies, virtually all HPV infections become undetectable by sensitive HPV DNA tests, usually within 2 years, except for those that lead to precancer. However, it is unknown if this lack of detection reflects true virological clearance or a latent stage due to immunologic control that permits long-term presence (latency) below levels of detection. Indeed, neither the cause of reemergence (reactivation) of viral types seen in immunocompromised individuals (e.g., transplant patients and HIV-immunosuppressed women) is known, nor is the clinical significance of latency in terms of the fraction that can progress to precancers and cancers clear (265). In the era of HPV vaccination, many of these issues will acquire increased significance, especially with the emergence of HPV genotyping assays in clinical practice.

Precancerous lesions (CIN3, in particular) tend not to regress over short-term follow-up; however, even among precancerous lesions, risk and timing of invasion versus eventual regression are matters of probability. The absolute risk of untreated precancer developing into invasive disease is argued, with estimates averaging 30% but ranging from 10% to 90% (266). The high ratio of precancerous lesions to cancers supports the belief that many cases of precancer, particularly CIN2, would not invade but rather would regress if followed for many years. Screened detected cases of invasive cancer, on average, occur approximately 15 to 20 years or later than precancer, suggesting a long sojourn time in the precancerous state (236). The median age moves toward even older ages as the quality of screening decreases, and

the average stage of cancer at diagnosis also worsens due to this diagnostic delay.

Cofactors Influencing Risk of Persistence of Carcinogenic HPV Infection and Progression of Cervical Precancer to Cancer

Given that carcinogenic HPV infection is a necessary and critical, although not sufficient, factor in the cervical carcinogenic processes, there has been substantial exploration of cofactors that influence the individual woman's risk for viral persistence, development of precancerous lesions, and finally invasion. Indeed, extensive epidemiologic investigations of a number of these risk factors (especially sexual behavior, parity, and smoking) were conducted even in the pre-HPV era. Some of these factors and the evidence supporting them are discussed in this section.

Sexual Behavior

HPV is highly transmissible via sexual contact in both genders. Numerous epidemiologic studies have shown that markers of sexual activity, such as number of sexual partners (recent or lifetime), are among the most important cofactors for HPV detection and subsequent risk of cervical precancer and cancer (267). HPV infections are easily transmitted with few acts of sexual intercourse and, therefore, sexual frequency is not a major risk factor for cervical neoplasia. The age at sexual debut serves as an apparent proxy for the time of HPV infection (268), and an early age of debut reflects higher risk, also accentuated by greater cervical ectopy during adolescence (269).

A protective effect against cervical cancer risk has been noted for careful, consistent condom use. Condom use affords modest protection against HPV infection and resultant external warts (HPV6 and HPV11) and cervical lesions caused by carcinogenic HPV types (270). Given that users of condoms may not report sporadic unprotected contacts, and that the entire skin and mucosal genital area at risk for infection is not protected with this contraceptive method, only modest protection against transmission would be expected (271).

HPV infection transmitted from a male partner to his female partner can be seen as "the male factor" for cervical cancer (272). Confirmed associations supporting this view include the geographic clustering of cervical and penile cancer, the increased risk of cervical cancer among wives of men who have penile cancer, the increased risk among partners of men who have had a previous partner who died of cervical cancer, and the increased risk among women whose partners travel (273). Circumcision is associated with a reduced risk of HPV detection in penile samples, and the wives of men with a history of multiple partners were at lower risk of cervical cancer if the men had been circumcised (273,274). Circumcision is associated with reduced prevalent male HPV infection, and randomized clinical trial evidence from Africa has now shown that voluntary adult male circumcision reduces transmission between sexual partners (274,275).

Parity and Other Obstetrical and Gynecologic Events

HPV-infected women who have many live births are at increased risk of cervical cancer and precancer. There is a dose-dependent increase in risk with numbers of live births, most evident among women with many live births. Although this epidemiologic association is firmly established, the explanatory mechanism is

not clear. Mechanisms underlying the association between parity and cervical neoplasia include trauma during parturition, hormonal changes associated with pregnancy, immunosuppression, and possibly altered anatomy of the transformation zone, specifically eversion. Other menstrual and reproductive factors, including miscarriages, abortions, stillbirths, ectopic pregnancies, cesarean sections, age at first pregnancy, age at menarche, and age at menopause, are not independently associated with risk (276,277).

Contraceptives

Studies examining the relationship of oral contraceptive use to cervical cancer risk among HPV-infected women are especially complex, with questions arising about the potential for confounding, particularly by the duration of HPV infection and screening behavior (278). Use of oral contraceptives could plausibly potentiate the carcinogenicity of HPV infection, because transcriptional regulatory regions of HPV DNA contain hormone-recognition elements and transformation of cells *in vitro* with viral DNA enhanced by hormones (279). Pooled analyses from multicenter case-control studies found an elevated risk of invasive cervical cancer among HPV-positive women who used oral contraceptives for more than 10 years (278). Shorter durations of use were not associated with elevated risk. Evidence linking oral contraceptives to cervical abnormalities has raised concern about long-acting steroid preparations, notably depot-medroxyprogesterone acetate (DMPA). Although these agents are widely used in many countries, studies evaluating their effects, particularly among HPV infected women, are limited (280).

A recent pooled analysis of ten case-control studies of cervical cancer and 16 HPV prevalence surveys from four continents has shown that intrauterine device (IUD) use, a common contraception option in developing countries, was associated with a lower risk of cervical cancer, regardless of duration of use (few months to 9 years) and after adjustment for screening status (281). This evidence contradicts a widely held assumption that IUDs may increase the risk of cervical cancer, and might suggest their role as protective cofactors in cervical carcinogenesis, much like a similar role they play in protecting against endometrial cancer. While the precise mechanisms are subject to future investigations, it has been suggested that local cellular immunity is triggered during the process of IUD insertion or by the device itself. That said, evidence from a recent study in female rhesus macaques has suggested that cervical microtrauma during collection of cytological smears actually increases the number of HPV infectious events (282).

Socioeconomic Status

Internationally, women defined as belonging to low social class were found in a meta-analysis to have twice the risk of cervical cancer compared to women defined as belonging to a high social class (283). In the U.S., a recent analysis of county-level incidence data noted that poverty-associated, infrequent screening leads to suboptimal stage at diagnosis profiles, resulting in elevated incidence and mortality rates. Some of these affected areas included Appalachia, the southeastern Atlantic states, and the lower Mississippi Valley, as well as central counties of large metropolitan areas (239).

Cigarette Smoking

Several case-control and cohort studies, as well as collaborative pooled analyses and registry linkage studies, among groups of women infected with carcinogenic HPV have shown that smokers are at increased risk compared with infected women who do not smoke (284,285). Current smoking is the main risk factor,

not past smoking, with no clear trend with time since stopping smoking. Among current smokers, evidence of increasing risk has been found with increasing intensity and duration (or early start) of smoking. Several investigations have attempted to define possible mechanisms by which smoking might alter cervical epithelium (286). Some investigations have looked into measurement of tobacco-driven carcinogens such as polycyclic aromatic hydrocarbon-DNA adducts in cervical tissue of HPV-infected women (287). The immunosuppressive effects of smoking may cause disturbance in the early immune responses or increase persistence through increased production of reactive oxygen species (288).

Host Factors

Whereas humoral (antibody-mediated) immunity appears to play a central role in preventing HPV infection (as in prophylactic vaccines), elimination of HPV seems more closely related to mounting an effective cellular immune response (262). Impaired cellular immunity, attributable to human immunodeficiency virus (HIV) infection, transplantation, or immunosuppressive drugs, has been shown to increase HPV prevalence, persistence, warts, CIN, and cancer (289,290). In contrast, deficiencies in humoral immunity appear unrelated to these conditions.

Polymorphisms in the human leukocyte antigen (HLA) genes have been implicated in the risk of HPV-associated diseases. HLAs are important determinants of the efficiency of antigen presentation to immune effector cells and, therefore, may influence the outcome of HPV infections (291). Both Class I HLA genes (those that encode HLA molecules that are present in all nucleated cells) and Class II HLA genes (those that encode HLA molecules that are present in lymphocytes and other immune-related cells) are involved in immune presentation (277). To date, HLA Class II genes have been more extensively studied than HLA Class I genes for their association with cervical cancer. A protective role for HLA DRB1*13 in cervical cancer has been consistently described in several populations. Activating combinations of HLA Class I alleles and the killer immunoglobulin-like receptor confers susceptibility to cervical cancer, whereas inhibitory combinations are associated with protection against the disease (291).

Although the biological basis is unknown, studies from nationwide tumor, twin, and other family registries in Scandinavian countries indicate that cervical cancer aggregates in families (292). In general, an approximate twofold increase in risk of precancer or invasive cervical cancer relative to general population risk is observed in family members of cervical cancer patients. It is not settled how much of this elevation in risk among relatives of individuals affected with cervical cancer can be attributed to shared environment versus genetic effects (292,293).

Nutrients

The influence of nutrient status on risk of cervical neoplasia has received substantial research attention. While dietary factors such as antioxidant micronutrient intake are likely important in cervical carcinogenesis, methodological difficulties prevent establishment of firm associations between a specific aspect of nutritional status and HPV infection or cervical cancer risk. A recent meta-analysis of case-control studies have suggested preventive effects of micronutrients such as folic acid, vitamins B, C, and E, and beta-carotene (294). However, lack of prospective studies and randomized trials preclude definitive evidence regarding role of supplementation. The association of low folate levels and high homocysteine levels with risk of cervical cancer has led to interest in markers of one-carbon metabolism and DNA repair (259).

Infectious Agents Other than HPV

HPV infection is known to be the central, necessary cause of cervical cancer, but other sexually transmitted agents could increase the risk of cervical cancer among HPV-infected women. Of the other agents examined, herpes simplex virus (HSV-2) was originally hypothesized to play a central role, but most attention now is focused on *Chlamydia trachomatis*. Although residual confounding by some aspect of HPV infection has not been completely ruled out, despite adjusting for HPV exposure using DNA tests and/or serology, *Chlamydia trachomatis* seropositive women are at increased risk compared to seronegative women (295).

Women with HIV and acquired immunodeficiency syndrome (AIDS) have higher prevalence, incidence, and persistence of HPV infection and precancerous lesions, strongly associated with immunosuppression (296). It is also well established that the incidence of cervical cancer is increased several fold in both women with HIV/AIDS as well as those who are iatrogenically immunosuppressed (e.g., organ transplant recipients), thus reinforcing the primary mediating role of immunosuppression in increasing this risk (297). However, it is also hypothesized that interaction between HPV and HIV in the affected cervical tissue leads to the persistence of HPV infection and cervical neoplasia by various mechanisms including depletion of Langerhans cells (298), host immune response (299), or via proinflammatory cytokine expression (300). An alternative explanation is at the cellular level; HIV-specific Tat protein upregulates expression of HPV E6 and E7 oncogenes and enhances their oncogenic transformation efficacy (301). These two mechanisms are, however, not exclusive, and a joint effect(s) most likely takes place at early precancerous stages.

Risk Factors for Cervical Adenocarcinoma

While infection with a carcinogenic HPV is a necessary cause of both squamous cell carcinomas and adenocarcinomas, the distribution of carcinogenic HPV types and variants detected in these two tumor types vary (302). Multiple studies suggest that HPV18 accounts for a relatively higher percentage of adenocarcinomas as compared to squamous cell carcinomas (249), although more recent evidence is pointing to an increasingly equitable role of HPV18 as well as HPV16 (248,303).

Interpreting increasing rates of cervical adenocarcinomas over time poses challenges because of gradual improvements in clinical practices (including the use of devices to obtain better endocervical sampling), stricter criteria for adequate Pap tests, development of cytologic criteria for recognizing adenocarcinoma *in situ* (AIS) and, recently, formal inclusion of the AIS category in the new Bethesda System (304). In addition, proposed but unsubstantiated explanations for these upward trends include increased rates of HPV infection without improved cytologic detection of AIS, a specific increase in rates of HPV 18 infection, and increased exposure to HPV cofactors specific to adenocarcinoma (236).

Although our understanding of the etiology of cervical adenocarcinoma is incomplete, a picture is emerging in which adenocarcinoma seems to share some risk factors with cervical squamous carcinomas (acquisition of HPV through sexual contact) and others with uterine carcinoma (a tumor etiologically related to hormones). While adenocarcinoma has most risk factors in common with squamous cell carcinoma, an important exception is smoking, which does not seem to increase the risk for adenocarcinoma (305). In contrast, increased weight (or related measures) appears to be related to increases in the risk of cervical adenocarcinomas (306). Oral contraceptives and menopausal hormone therapy have been linked to an increased risk

for AIS or adenocarcinoma (307). The increased risk of cervical adenocarcinoma associated with obesity and reduced risk with smoking resemble the epidemiology of endometrial adenocarcinoma. However, the relationship between cervical adenocarcinoma and oral contraceptives is more similar to reported results for squamous carcinomas of the cervix.

Conclusions

Knowledge of the epidemiology of HPV and its causal role in cervical carcinogenesis has been successfully translated into clinical practice (232,308), particularly to reduce rates of squamous lesions. In many developed countries, newer consensus guidelines now encourage cotesting with HPV DNA testing and cytology to improve screening performance and reduce screening intervals, since a negative result provides strong reassurance that immediate follow up is not required and can reduce patient anxiety and health costs (308). Repeated HPV testing is also finding application in following women without intervention and in determining the risk of recurrence among those treated for CIN. Screening studies are underway to develop new approaches that optimize resource utilization. Finally, the increasing use of prophylactic HPV vaccines is expected to impact rates of cervical precancer in the coming years, although reduction in cancer incidence will take longer. Epidemiologic research on HPV and cervical cancer will remain integral to clinical practice recommendations and public health strategies, with a goal to improve patient management and guide and monitor successes in cervical cancer prevention and control.

VULVAR CANCER

Demographic Patterns and the Importance of Pathologic Classifications

Carcinoma of the vulva is a rare genital neoplasm with an average annual age-adjusted incidence in all SEER areas during 2004 to 2008 of 2.3 per 100,000 women (238,309). During 2012, an estimated 4,490 women developed the disease and 950 died as a consequence (1).

Vulvar cancer is etiologically heterogeneous, and pathologic subtypes have distinct epidemiologic features (310,311). The great majority of cases are squamous, but two subclassifications of squamous cancers, basaloid and warty, are more linked to HPV than keratinizing squamous tumors (312). Most vulvar intraepithelial neoplasias (VIN), similar to CIN, show risk factors that resemble basaloid and warty carcinomas. The HPV-associated subtypes are associated with younger age and Black ethnic group. The non-HPV-associated types are associated with chronic inflammatory states such as lichen sclerosus.

Because vulvar cancer is heterogeneous, and because epidemiologic data do not separate the subtypes, compiled data must be interpreted very cautiously, with the recognition that summaries can obscure subgroup differences. Although vulvar cancer has been noted in clinical series to occur frequently among Blacks, recent incidence data do not support any substantial differences in *overall* incidence by race (2.4 per 100,000 for White women and 1.8 per 100,000 for Black women) (238,309). Although the disease occurs primarily among older women (median age at diagnosis being 68 years), recent analyses of SEER data indicate substantial increases in the incidence of *in situ* vulvar carcinomas (mainly HPV-related), which generally occur at much younger ages than invasive diseases (313).

Cancer of the vulva occurs significantly more frequently among women with primary cancers of the cervix, and the two diseases often occur simultaneously. Approximately 15% to 20% of women with vulvar cancer have a second primary cancer occurring simultaneously or nonsimultaneously in the cervix, vagina, or anogenital area. As many as 10% to 15% of women with cancer of the vulva have a second primary lesion of the cervix (314). This association probably reflects multifocal HPV infection. When multiple primaries are not diagnosed simultaneously, cancer of the cervix usually precedes cancer of the vulva. Many patients with vulvar cancer have multifocal genital lesions, commonly including a mixture of condyloma acuminatum planum and intraepithelial neoplasia. They may also have similar changes at other anogenital sites, including the vagina, cervix, and perianal region (314).

Rates of vulvar cancer overall have remained relatively stable over the past 3 decades per SEER data (238,309). Given that *in situ* cancers develop on average significantly earlier than invasive vulvar cancers, it may be that changes in certain risk factors (e.g., increased sexual activity and HPV infection) may have been too recent in order for effects to be seen for invasive cancers. Alternatively, successful treatment of *in situ* tumors may have prevented the occurrence of invasive disease. Again, the most likely explanation for the patterns observed is etiologic differences, with HPV being more important for *in situ* cancers.

Risk Factors

While early case-control studies reported higher risks among women reporting multiple sexual partners, subsequent studies postulated a role for HPV in the etiology of the tumors, finding high rates of detection of the virus in vulvar tumor tissue and high subsequent disease risks among patients with seropositive tests to HPV16 (315). HPV16 appears to be the predominant type detected among vulvar cancer patients (316). Studies have found particularly high risks associated with HPV seropositivity among cigarette smokers, suggesting that the effect of HPV may depend on smoking as a cofactor (317,318).

Although the incidence of vulvar cancer has been previously thought to be related to social class, results from one case-control study indicated that control for sexual factors eliminated this effect (319). Suggestions that the risk of vulvar cancer is elevated among nulliparous women and those with late ages at first birth were not confirmed in this study.

Vulvar carcinomas often arise within genital warts, but more specific temporal associations between the two remain unclear. Several studies have suggested that a history of vulvar and anogenital warts is associated with an elevated risk of vulvar cancer (320). However, the HPV types that cause vulvar warts, HPV6 and HPV11, are not genetically close to the major types in vulvar cancers (predominantly HPV16), so the exact relationship between warts and cancer is somewhat obscure.

Several clinical studies have suggested that vulvar cancer may be elevated among women with diabetes, obesity, or hypertension, and among users of oral contraceptives. However, these findings have not been definitively confirmed in epidemiologic studies. While certain immunosuppressed populations, such as HIV-infected women, also have high prevalence of anogenital warts and VIN, regression is still common and vulvar cancers are infrequent (297,321). Recent attention has also focused on the possible etiologic role of genetic and local inflammatory factors in pathogenesis of VIN and invasive vulvar carcinoma (322,323).

Conclusions

The cervix and vulva are covered by squamous-cell epithelium with a common embryologic origin from the cloacogenic

membrane. These similarities have led to the theory that the entire lower genital tract responds to various carcinogens as a single tissue field, resulting in a relatively high proportion of multicentric squamous carcinomas. The multicentric nature of the disease; its association with cervical, vaginal, and perianal malignancies; and several risk factors common to it and cervical cancer suggest that the etiologic mechanisms for a fraction of vulvar cancer and cervical cancer may be similar, linked to HPV infection.

VAGINAL CANCER

Demographic Patterns

Cancer of the vagina is also rare, with an average annual age-adjusted incidence of 0.7 per 100,000 women in the SEER areas for the period 2000 to 2004. In contrast to vulvar cancers, the incidence is higher for Blacks (1.0 per 100,000 for Blacks vs. 0.7 per 100,000 for Whites), but the reasons for the discrepancy are unknown. During 2012 it is estimated that 2,680 women developed the disease and 840 died from it (1). The average 5-year survival rate is 52% for Whites (50% for all races). The majority of vaginal cancers are squamous cell carcinomas and occur in the upper part of the vagina.

Vaginal cancer is primarily a disease of older women, with almost 60% occurring among women 60 years of age or older (324). In the past, carcinoma of the vagina was only rarely reported in infants and children but, beginning in the late 1960s, cases of clear cell adenocarcinoma of the vagina, an uncommon cancer in any age group, began to be observed with much greater frequency than expected among women between 15 and 22 years of age. Most of these cases have been linked to prenatal exposure to diethylstilbestrol (DES) (325).

Risk Factors

The rarity of vaginal cancer has limited the conduct of definitive epidemiologic investigations. A case-control study of vaginal cancer, based on relatively few cases, found associations of risk with low socioeconomic status, histories of genital warts or other genital irritations, and previous abnormal Pap smears (326). A more recent and larger study linked risk with histories of multiple sexual partners, early ages at first intercourse, and current cigarette smoking (327). Epidemiologic studies have also shown high risks associated with prior hysterectomies, although this apparently is due to the predisposition of women with anogenital cancers (particularly those with cervical cancer) to subsequently develop vaginal cancers (328).

HPV Infection

Findings that vaginal cancer is frequently found as a synchronous or a metachronous neoplasm with cervical cancer have led to the suggestion that there may be shared etiologic features between vaginal and cervical cancers (328). HPV has been related to disease risk through findings of HPV antigens or DNA in vaginal cancer tissue (329). HPV DNA has been reported in tumor blocks of greater than 80% of patients with *in situ* and greater than 60% of patients with invasive cancers (330). In addition, serologic antibodies to HPV have been linked to subsequent disease risk.

Diethylstilbestrol and Vaginal Clear-Cell Adenocarcinomas

In 1971, seven clear cell carcinomas of the vagina and one closely related endometrioid carcinoma were observed in young women (15 to 22 years of age) (331). An epidemiologic study found that the mothers of seven of the eight women had taken DES during the first trimester of pregnancy as opposed to none of the mothers of 32 matched controls. The relationship between DES exposure *in utero* and adenocarcinoma of the vagina was soon confirmed in New York State and at the Mayo Clinic. A registry of clear cell cancer of the vagina and cervix has been established, and many more cases have been reported (332). Among these patients, about twice as many have clear cell adenocarcinoma of the vagina as have clear cell adenocarcinoma of the cervix.

Recent data from an assembly of all established DES cohorts indicate that the majority of patients with vaginal or cervical adenocarcinomas are diagnosed prior to age 25, with the incidence after this age decreasing by 80% (333). The estimated rate for clear cell adenocarcinoma of the vagina and cervix through 39 years of age was estimated to be 1.6 per 1,000 DES-exposed daughters (325). Thus, DES exposure leads to a large relative increase in risk, but it affects only a small proportion of all exposed women. It remains to be seen what risk will be encountered by DES daughters when they reach their fifties and sixties, the peak ages of adenocarcinomas of the vagina in women unexposed to DES (325). When assessing a woman's cancer risk, whether her mother took DES in pregnancy might still be a relevant aspect of the medical history for women born during the period of DES use in pregnancy (331).

Conclusions

Less is known about risk factors for vaginal cancer than is known for vulvar cancer. It has recently been suggested that there may be two types of vaginal cancers with age-related etiology (333). In young patients, the etiology may be similar to cervical cancer and related to HPV, smoking, and low socioeconomic status, while the most common occurrences in older women may be due to hormonal factors or trauma to the vagina. Further attention should focus on the relative contributions of these factors.

The rare occurrence of vaginal adenocarcinoma in young women is distinctive in being essentially an iatrogenic disease related to *in utero* exposure to DES and other estrogens (325). A proposed mechanism involves nests of abnormal cells of müllerian duct origin, which are stimulated by endogenous hormones during puberty and promoted into adenocarcinomas.

GESTATIONAL TROPHOBLASTIC DISEASES

Gestational trophoblastic diseases (GTDs) (which include hydatidiform moles, invasive moles, and choriocarcinoma) encompass a range of interrelated conditions characterized by abnormal growth of chorionic tissues with various propensities for local invasion and metastasis (334,335). Hydatidiform moles can be either complete or partial and have distinctive pathologies and etiologies. Complete moles have paternally derived nuclear DNA but maternally derived cytoplasmic DNA. In contrast, partial moles generally have a triploid karyotype, with the extra haploid set of chromosomes being of paternal origin.

Demographic Patterns

Choriocarcinoma is a rare malignancy in the United States, with a reported incidence in all SEER areas of 0.1 per 100,000 women, or approximately 1 per 25,674 live births (336). Hydatidiform mole occurs about once in every 1,000 pregnancies, and approximately one of six occurrences results in invasive complications (either invasive mole or choriocarcinoma). Trophoblastic diseases have been reported to be more common in certain parts of the world, although some of the differences may be due to a variety of selection, detection, and reporting biases (337), including whether risk is expressed in relation to women at risk, conceptions, or live births. In the U.S., incidence rates have declined over time, and survival improved, but Blacks continue to have higher incidence and lower survival than women of other ethnicities.

The epidemiologic study of choriocarcinoma has been complicated by its relative infrequency. Most studies have, therefore, focused on defining risk factors for hydatidiform moles, but it is uncertain the extent to which these findings can be extrapolated to malignant trophoblastic disease.

Host Factors

Trophoblastic disease rates are considerably higher in Asian and African countries, but the true extent of difference from Western rates is difficult to decipher because of variations in reporting practices (338). In Europe and North America, the incidence of hydatidiform mole ranges from 0.57 to 1.1 per 1,000 pregnancies, while in Southeast Asia and Japan the incidence is closer to 2.0 (334). Corresponding incidence rates in the two parts of the world for choriocarcinoma are 1 versus 9.3 per 40,000 pregnancies. These differences persist in migrants, with one study showing that the incidence of GTDs in Asians was nearly twice as high as among non-Asians (339). One survey in the U.S. showed that even after adjustment for age and birth distribution effects, Blacks had a 2.1-fold greater risk and other non-White races had a 1.8-fold greater risk than Whites (340). American Indian and Alaskan native populations have also been shown to have high rates of GTDs (341).

One clearly established risk factor for choriocarcinoma and hydatidiform mole is maternal age. Women with extreme maternal ages (either very early or late) have nearly two-fold elevated rates, with even further age differences noted for the occurrence of complete moles (339). The recent increase in incidence of GTDs in certain European countries has been attributed in large part to increases in maternal ages (342,343).

A history of hydatidiform mole is also a strong risk factor. The risk of another molar pregnancy in a subsequent conception is approximately 1% (344), and the risk appears to increase to about 25% in women who have had more than one previous hydatidiform mole (345). One study suggested that some women might have multiple episodes of hydatidiform mole despite different male partners, suggesting either a role for oocyte defects or environmental factors (346). Familial clusters of biparental complete hydatidiform moles associated with novel missense NLRP7 gene mutations on chromosome 19q have recently been identified (347). Hydatidiform mole is associated with a 1,000 to 2,000 time increased risk for development of subsequent choriocarcinoma, with an even further enhancement after a complete molar pregnancy (2,500 times higher than after a live birth).

Two studies have found an association between blood group A and choriocarcinoma (348,349). The combination of mother's group A and father's group O generated over a 10-fold increased risk. Blood groups A and AB were associated with elevated risks of hydatidiform mole in one study but not in another (350,351). These findings may support a role for genetic

factors or immunologic factors related to the histocompatibility of maternal and trophoblastic tissues.

Menstrual, Reproductive, and Anthropometric Risk Factors

In several studies that have adjusted for the effects of late maternal age, parous women have remained at a substantially reduced risk of GTD compared with nulliparous women, with some evidence of further reductions in risk with multiple births (350,352,353). A number of studies have found an increased risk associated with a prior spontaneous abortion, although this has not been consistently observed (350,352–355). An increased risk of GTDs has been found in relation to a history of induced abortions in a number of studies, although information was not available on reasons for the terminations (352). A history of infertility has also been suggested as a risk factor for GTD, although not confirmed in all studies (350,352,355). In one study, Chinese patients reporting the use of herbal medicines during the first trimester of a previous pregnancy were at elevated risk (352).

Low body mass, unrelated to dieting or exercise, was reported as a risk factor for choriocarcinoma in one study (356). Patients also had late onset of menarche and lighter menstrual periods than controls, possibly reflecting lower estrogen levels.

Exogenous Hormones

Several studies have found an increased risk of trophoblastic diseases associated with long-term use of oral contraceptives (352,357,358). Two other case-control studies, however, found no influence of oral contraceptives on risk (350,355). In one study, the association was considerably stronger for partial than for complete moles (359). Others have suggested that oral contraceptives may increase the risk of malignant sequelae after mole evacuation through a tumor-stimulating effect (360,361). In one study, this effect was restricted to users of high-dose estrogens, although in others, there were no effects of the pill on postmolar complications (357,362,363).

Other Risk Factors

Late paternal age was suggested in one study to increase the risk of trophoblastic diseases, but other investigations failed to confirm this (350,352,364). Cigarette smoking has also been linked with the occurrence of trophoblastic disease (355). One study suggested that low carotene intake affected the risk of hydatidiform mole, but no specific dietary associations were observed in another study (352,357).

Conclusions

Although a genetic role in the development of hydatidiform mole is now certain, little is known about genotypes that predispose to hydatidiform mole or environmental factors that may increase the risk of defective ova. Except for the possible role of oral contraceptives, few potential environmental promoters have been identified.

The trophoblast plays an active role in pregnancy, including metabolizing and detoxifying xenobiotic substances, regulating nutrient and waste product transfer, synthesizing steroid and protein hormones, and controlling the immune response of the maternofetal unit. Injury to the trophoblast can occur in pregnancy as a result of environmental exposure (e.g., heavy metals and polycyclic hydrocarbons), resulting in the breakdown

of trophoblastic processes. When the trophoblast malfunctions, mutagenic, teratogenic, lethotoxic, and carcinogenic compounds gain access to the developing embryo, causing injury and death. The genotype of hydatidiform mole results in a trophoblast that malfunctions, and exposure to certain environmental agents during the molar pregnancy may promote choriocarcinoma. Before implantation, the trophoblast forms most of the embryonic tissue, which already metabolizes environmental agents. Even preimplanted moles, with their impaired metabolic capabilities, may increase the toxicity of environmental agents and promote carcinogenesis.

Recent advances in identifying genetic and molecular markers involved with partial versus complete moles (334,365) open a number of avenues for assessing the interaction of these markers with a variety of proposed environmental risk factors. This could include a focus on early stages in the disease process or on factors involved in the progression of molar pregnancies to more invasive complications.

SUMMARY

The goal of both medical practice and epidemiology is to reduce morbidity and mortality. For many diseases, the focus has turned to the ultimate aim of prevention. The link between identification of etiologic factors and possibilities for prevention is well illustrated for tobacco-and alcohol-related tumors and for those associated with specific pharmaceutical, radiogenic, and occupational exposures. Fortunately, for gynecologic cancers, there are a number of identified etiologic factors that are also amenable to preventive approaches.

Undoubtedly, the prospects for prevention are best for cervical cancer. For some time, secondary prevention in the form of screening for pathologic precursors of invasive disease has been the hallmark of the public health approach to this malignancy. The establishment of HPV as a central etiologic agent for the disease presents other avenues for prevention, including application of recently developed vaccines against the virus. Knowledge of when and how infection and other factors operate in the natural history of the disease has revolutionized screening strategies and shifted treatment from cell ablation to antiviral therapies. As always, combined laboratory, clinical, and epidemiologic research is needed to realize these propositions.

Many believe that more is known about the cause of uterine carcinoma than for almost any other tumor. A unified theory of how all risk factors may operate through a final common estrogenic pathway is popular and well supported. A woman's hormonal milieu may prove to be favorable to modification at a practical level. There is substantial evidence that elimination of obesity and a reduction in fat in the diet—two interventions actively promoted for other reasons—reduces endometrial cancer risk. After the epidemic of uterine cancer due to use of unopposed estrogen therapy, changes in the management of menopause occurred, resulting in a marked decline in the rates of uterine cancer. More care is devoted to identifying women who truly need estrogen therapy, treatment of menopausal

symptoms is for a much shorter period of time, the use of cyclic progestin in combination with estrogen is advised if indicated, and regular endometrial sampling is frequently practiced for long-term estrogen users.

Although past alterations in patient management led to a decline in uterine cancer, current events make future patterns less clear. Previous enthusiasm for long-term treatment of large segments of the population of menopausal women with hormones to control symptoms and prevent osteoporosis and heart disease may have implications for endometrial cancer in the future. On the other hand, current patterns of use of oral contraceptives could lead to reductions in endometrial cancer rates in the general population. The impact of widespread oral contraceptive use at young ages on endometrial cancer risk at older ages is not well studied. However, if it is anywhere near the reduced risk seen at young ages, the resulting reduction in uterine cancer overall could be substantial.

With further research, it is also possible that pharmacologic interventions aimed specifically at groups at high risk for uterine cancer due to endogenous hormonal factors could be justified. More must be learned about the associations of risk for endometrial cancer and the quantitative levels of estrogens and other hormones and their relative proportions. Once these factors are known, women with PCOS, diabetes, morbid obesity, or other predisposing conditions could be evaluated for unfavorable hormone profiles and appropriately targeted for treatment.

Although a substantial amount has been learned about ovarian cancer risks, the prospects for meaningful preventive measures aimed at this tumor are probably worse than for other gynecologic malignancies. Although several ovarian cancer risk factors seem to indict ovulatory activity as a common pathway to increased risk, the mechanism by which this occurs is unknown. Even if some of the hypothesized mechanisms prove to be correct, it is unclear how reasonable any interventions may be. However, if the long-term effect of oral contraceptive use on ovarian cancer risk is similar to its short-term effect, a substantial decline in ovarian cancer rates should result from pill use patterns of the past 40 years. Another reason for the limited prospects for prevention is that for several risk factors (e.g., protection associated with hysterectomy) no credible mechanism has been suggested. The associations promising the greatest opportunities for preventive actions are several recently suggested dietary relationships, specifically, decreased risks with consumption of diets high in fruits and vegetables and certain micronutrients. However, these observations need to be replicated in additional studies. Because of the preventive implications, attempts at confirmation should have high priority.

For cervical cancer, uterine cancer, and ovarian cancers, much is known about the risk factors. However, less is known about the precise biologic mechanisms through which the known risk factors operate. There is substantial enthusiasm for current interdisciplinary studies that incorporate state of the art laboratory assays into robust epidemiologic research designs focused on answering these mechanistic questions. Even among some of the more conservative etiologists, there is a belief that the gynecologic oncologist may soon be able to intervene much earlier in the natural history of these diseases, and in some instances, engage in primary prevention.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures* 2012. Atlanta, GA: American Cancer Society; 2012.
2. Howlander N, Noone AM, Neyman N, et al. *SEER Cancer Statistics Review, 1975–2008*. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
3. Parkin DM, Whelan SL, Ferlay J, et al. *Cancer Incidence in Five Continents*, Vol. I to VIII. Lyon, France; 2005. Report No.: IARC CancerBase No. 7.
4. Weiss NS, Szkely DR, Austin DF. Increasing incidence of endometrial cancer in the United States. *N Engl J Med*. 1976;294:1259–1262.
5. Brinton LA, Berman ML, Mortel R, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. *Am J Obstet Gynecol*. 1992;167:1317–1325.
6. Modan B, Ron E, Lerner-Geva L, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol*. 1998;147:1038–1042.
7. Bernstein L, Pike MC, Ross RK, et al. Estrogen and sex hormone-binding globulin levels in

- nulliparous and parous women. *J Natl Cancer Inst.* 1985;74:741–745.
8. La Vecchia C, Franceschi S, Decarli A, et al. Risk factors for endometrial cancer at different ages. *J Natl Cancer Inst.* 1984;73:667–671.
 9. Brinton LA, Sakoda LC, Lissowska J, et al. Reproductive risk factors for endometrial cancer among Polish women. *Br J Cancer.* 2007;96:1450–1456.
 10. Lambe M, Wu J, Weiderpass E, et al. Childbearing at older age and endometrial cancer risk (Sweden). *Cancer Causes Control.* 1999;10:43–49.
 11. Dossus L, Allen N, Kaaks R, et al. Reproductive risk factors and endometrial cancer: The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2010;127:442–451.
 12. Beining RM, Dennis LK, Smith EM, et al. Uterine cancer after intrauterine device use and risk of endometrial cancer. *Ann Epidemiol.* 2008;18:492–499.
 13. Althuis MD, Moghissi KS, Westhoff CL, et al. Uterine cancer after use of clomiphene citrate to induce ovulation. *Am J Epidemiol.* 2005;161:607–615.
 14. Calderon-Margalit R, Friedlander Y, Yanetz R, et al. Cancer risk after exposure to treatments for ovulation induction. *Am J Epidemiol.* 2009;169:365–375.
 15. Newcomb PA, Trentham-Dietz A. Breast feeding practices in relation to endometrial cancer risk, USA. *Cancer Causes Control.* 2000;11:663–667.
 16. MacMahon B. Risk factors for endometrial cancer. *Gynecol Oncol.* 1974;2:122–129.
 17. Cibula D, Gompel A, Mueck AO, et al. Hormonal contraception and risk of cancer. *Hum Reprod Update.* 2010;16:631–650.
 18. Schlesselman JJ. Cancer of the breast and reproductive tract in relation to use of oral contraceptives. *Contraception.* 1989;40:1–38.
 19. Maxwell GL, Schildkraut JM, Calingaert B, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. *Gynecol Oncol.* 2006;103:535–540.
 20. Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2005;365:1543–1551.
 21. Cushing KL, Weiss NS, Voigt LF, et al. Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. *Obstet Gynecol.* 1998;91:35–39.
 22. Montgomery BE, Daum GS, Dunton CJ. Endometrial hyperplasia: a review. *Obstet Gynecol Surv.* 2004;59:368–378.
 23. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA.* 2003;290:1739–1748.
 24. Jaakkola S, Lyytinen H, Pukkala E, et al. Endometrial cancer in postmenopausal women using estradiol-progestin therapy. *Obstet Gynecol.* 2009;114:1197–1204.
 25. Razavi P, Pike MC, Horn-Ross PL, et al. Long-term postmenopausal hormone therapy and endometrial cancer. *Cancer Epidemiol Biomarkers Prev.* 2010;19:475–483.
 26. Newcomb PA, Trentham-Dietz A. Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). *Cancer Causes Control.* 2003;14:195–201.
 27. Allen NE, Key TJ, Dossus L, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer.* 2008;15:485–497.
 28. Trabert B, Wentzensen N, Yang HP, et al. Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk?. *Int J Cancer.* 2012. doi: 10.1002/ijc.27623.
 29. Friedenreich C, Cust A, Lahmann PH, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. *Cancer Causes Control.* 2007;18:399–413.
 30. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst.* 2007;99:272–282.
 31. Nelson HD, Fu R, Griffin JC, et al. Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer. *Ann Intern Med.* 2009;151:703–226.
 32. van Leeuwen FE, Benraadt J, Coebergh JW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet.* 1994;343:448–452.
 33. Bland AE, Calingaert B, Secord AA, et al. Relationship between tamoxifen use and high risk endometrial cancer histologic types. *Gynecol Oncol.* 2009;112:150–154.
 34. Schmandt RE, Iglesias DA, Co NN, et al. Understanding obesity and endometrial cancer risk: opportunities for prevention. *Am J Obstet Gynecol.* 2011;205:518–525.
 35. Yang TY, Cairns BJ, Allen N, et al. Postmenopausal endometrial cancer risk and body size in early life and middle age: prospective cohort study. *Br J Cancer.* 2012;107(1):169–175.
 36. Chang SC, Lacey JV Jr. Lifetime weight history and endometrial cancer risk by type of menopausal hormone use in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev.* 2007;16:723–730.
 37. Moore SC, Gierach GL, Schatzkin A, et al. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. *Br J Cancer.* 2010;103:933–938.
 38. Gierach GL, Chang SC, Brinton LA, et al. Physical activity, sedentary behavior, and endometrial cancer risk in the NIH-AARP Diet and Health Study. *Int J Cancer.* 2009;124:2139–2147.
 39. Loerbroeks A, Schouten LJ, Goldbohm RA, et al. Alcohol consumption, cigarette smoking, and endometrial cancer risk: results from the Netherlands Cohort Study. *Cancer Causes Control.* 2007;18:551–560.
 40. Terry PD, Miller AB, Jones JG, et al. Cigarette smoking and the risk of invasive epithelial ovarian cancer in a prospective cohort study. *Eur J Cancer.* 2003;39:1157–1164.
 41. Yang HP, Brinton LA, Platz EA, et al. Active and passive cigarette smoking and the risk of endometrial cancer in Poland. *Eur J Cancer.* 2010;46:690–696.
 42. Polesel J, Serraino D, Zucchetto A, et al. Cigarette smoking and endometrial cancer risk: the modifying effect of obesity. *Eur J Cancer Prev.* 2009;18:476–481.
 43. Austin H, Drews C, Partridge EE. A case-control study of endometrial cancer in relation to cigarette smoking, serum estrogen levels, and alcohol use. *Am J Obstet Gynecol.* 1993;169:1086–91.
 44. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer.* 1975;15:617–631.
 45. Cui X, Rosner B, Willett WC, et al. Dietary fat, fiber, and carbohydrate intake in relation to risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev.* 2011;20:978–989.
 46. Jain MG, Rohan TE, Howe GR, et al. A cohort study of nutritional factors and endometrial cancer. *Eur J Epidemiol.* 2000;16:899–905.
 47. van LL, Kirsh VA, Kreiger N, et al. Endometrial cancer and meat consumption: a case-cohort study. *Eur J Cancer Prev.* 2011;20:334–339.
 48. Prentice RL, Thomson CA, Caan B, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. *J Natl Cancer Inst.* 2007;99:1534–1543.
 49. Biel RK, Friedenreich CM, Csizmadia I, et al. Case-control study of dietary patterns and endometrial cancer risk. *Nutr Cancer.* 2011;63:673–686.
 50. Yeh M, Moysich KB, Jayaprakash V, et al. Higher intakes of vegetables and vegetable-related nutrients are associated with lower endometrial cancer risks. *J Nutr.* 2009;139:317–322.
 51. Uccella S, Mariani A, Wang AH, et al. Dietary and supplemental intake of one-carbon nutrients and the risk of type I and type II endometrial cancer: a prospective cohort study. *Ann Oncol.* 2011;22:2129–2136.
 52. Kabat GC, Park Y, Hollenbeck AR, et al. Intake of fruits and vegetables, and risk of endometrial cancer in the NIH-AARP Diet and Health Study. *Cancer Epidemiol.* 2010;34:568–573.
 53. McCullough ML, Bandera EV, Patel R, et al. A prospective study of fruits, vegetables, and risk of endometrial cancer. *Am J Epidemiol.* 2007;166:902–911.
 54. Galeone C, Augustin LS, Filomeno M, et al. Dietary glycemic index, glycemic load, and the risk of endometrial cancer: a case-control study and meta-analysis. *Eur J Cancer Prev.* 2012.
 55. Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: a prospective study of Swedish women. *Int J Cancer.* 2007;120:1103–1107.
 56. Nagle CM, Olsen CM, Ibiebele TI, et al. Glycemic index, glycemic load and endometrial cancer risk: results from the Australian National Endometrial Cancer study and an updated systematic review and meta-analysis. *Eur J Nutr.* 2012. [Epub ahead of print].
 57. Hogervorst JG, Schouten LJ, Konings EJ, et al. A prospective study of dietary acrylamide intake and the risk of endometrial, ovarian, and breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16:2304–2313.
 58. Wilson KM, Mucci LA, Rosner BA, et al. A prospective study on dietary acrylamide intake and the risk for breast, endometrial, and ovarian cancers. *Cancer Epidemiol Biomarkers Prev.* 2010;19:2503–2515.
 59. Horn-Ross PL, John EM, Canchola AJ, et al. Phytoestrogen intake and endometrial cancer risk. *J Natl Cancer Inst.* 2003;95:1158–1164.
 60. Ollberding NJ, Lim U, Wilkens LR, et al. Legume, soy, tofu, and isoflavone intake and endometrial cancer risk in postmenopausal women in the multiethnic cohort study. *J Natl Cancer Inst.* 2012;104:67–76.
 61. Friberg E, Orsini N, Mantzoros CS, et al. Alcohol intake and endometrial cancer risk: a meta-analysis of prospective studies. *Br J Cancer.* 2010;103:127–131.
 62. Yang HP, Gierach GL, Danforth KN, et al. Alcohol and endometrial cancer risk in the NIH-AARP diet and health study. *Int J Cancer.* 2011;128:2953–2961.
 63. Je Y, Giovannucci E. Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *Int J Cancer.* 2012;131:1700–1710.
 64. Butler LM, Wu AH. Green and black tea in relation to gynecologic cancers. *Mol Nutr Food Res.* 2011;55:931–940.

65. Haoula Z, Salman M, Atiomo W. Evaluating the association between endometrial cancer and polycystic ovary syndrome. *Hum Reprod*. 2012;27:1327–1331.
66. Dahlgren E, Friberg LG, Johansson S, et al. Endometrial carcinoma; ovarian dysfunction—a risk factor in young women. *Eur J Obstet Gynecol Reprod Biol*. 1991;41:143–150.
67. Weiderpass E, Ye W, Vainio H, et al. Diabetes mellitus and ovarian cancer (Sweden). *Cancer Causes Control*. 2002;13:759–764.
68. Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. *Cancer Epidemiol Biomarkers Prev*. 2007;16:276–280.
69. Lindemann K, Vatten LJ, Ellstrom-Eng M, et al. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. *Br J Cancer*. 2008;98:1582–1585.
70. Friedenreich CM, Biel RK, Lau DC, et al. Case-control study of the metabolic syndrome and metabolic risk factors for endometrial cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20:2384–2395.
71. Rosato V, Zucchetto A, Bosetti C, et al. Metabolic syndrome and endometrial cancer risk. *Ann Oncol*. 2011;22:884–889.
72. Fortuny J, Sima C, Bayuga S, et al. Risk of endometrial cancer in relation to medical conditions and medication use. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1448–1456.
73. Morimoto LM, Newcomb PA, Hampton JM, et al. Cholecystectomy and endometrial cancer: a marker of long-term elevated estrogen exposure? *Int J Gynecol Cancer*. 2006;16:1348–1353.
74. Newcomb PA, Trentham-Dietz A, Egan KM, et al. Fracture history and risk of breast and endometrial cancer. *Am J Epidemiol*. 2001;153:1071–1078.
75. Modugno F, Ness RB, Chen C, et al. Inflammation and endometrial cancer: a hypothesis. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2840–2847.
76. Bodelon C, Doherty JA, Chen C, et al. Use of nonsteroidal antiinflammatory drugs and risk of endometrial cancer. *Am J Epidemiol*. 2009;170:1512–1517.
77. Viswanathan AN, Feskanich D, Schernhammer ES, et al. Aspirin, NSAID, and acetaminophen use and the risk of endometrial cancer. *Cancer Res*. 2008;68:2507–2513.
78. Lucenteforte E, Talamini R, Montella M, et al. Family history of cancer and the risk of endometrial cancer. *Eur J Cancer Prev*. 2009;18:95–99.
79. Hemminki K, Bermejo JL, Granstrom C. Endometrial cancer: population attributable risks from reproductive, familial and socioeconomic factors. *Eur J Cancer*. 2005;41:2155–2159.
80. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. *JAMA*. 2006;296:1479–1487.
81. Gaudet MM, Yang HP, Bosquet JG, et al. No association between FTO or HHEX and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2106–2109.
82. Lundin E, Wirgin I, Lukanova A, et al. Selected polymorphisms in sex hormone-related genes, circulating sex hormones and risk of endometrial cancer. *Cancer Epidemiol*. 2012;36:445–452.
83. O'Mara TA, Fahey P, Ferguson K, et al. Progesterone receptor gene variants and risk of endometrial cancer. *Carcinogenesis*. 2011;32:331–335.
84. O'Mara TA, Ferguson K, Fahey P, et al. CHEK2, MGMT, SULT1E1 and SULT1A1 polymorphisms and endometrial cancer risk. *Twin Res Hum Genet*. 2011;14:328–332.
85. Xu WH, Shrubsole MJ, Xiang YB, et al. Dietary folate intake, MTHFR genetic polymorphisms, and the risk of endometrial cancer among Chinese women. *Cancer Epidemiol Biomarkers Prev*. 2007;16:281–287.
86. Spurdle AB, Thompson DJ, Ahmed S, et al. Genome-wide association study identifies a common variant associated with risk of endometrial cancer. *Nat Genet*. 2011;43:451–454.
87. Long J, Zheng W, Xiang YB, et al. Genome-wide association study identifies a possible susceptibility locus for endometrial cancer. *Cancer Epidemiol Biomarkers Prev*. 2012.
88. Sturgeon SR, Brock JW, Potischman N, et al. Serum concentrations of organochlorine compounds and endometrial cancer risk (United States). *Cancer Causes Control*. 1998;9:417–424.
89. Weiderpass E, Adami HO, Baron JA, et al. Organochlorines and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2000;9:487–493.
90. Hardell L, van BB, Lindstrom G, et al. Adipose tissue concentrations of p,p'-DDE and the risk for endometrial cancer. *Gynecol Oncol*. 2004;95:706–711.
91. Abel EL, Hendrix SL, McNeeley GS, et al. Use of electric blankets and association with prevalence of endometrial cancer. *Eur J Cancer Prev*. 2007;16:243–250.
92. McElroy JA, Newcomb PA, Trentham-Dietz A, et al. Endometrial cancer incidence in relation to electric blanket use. *Am J Epidemiol*. 2002;156:262–267.
93. Bernstein L, Allen M, Anton-Culver H, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). *Cancer Causes Control*. 2002;13:625–635.
94. Weiderpass E, Pukkala E, Vasama-Neuvonen K, et al. Occupational exposures and cancers of the endometrium and cervix uteri in Finland. *Am J Ind Med*. 2001;39:572–580.
95. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol*. 1983;15:10–17.
96. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. *Mod Pathol*. 2000;13:295–308.
97. Arafa M, Somja J, Dehan P, et al. Current concepts in the pathology and epigenetics of endometrial carcinoma. *Pathology*. 2010;42:613–617.
98. Lim D, Oliva E. Nonendometrioid endometrial carcinomas. *Semin Diagn Pathol*. 2010;27:241–260.
99. Felix AS, Weissfeld JL, Stone RA, et al. Factors associated with Type I and Type II endometrial cancer. *Cancer Causes Control*. 2010;21:1851–1856.
100. Yang HP, Wentzensen N, Trabert B, et al. Endometrial cancer risk factors by two main histologic subtypes in the NIH-AARP Diet and Health Study. *Am J Epidemiol*. In press 2012.
101. Auder-Walsh E, Lepine J, Gregoire J, et al. Profiling of endogenous estrogens, their precursors, and metabolites in endometrial cancer patients: association with risk and relationship to clinical characteristics. *J Clin Endocrinol Metab*. 2011;96:E330–E339.
102. Potischman N, Hoover RN, Brinton LA, et al. Case-control study of endogenous steroid hormones and endometrial cancer. *J Natl Cancer Inst*. 1996;88:1127–1135.
103. Key TJ, Pike MC. The dose-effect relationship between “unopposed” oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer*. 1988;57:205–212.
104. Lukanova A, Lundin E, Micheli A, et al. Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. *Int J Cancer*. 2004;108:425–432.
105. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev*. 2002;11:1531–1543.
106. Zeleniuch-Jacquette A, Akhmedkhanov A, Kato I, et al. Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. *Br J Cancer*. 2001;84:975–981.
107. Troisi R, Potischman N, Hoover RN, et al. Insulin and endometrial cancer. *Am J Epidemiol*. 1997;146:476–482.
108. Weiderpass E, Brismar K, Bellocchio R, et al. Serum levels of insulin-like growth factor-I, IGF-binding protein 1 and 3, and insulin and endometrial cancer risk. *Br J Cancer*. 2003;89:1697–1704.
109. Siiteri PK. Steroid hormones and endometrial cancer. *Cancer Res*. 1978;38:4360–4366.
110. Mink PJ, Sherman ME, Devesa SS. Incidence patterns of invasive and borderline ovarian tumors among white women and black women in the United States. Results from the SEER Program, 1978–1998. *Cancer*. 2002;95:2380–2389.
111. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. <http://globocan.iarc.fr>. Accessed December 2, 2010.
112. Gregg S, Parazzini F, Paratore MP, et al. Risk factors for ovarian cancer in central Italy. *Gynecol Oncol*. 2000;79:50–54.
113. Braem MG, Onland-Moret NC, van den Brandt PA, et al. Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. *Am J Epidemiol*. 2010;172:1181–1189.
114. Cooper GS, Schildkraut JM, Whittemore AS, et al. Pregnancy recency and risk of ovarian cancer. *Cancer Causes Control*. 1999;10:397–402.
115. Negri E, Franceschi S, Tzonou A, et al. Reproductive factors and risk of epithelial ovarian cancer. *Int J Cancer*. 1991;49:50–56.
116. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer*. 1989;60:592–598.
117. Whittemore AS, Wu ML, Paffenbarger RS Jr, et al. Epithelial ovarian cancer and the ability to conceive. *Cancer Res*. 1989;49:4047–4052.
118. Rossing MA, Daling JR, Weiss NS, et al. Ovarian tumors in a cohort of infertile women. *N Engl J Med*. 1994;331:771–776.
119. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol*. 1992;136:1184–1203.
120. Brinton LA, Sahasrabudde VV, Scoccia B. Fertility drugs and the risk of breast and gynecologic cancers. *Semin Reprod Med*. 2012;30:131–145.
121. van Leeuwen FE, Klip H, Mooij TM, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod*. 2011;26:3456–3465.
122. Chiaffarino F, Pelucchi C, Negri E, et al. Breast-feeding and the risk of epithelial ovarian cancer in an Italian population. *Gynecol Oncol*. 2005;98:304–308.

123. Zhang M, Xie X, Lee AH, et al. Prolonged lactation reduces ovarian cancer risk in Chinese women. *Eur J Cancer Prev*. 2004;13:499–502.
124. Danforth KN, Tworoger SS, Hecht JL, et al. Breastfeeding and risk of ovarian cancer in two prospective cohorts. *Cancer Causes Control*. 2007;18:517–523.
125. Jordan SJ, Cushing-Haugen KL, Wicklund KG, et al. Breast-feeding and risk of epithelial ovarian cancer. *Cancer Causes Control*. 2012;23:919–927.
126. Cibula D, Widschwendter M, Majek O, et al. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. *Hum Reprod Update*. 2011;17:55–67.
127. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: a meta-analysis. *J Ovarian Res*. 2012;5:13.
128. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst*. 1999;91:1459–1467.
129. Chiaffarino F, Pelucchi C, Parazzini F, et al. Reproductive and hormonal factors and ovarian cancer. *Ann Oncol*. 2001;12:337–341.
130. Tsilidis KK, Allen NE, Key TJ, et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer*. 2011;105:1436–1442.
131. Schildkraut JM, Bastos E, Berchuck A. Relationship between lifetime ovulatory cycles and overexpression of mutant p53 in epithelial ovarian cancer. *J Natl Cancer Inst*. 1997;89:932–938.
132. Franceschi S, La Vecchia C, Booth M, et al. Age at menarche and at menopause. *Int J Cancer*. 1991;49:57–60.
133. Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet*. 2008;371:303–314.
134. Lurie G, Thompson P, McDuffie KE, et al. Association of estrogen and progestin potency of oral contraceptives with ovarian carcinoma risk. *Obstet Gynecol*. 2007;109:597–607.
135. Ness RB, Grisso JA, Klapper J, et al. SHARE Study Group. Steroid Hormones and Reproductions. *Am J Epidemiol*. 2000;152:233–241.
136. Schildkraut JM, Calingaert B, Marchbanks PA, et al. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst*. 2002;94:32–38.
137. Greer JB, Modugno F, Allen GO, et al. Androgenic progestins in oral contraceptives and the risk of epithelial ovarian cancer. *Obstet Gynecol*. 2005;105:731–740.
138. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab*. 2010;95:s1–s66.
139. Pearce CL, Chung K, Pike MC, et al. Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. *Cancer*. 2009;115:531–539.
140. Morch LS, Lokkegaard E, Andreassen AH, et al. Hormone therapy and ovarian cancer. *JAMA*. 2009;302:298–305.
141. Helzlsouer KJ, Alberg AJ, Gordon GB, et al. Serum gonadotropins and steroid hormones and the development of ovarian cancer. *JAMA*. 1995;274:1926–1930.
142. Rinaldi S, Dossus L, Lukanova A, et al. Endogenous androgens and risk of epithelial ovarian cancer: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Epidemiol Biomarkers Prev*. 2007;16:23–29.
143. Lukanova A, Lundin E, Akhmedkhanov A, et al. Circulating levels of sex steroid hormones and risk of ovarian cancer. *Int J Cancer*. 2003;104:636–642.
144. Tworoger SS, Lee IM, Buring JE, et al. Plasma androgen concentrations and risk of incident ovarian cancer. *Am J Epidemiol*. 2008;167:211–218.
145. McSorley MA, Alberg AJ, Allen DS, et al. Prediagnostic circulating follicle stimulating hormone concentrations and ovarian cancer risk. *Int J Cancer*. 2009;125:674–679.
146. Lukanova A, Lundin E, Micheli A, et al. Risk of ovarian cancer in relation to prediagnostic levels of C-peptide, insulin-like growth factor binding proteins-1 and -2 (USA, Sweden, Italy). *Cancer Causes Control*. 2003;14:285–292.
147. Parazzini F, Moroni S, La Vecchia C, et al. Ovarian cancer risk and history of selected medical conditions linked with female hormones. *Eur J Cancer*. 1997;33:1634–1637.
148. Brinton LA, Gridley G, Persson I, et al. *Am J Obstet Gynecol*. 1997;176:572–579.
149. Brinton LA, Sakoda LC, Sherman ME, et al. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2929–2935.
150. Ness RB, Cramer DW, Goodman MT, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol*. 2002;155:217–224.
151. Pearce CL, Templeman C, Rossing MA, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol*. 2012;13:385–394.
152. Ness RB. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. *Am J Obstet Gynecol*. 2003;189:280–294.
153. Risch HA, Howe GR. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 1995;4:447–451.
154. Lin HW, Tu YY, Lin SY, et al. Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol*. 2011;12:900–904.
155. Harlow BL, Cramer DW, Baron JA, et al. Psychotropic medication use and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 1998;7:697–702.
156. Dalton SO, Johansen C, Mellekjaer L, et al. Antidepressant medications and risk for cancer. *Epidemiology*. 2000;11:171–176.
157. Dublin S, Rossing MA, Heckbert SR, et al. Risk of epithelial ovarian cancer in relation to use of antidepressants, benzodiazepines, and other centrally acting medications. *Cancer Causes Control*. 2002;13:35–45.
158. Kato I, Zeleniuch-Jacquotte A, Toniolo PG, et al. Psychotropic medication use and risk of hormone-related cancers: the New York University Women's Health Study. *J Public Health Med*. 2000;22:155–160.
159. Lacey JV Jr, Sherman ME, Hartge P, et al. Medication use and risk of ovarian carcinoma: a prospective study. *Int J Cancer*. 2004;108:281–286.
160. Cramer DW, Harlow BL, Titus-Ernstoff L, et al. Over-the-counter analgesics and risk of ovarian cancer. *Lancet*. 1998;351:104–107.
161. Rodriguez C, Henley SJ, Calle EE, et al. Paracetamol and risk of ovarian cancer mortality in a prospective study of women in the USA. *Lancet*. 1998;352:1354–1355.
162. Schildkraut JM, Moorman PG, Halabi S, et al. Analgesic drug use and risk of ovarian cancer. *Epidemiology*. 2006;17:104–107.
163. Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol*. 2005;60:194–203.
164. Olsen CM, Green AC, Whiteman DC, et al. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2007;43:690–709.
165. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and body size: individual participant meta-analysis including 25,157 women with ovarian cancer from 47 epidemiological studies. *PLOS Med*. 2012;9:e1001200.
166. Schouten LJ, Rivera C, Hunter DJ, et al. Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev*. 2008;17:902–912.
167. Lahmann PH, Cust AE, Friedenreich CM, et al. Anthropometric measures and epithelial ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2010;126:2404–2415.
168. Greer JB, Modugno F, Ness RB, et al. Anthropometry and the risk of epithelial ovarian cancer. *Cancer*. 2006;106:2247–2257.
169. Leitzmann MF, Koebeck C, Danforth KN, et al. Body mass index and risk of ovarian cancer. *Cancer*. 2009;115:812–822.
170. Purdie DM, Bain CJ, Webb PM, et al. Body size and ovarian cancer: case-control study and systematic review (Australia). *Cancer Causes Control*. 2001;12:855–863.
171. Yang HP, Trabert B, Murphy MA, et al. Ovarian cancer risk factors by histologic subtypes in the NIH-AARP diet and health study. *Int J Cancer*. 2011;131(4):938–948.
172. Gram IT, Lukanova A, Brill I, et al. Cigarette smoking and risk of histological subtypes of epithelial ovarian cancer in the EPIC cohort study. *Int J Cancer*. 2012;130:2204–2210.
173. Jordan SJ, Whiteman DC, Purdie DM, et al. Does smoking increase risk of ovarian cancer? A systematic review. *Gynecol Oncol*. 2006;103:1122–1129.
174. Baker JA, Odunuga OO, Rodabaugh KJ, et al. Active and passive smoking and risk of ovarian cancer. *Int J Gynecol Cancer*. 2006;16(suppl 1):211–218.
175. Goodman MT, Tung KH. Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States). *Cancer Causes Control*. 2003;14:569–577.
176. Cramer DW, Harlow BL, Willett WC, et al. Galactose consumption and metabolism in relation to the risk of ovarian cancer. *Lancet*. 1989;2:66–71.
177. Bosetti C, Negri E, Franceschi S, et al. Diet and ovarian cancer risk: a case-control study in Italy. *Int J Cancer*. 2001;93:911–915.
178. Goodman MT, Wu AH, Tung KH, et al. Association of dairy products, lactose, and calcium with the risk of ovarian cancer. *Am J Epidemiol*. 2002;156:148–157.
179. Kushi LH, Mink PJ, Folsom AR, et al. Prospective study of diet and ovarian cancer. *Am J Epidemiol*. 1999;149:21–31.
180. Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr*. 2004;80:1353–1357.
181. Fairfield KM, Hunter DJ, Colditz GA, et al. A prospective study of dietary lactose and ovarian cancer. *Int J Cancer*. 2004;110:271–277.

182. Genkinger JM, Hunter DJ, Spiegelman D, et al. A pooled analysis of 12 cohort studies of dietary fat, cholesterol and egg intake and ovarian cancer. *Cancer Causes Control*. 2006;17:273–285.
183. Wallin A, Orsini N, Wolk A. Red and processed meat consumption and risk of ovarian cancer: a dose-response meta-analysis of prospective studies. *Br J Cancer*. 2011;104:1196–1201.
184. Kolahdooz F, van der Pols JC, Bain CJ, et al. Meat, fish, and ovarian cancer risk: results from 2 Australian case-control studies, a systematic review, and meta-analysis. *Am J Clin Nutr*. 2010;91:1752–1763.
185. Larsson SC, Holmberg L, Wolk A. Fruit and vegetable consumption in relation to ovarian cancer incidence: the Swedish Mammography Cohort. *Br J Cancer*. 2004;90:2167–2170.
186. McCann SE, Freudenheim JL, Marshall JR, et al. Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. *J Nutr*. 2003;133:1937–1942.
187. Pelucchi C, La Vecchia C, Chatenoud L, et al. Dietary fibres and ovarian cancer risk. *Eur J Cancer*. 2001;37:2235–2239.
188. Koushik A, Hunter DJ, Spiegelman D, et al. Fruits and vegetables and ovarian cancer risk in a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2160–2167.
189. Pan SY, Ugnat AM, Mao Y, et al. A case-control study of diet and the risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2004;13:1521–1527.
190. Tung KH, Wilkens LR, Wu AH, et al. Association of dietary vitamin A, carotenoids, and other antioxidants with the risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14:669–676.
191. Harris HR, Cramer DW, Vitonis AF, et al. Folate, vitamin B6, vitamin B12, methionine and alcohol intake in relation to ovarian cancer risk. *Int J Cancer*. 2011;131:E518–E529.
192. Navarro Silvera SA, Jain M, Howe GR, et al. Dietary folate consumption and risk of ovarian cancer: a prospective cohort study. *Eur J Cancer Prev*. 2006;15:511–515.
193. Cook LS, Neilson HK, Lorenzetti DL, et al. A systematic literature review of vitamin D and ovarian cancer. *Am J Obstet Gynecol*. 2010;203:70–78.
194. Genkinger JM, Hunter DJ, Spiegelman D, et al. Alcohol intake and ovarian cancer risk: a pooled analysis of 10 cohort studies. *Br J Cancer*. 2006;94:757–762.
195. Lueth NA, Anderson KE, Harnack LJ, et al. Coffee and caffeine intake and the risk of ovarian cancer: the Iowa Women's Health Study. *Cancer Causes Control*. 2008;19:1365–1372.
196. Kuper H, Titus-Ernstoff L, Harlow BL, et al. Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. *Int J Cancer*. 2000;88:313–318.
197. Riman T, Dickman PW, Nilsson S, et al. Some life-style factors and the risk of invasive epithelial ovarian cancer in Swedish women. *Eur J Epidemiol*. 2004;19:1011–1019.
198. Jordan SJ, Purdie DM, Green AC, et al. Coffee, tea and caffeine and risk of epithelial ovarian cancer. *Cancer Causes Control*. 2004;15:359–365.
199. Oppeneer SJ, Robien K. Tea consumption and epithelial ovarian cancer risk: a systematic review of observational studies. *Nutr Cancer*. 2011;63:817–826.
200. Tworoger SS, Gertig DM, Gates MA, et al. Caffeine, alcohol, smoking, and the risk of incident epithelial ovarian cancer. *Cancer*. 2008;112:1169–1177.
201. Pharoah PD, Ponder BA. The genetics of ovarian cancer. *Best Pract Res Clin Obstet Gynaecol*. 2002;16:449–468.
202. Hemminki K, Granstrom C. Familial invasive and borderline ovarian tumors by proband status, age and histology. *Int J Cancer*. 2003;105:701–705.
203. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. *Cell*. 2002;108:171–182.
204. Hartge P, Whittemore AS, Itnyre J, et al. The Collaborative Ovarian Cancer Group. *Obstet Gynecol*. 1994;84:760–764.
205. Wooster R, Weber BL. Breast and ovarian cancer. *N Engl J Med*. 2003;348:2339–2347.
206. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med*. 2008;359:2143–2153.
207. Gayther SA, Pharoah PD. The inherited genetics of ovarian and endometrial cancer. *Curr Opin Genet Dev*. 2010;20:231–238.
208. Mills PK, Riordan DG, Cress RD, et al. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer*. 2004;112:458–464.
209. Wu AH, Pearce CL, Tseng CC, et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer*. 2009;124:1409–1415.
210. Boffetta P, Andersen A, Lynge E, et al. Employment as hairdresser and risk of ovarian cancer and non-Hodgkin's lymphomas among women. *J Occup Med*. 1994;36:61–65.
211. Donna A, Crosignani P, Robutti F, et al. Triazine herbicides and ovarian epithelial neoplasms. *Scand J Work Environ Health*. 1989;15:47–53.
212. Vasama-Neuvonen K, Pukkala E, Paakkulainen H, et al. Ovarian cancer and occupational exposures in Finland. *Am J Ind Med*. 1999;36:83–89.
213. Langseth H, Kjaerheim K. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. *Scand J Work Environ Health*. 2004;30:356–361.
214. Shields T, Gridley G, Moradi T, et al. Occupational exposures and the risk of ovarian cancer in Sweden. *Am J Ind Med*. 2002;42:200–213.
215. Macarthur AC, Le ND, Abanto ZU, et al. Occupational female breast and reproductive cancer mortality in British Columbia, Canada, 1950–94. *Occup Med (Lond)*. 2007;57:246–253.
216. Sala M, Dosemeci M, Zahm SH. A death certificate-based study of occupation and mortality from reproductive cancers among women in 24 US states. *J Occup Environ Med*. 1998;40:632–639.
217. Camargo MC, Stayner LT, Straif K, et al. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect*. 2011;119:1211–1217.
218. Shen N, Weiderpass E, Antilla A, et al. Epidemiology of occupational and environmental risk factors related to ovarian cancer. *Scand J Work Environ Health*. 1998;24:175–182.
219. Permutth-Wey J, Sellers TA. Epidemiology of ovarian cancer. *Methods Mol Biol*. 2009;472:413–437.
220. Kurman RJ, Shih I. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm. *Hum Pathol*. 2011;42:918–931.
221. Modugno F, Ness RB, Wheeler JE. Reproductive risk factors for epithelial ovarian cancer according to histologic type and invasiveness. *Ann Epidemiol*. 2001;11:568–574.
222. Risch HA, Marrett LD, Jain M, et al. Results of a case-control study. *Am J Epidemiol*. 1996;144:363–372.
223. Gates MA, Rosner BA, Hecht JL, et al. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol*. 2010;171:45–53.
224. Franceschi S, La Vecchia C, Helmrigh SP, et al. Risk factors for epithelial ovarian cancer in Italy. *Am J Epidemiol*. 1982;115:714–719.
225. Purdie DM, Bain CJ, Siskind V, et al. Ovulation and risk of epithelial ovarian cancer. *Int J Cancer*. 2003;104:228–232.
226. Moorman PG, Schildkraut JM, Calingaert B, et al. Ovulation and ovarian cancer: a comparison of two methods for calculating lifetime ovulatory cycles (United States). *Cancer Causes Control*. 2002;13:807–811.
227. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. *J Natl Cancer Inst*. 1998;90:1774–1786.
228. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. *J Natl Cancer Inst*. 1983;71:717–721.
229. Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? *Lancet*. 1971;2:163.
230. Zajicek J. Ovarian cystomas and ovulation, a histogenetic concept. *Tumori*. 1977;63:429–435.
231. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—Part B: biological agents. *Lancet Oncol*. 2009;10:321–322.
232. Schiffman M, Wentzensen N, Wacholder S, et al. Human papillomavirus testing in the prevention of cervical cancer. *J Natl Cancer Inst*. 2011;103:368–383.
233. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127:2893–2917.
234. Arbyn M, Castellsague X, de Sanjose S, et al. Worldwide burden of cervical cancer in 2008. *Ann Oncol*. 2011;22:2675–2686.
235. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. *PLOS Med*. 2008;5:e132.
236. Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. *Lancet*. 2007;370:890–907.
237. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10–29.
238. National Cancer Institute. SEER Cancer Statistics Review. 1975–2008. 2012.
239. Horner MJ, Altekruse SF, Zou Z, et al. U.S. geographic distribution of prevaccine era cervical cancer screening, incidence, stage, and mortality. *Cancer Epidemiology, Biomarkers & Prevention*. 2011;20:591–599.
240. Chan PG, Sung HY, Sawaya GF. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. *Obstet Gynecol*. 2003;102:765–773.
241. Reimers LL, Anderson WF, Rosenberg PS, et al. Etiologic heterogeneity for cervical carcinoma by histopathologic type, using comparative age-period-cohort models. *Cancer Epidemiol Biomarkers Prev*. 2009;18:792–800.
242. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189:12–19.
243. Liebrich C, Brummer O, Von Wasielewski R, et al. Primary cervical cancer truly negative for high-risk human papillomavirus is a rare but distinct entity that can affect virgins and young adolescents. *Eur J Gynaecol Oncol*. 2009;30:45–48.

244. Plummer M, Schiffman M, Castle PE, et al. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. *J Infect Dis.* 2007;195:1582–1589.
245. Castle PE, Schiffman M, Herrero R, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. *J Infect Dis.* 2005;191:1808–1816.
246. Koshiol J, Lindsay L, Pimenta JM, et al. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis. *Am J Epidemiol.* 2008;168:123–137.
247. Wentzensen N, Walker J, Schiffman M, et al. Heterogeneity of high grade cervical intraepithelial neoplasia related to HPV16: implications for natural history and management. *Int J Cancer.* 2013;132:148–154.
248. Li N, Franceschi S, Howell-Jones R, et al. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. *Int J Cancer.* 2011;128:927–935.
249. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer.* 2007;121.
250. Wheeler CM, Hunt WC, Joste NE, et al. Human papillomavirus genotype distributions: implications for vaccination and cancer screening in the United States. *J Natl Cancer Inst.* 2009;101:475–487.
251. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol.* 2010;11:1048–1056.
252. Cornet I, Gheit T, Franceschi S, et al. HPV16 genetic variants: phylogeny and classification based on E6 and LCR. *J Virol.* 2012;86:6855–6861.
253. Ramanakumar AV, Goncalves O, Richardson H, et al. Human papillomavirus (HPV) types 16, 18, 31, 45 DNA loads and HPV-16 integration in persistent and transient infections in young women. *BMC Infect Dis.* 2010;10:326.
254. Gravitt PE, Kovacic MB, Herrero R, et al. High load for most high risk human papillomavirus genotypes is associated with prevalent cervical cancer precursors but only HPV16 load predicts the development of incident disease. *Int J Cancer.* 2007;121:2787–2793.
255. Chen HC, Schiffman M, Lin CY, et al. Persistence of type-specific human papillomavirus infection and increased long-term risk of cervical cancer. *J Natl Cancer Inst.* 2011;103:1387–1396.
256. Schiffman M, Rodriguez AC, Chen Z, et al. A population-based prospective study of carcinogenic human papillomavirus variant lineages, viral persistence, and cervical neoplasia. *Cancer Res.* 2010;70:3159–3169.
257. Schiffman M, Glass AG, Wentzensen N, et al. A long-term prospective study of type-specific human papillomavirus infection and risk of cervical neoplasia among 20,000 women in the Portland Kaiser Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2011;20:1398–1409.
258. Castle PE, Fetterman B, Thomas Cox J, et al. The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical precancer and cancer. *Obstet Gynecol.* 2010;116:76–81.
259. Sahasrabudhe VV, Luhn P, Wentzensen N. Human papillomavirus and cervical cancer: biomarkers for improved prevention efforts. *Future Microbiol.* 2011;6:1083–1098.
260. Castle PE, Schiffman M, Wheeler CM, et al. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstet Gynecol.* 2009;113:18–25.
261. Wang SS, Bratti MC, Rodriguez AC, et al. Common variants in immune and DNA repair genes and risk for human papillomavirus persistence and progression to cervical cancer. *J Infect Dis.* 2009;199:20–30.
262. Einstein MH, Schiller JT, Viscidi RP, et al. Clinician's guide to human papillomavirus immunology: knowns and unknowns. *Lancet Infect Dis.* 2009;9:347–356.
263. Einstein MH. Acquired immune response to oncogenic human papillomavirus associated with prophylactic cervical cancer vaccines. *Cancer Immunol Immunother.* 2008;57:443–451.
264. Ferguson M, Wilkinson DE, Heath A, et al. The first international standard for antibodies to HPV 16. *Vaccine.* 2011;29:6520–6526.
265. Gravitt PE. The known unknowns of HPV natural history. *J Clin Invest.* 2011;121:4593–4599.
266. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol.* 2008;9:425–434.
267. Shepherd JP, Frampton GK, Harris P. Interventions for encouraging sexual behaviours intended to prevent cervical cancer. *Cochrane Database Syst Rev.* 2011;4:CD001035.
268. Plummer M, Peto J, Franceschi S. Time since first sexual intercourse and the risk of cervical cancer. *Int J Cancer.* 2012;130:2638–2644.
269. Monroy OL, Aguilar C, Lizano M, et al. Prevalence of human papillomavirus genotypes, and mucosal IgA anti-viral responses in women with cervical ectopy. *J Clin Virol.* 47:43–48.
270. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med.* 2006;354:2645–2654.
271. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis.* 2002;29:725–735.
272. Burchell AN, Tellier PP, Hanley J, et al. Influence of partner's infection status on prevalent human papillomavirus among persons with a new sex partner. *Sex Transm Dis.* 2010;37:34–40.
273. Castellsague X, Bosch FX, Munoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med.* 2002;346:1105–1112.
274. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. *J Infect Dis.* 2009;199:14–19.
275. Wawer MJ, Tobian AA, Kigozi G, et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. *Lancet.* 2011;377:209–218.
276. Munoz N, Franceschi S, Bosetti C, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *Lancet.* 2002;359:1093–1101.
277. Hildesheim A, Wang SS. Host and viral genetics and risk of cervical cancer: a review. *Virus Res.* 2002;89:229–240.
278. Appleby P, Beral V, Berrington de Gonzalez A, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet.* 2007;370:1609–1621.
279. de Villiers EM. Relationship between steroid hormone contraceptives and HPV, cervical intraepithelial neoplasia and cervical carcinoma. *Int J Cancer.* 2003;103:705–708.
280. Harris TG, Miller L, Kulasingam SL, et al. Depot-medroxyprogesterone acetate and combined oral contraceptive use and cervical neoplasia among women with oncogenic human papillomavirus infection. *Am J Obstet Gynecol.* 2009;200:489.e1–e8.
281. Castellsague X, Diaz M, Vaccarella S, et al. Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: a pooled analysis of 26 epidemiological studies. *Lancet Oncol.* 2011;12:1023–1031.
282. Roberts JN, Kines RC, Katki HA, et al. Effect of Pap smear collection and carrageenan on cervicovaginal human papillomavirus-16 infection in a rhesus macaque model. *J Natl Cancer Inst.* 2011;103:737–743.
283. Parikh S, Brennan P, Boffetta P. Meta-analysis of social inequality and the risk of cervical cancer. *Int J Cancer.* 2003;105:687–691.
284. Louie KS, Castellsague X, de Sanjose S, et al. Smoking and passive smoking in cervical cancer risk: pooled analysis of couples from the IARC multicentric case-control studies. *Cancer Epidemiol Biomarkers Prev.* 2011;20:1379–1390.
285. Kapeu AS, Luostarinen T, Jellum E, et al. Is smoking an independent risk factor for invasive cervical cancer? A nested case-control study within Nordic biobanks. *Am J Epidemiol.* 2009;169:480–488.
286. Hellberg D, Stendahl U. The biological role of smoking, oral contraceptive use and endogenous sexual steroid hormones in invasive squamous epithelial cervical cancer. *Anticancer Res.* 2005;25:3041–3046.
287. Pratt MM, Sirajuddin P, Poirier MC, et al. Polycyclic aromatic hydrocarbon-DNA adducts in cervix of women infected with carcinogenic human papillomavirus types: an immunohistochemistry study. *Mutation Res.* 2007;624:114–123.
288. Siegel EM, Patel N, Lu B, et al. Biomarkers of oxidant load and type-specific clearance of prevalent oncogenic human papillomavirus infection: markers of immune response? *Int J Cancer.* 2012;131:219–228.
289. Nowak RG, Gravitt PE, Morrison CS, et al. Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. *J Infect Dis.* 2011;203:1182–1191.
290. Cohen CR, Moscicki AB, Scott ME, et al. Increased levels of immune activation in the genital tract of healthy young women from sub-Saharan Africa. *AIDS.* 2010;24.
291. de Araujo Souza PS, Sichero L, Maciag PC. HPV variants and HLA polymorphisms: the role of variability on the risk of cervical cancer. *Future Oncol.* 2009;5:359–370.
292. Vink JM, van Kemenade FJ, Meijer CJ, et al. Cervix smear abnormalities: linking pathology data in female twins, their mothers and sisters. *Eur J Hum Genet.* 2011;19:108–111.
293. Engelmark MT, Ivansson EL, Magnusson JJ, et al. Polymorphisms in 9q32 and TSCOT are linked to cervical cancer in affected sib-pairs with high mean age at diagnosis. *Hum Genet.* 2008;123:437–443.

294. Myung SK, Ju W, Kim SC, et al. Vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm: a meta-analysis. *BJOG: Int J Obs Gynaecol*. 2011;118:1285–1291.
295. Madeleine MM, Anttila T, Schwartz SM, et al. Risk of cervical cancer associated with Chlamydia trachomatis antibodies by histology, HPV type and HPV cofactors. *Int J Cancer*. 2007;120:650–655.
296. Bratcher LF, Sahasrabudhe VV. The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. *Infect Agent Cancer*. 2010;5:8.
297. Chaturvedi AK, Madeleine MM, Biggar RJ, et al. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst*. 2009;101:1120–1130.
298. Walker F, Adle-Biasette H, Madelenat P, et al. Increased apoptosis in cervical intraepithelial neoplasia associated with HIV infection: implication of oncogenic human papillomavirus, caspases, and Langerhans cells. *Clin Cancer Res: Official J Am Assoc Cancer Res*. 2005;11:2451–2458.
299. Shrestha S, Wang C, Aissani B, et al. Interleukin-10 gene (IL10) polymorphisms and human papillomavirus clearance among immunosuppressed adolescents. *Cancer Epidemiol Biomarkers Prev*. 2007;16:1626–1632.
300. Behbahani H, Walther-Jallow L, Klareskog E, et al. Proinflammatory and type 1 cytokine expression in cervical mucosa during HIV-1 and human papillomavirus infection. *J Acquir Immune Defic Syndr*. 2007;45:9–19.
301. Syrjanen S. Human papillomavirus infection and its association with HIV. *Adv Dent Res*. 2011;23:84–89.
302. Seoud M, Tjalma WA, Ronsse V. Cervical adenocarcinoma: moving towards better prevention. *Vaccine*. 2011;29:9148–9158.
303. Clifford G, Franceschi S. Members of the human papillomavirus type 18 family (alpha-7 species) share a common association with adenocarcinoma of the cervix. *Int J Cancer*. 2008;122:1684–1685.
304. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA*. 2002;287:2114–2119.
305. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer*. 2007;120:885–891.
306. Lacey JV, Jr, Swanson CA, Brinton LA, et al. Obesity as a potential risk factor for adenocarcinoma and squamous cell carcinomas of the uterine cervix. *Cancer*. 2003;98:814–821.
307. Jaakkola S, Pukkala E, K. Postmenopausal estradiol-progestagen therapy and risk for uterine cervical cancer. *Int J Cancer*. 2011;131:E537–E543.
308. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*. 2012;62:147–172.
309. Saraiya M, Watson M, Wu X, et al. Incidence of in situ and invasive vulvar cancer in the US, 1998–2003. *Cancer*. 2008;113(10Suppl):2865–2872.
310. van der Avoort IA, Shirango H, Hoevenaars BM, et al. Vulvar squamous cell carcinoma is a multifactorial disease following two separate and independent pathways. *Int J Gynecol Pathol*. 2006;25:22–29.
311. Eva LJ, Ganesan R, Chan KK, et al. Vulvar squamous cell carcinoma occurring on a background of differentiated vulvar intraepithelial neoplasia is more likely to recur: a review of 154 cases. *J Reprod Med*. 2008;53:397–401.
312. van Seters M, ten Kate FJ, van Beurden M, et al. In the absence of (early) invasive carcinoma, vulvar intraepithelial neoplasia associated with lichen sclerosis is mainly of undifferentiated type: new insights in histology and aetiology. *J clinic pathol*. 2007;60:504–509.
313. Judson PL, Habermann EB, Baxter NN, et al. Trends in the incidence of invasive and in situ vulvar carcinoma. *Obstet Gynecol*. 2006;107:1018–1022.
314. Beckmann AM, Kiviat NB, Daling JR, et al. Human papillomavirus type 16 in multifocal neoplasia of the female genital tract. *Int J Gynecol Pathol*. 1988;7:39–47.
315. Garland SM, Insinga RP, Sings HL, et al. Human papillomavirus infections and vulvar disease development. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1777–1784.
316. De Vuyst H, Clifford GM, Nascimento MC, et al. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009;124:1626–1636.
317. Madsen BS, Jensen HL, van den Brule AJ, et al. Risk factors for invasive squamous cell carcinoma of the vulva and vagina—population-based case-control study in Denmark. *Int J Cancer*. 2008;122:2827–2834.
318. Hussain SK, Madeleine MM, Johnson LG, et al. Cervical and vulvar cancer risk in relation to the joint effects of cigarette smoking and genetic variation in interleukin 2. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1790–1799.
319. Brinton LA, Nasca PC, Mallin K, et al. Case-control study of cancer of the vulva. *Obstet Gynecol*. 1990;75:859–866.
320. Nordenvall C, Chang ET, Adami HO, et al. Cancer risk among patients with condylomata acuminata. *Int J Cancer*. 2006;119:888–893.
321. Massad LS, Xie X, Darragh T, et al. Genital warts and vulvar intraepithelial neoplasia: natural history and effects of treatment and human immunodeficiency virus infection. *Obstet Gynecol*. 2011;118:831–839.
322. Hussain SK, Sundquist J, Hemminki K. Familial clustering of cancer at human papillomavirus-associated sites according to the Swedish Family-Cancer Database. *Int J Cancer*. 2008;122:1873–1878.
323. Santegoets LA, van Seters M, Heijmans-Antonissen C, et al. Reduced local immunity in HPV-related VIN: expression of chemokines and involvement of immunocompetent cells. *Int J Cancer*. 2008;123:616–622.
324. Lilic V, Lilic G, Filipovic S, et al. Primary carcinoma of the vagina. *J BUON*. 2010;15:241–247.
325. Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*. 2011;365:1304–1314.
326. Brinton LA, Reeves WC, Brenes MM, et al. Oral contraceptive use and risk of invasive cervical cancer. *Int J Epidemiol*. 1990;19:4–11.
327. Sherman JF, Mount SL, Evans MF, et al. Smoking increases the risk of high-grade vaginal intraepithelial neoplasia in women with oncogenic human papillomavirus. *Gynecol Oncol*. 2008;110:396–401.
328. Balamurugan A, Ahmed F, Saraiya M, et al. Potential role of human papillomavirus in the development of subsequent primary in situ and invasive cancers among cervical cancer survivors. *Cancer*. 2008;113(10Suppl):2986–2945.
329. Madkan VK, Cook-Norris RH, Steadman MC, et al. The oncogenic potential of human papillomaviruses: a review on the role of host genetics and environmental cofactors. *Br J Dermatol*. 2007;157:228–241.
330. Srodon M, Stoler MH, Baber GB, et al. The distribution of low and high-risk HPV types in vulvar and vaginal intraepithelial neoplasia (VIN and VaIN). *Am J Surg Pathol*. 2006;30:1513–1518.
331. Smith EK, White MC, Weir HK, et al. Higher incidence of clear cell adenocarcinoma of the cervix and vagina among women born between 1947 and 1971 in the United States. *Cancer Causes Control*. 2012;23:207–211.
332. Herbst AL, Anderson S, Hubby MM, et al. Risk factors for the development of diethylstilbestrol-associated clear cell adenocarcinoma: a case-control study. *Am J Obstet Gynecol*. 1986;154:814–822.
333. Troisi R, Hatch EE, Titus-Ernstoff L, et al. Cancer risk in women prenatally exposed to diethylstilbestrol. *Int J Cancer*. 2007;121:356–360.
334. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol*. 2010;203:531–539.
335. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *Lancet*. 2010;376:717–729.
336. Smith HO, Qualls CR, Prairie BA, et al. Trends in gestational choriocarcinoma: a 27-year perspective. *Obstet Gynecol*. 2003;102:978–987.
337. Bracken MB, Brinton LA, Hayashi K. Epidemiology of hydatidiform mole and choriocarcinoma. *Epidemiol Rev*. 1984;6:52–75.
338. Steigrad SJ. Epidemiology of gestational trophoblastic diseases. *Best Pract Res Clin Obstet Gynaecol*. 2003;17:837–847.
339. Tham BW, Everard JE, Tidy JA, et al. Gestational trophoblastic disease in the Asian population of Northern England and North Wales. *BJOG: Int J Obs Gynaecol*. 2003;110:555–559.
340. Brinton LA, Bracken MB, Connelly RR. Choriocarcinoma incidence in the United States. *Am J Epidemiol*. 1986;123:1094–1100.
341. Smith HO, Hilgers RD, Bedrick EJ, et al. Ethnic differences at risk for gestational trophoblastic disease in New Mexico: a 25-year population-based study. *Am J Obstet Gynecol*. 2003;188:357–366.
342. Lybol C, Thomas CM, Bulten J, et al. Increase in the incidence of gestational trophoblastic disease in the Netherlands. *Gynecol Oncol*. 2011;121:334–338.
343. Salehi S, Eloranta S, Johansson AL, et al. Reporting and incidence trends of hydatidiform mole in Sweden 1973–2004. *Acta Oncol*. 2011;50:367–372.
344. Garrett LA, Garner EI, Feltmate CM, et al. Subsequent pregnancy outcomes in patients with molar pregnancy and persistent gestational trophoblastic neoplasia. *Journal Reprod Med*. 2008;53:481–486.
345. Altieri A, Franceschi S, Ferlay J, et al. Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol*. 2003;4:670–678.

346. Tuncer ZS, Bernstein MR, Wang J, et al. Repetitive hydatidiform mole with different male partners. *Gynecol Oncol.* 1999;75:224–226.
347. Wang SS, Trunk M, Schiffman M, et al. Validation of p16INK4a as a marker of oncogenic human papillomavirus infection in cervical biopsies from a population-based cohort in Costa Rica. *Cancer Epidemiol Biomarkers Prev.* 2004;13:1355–1360.
348. Bagshawe KD, Rawlins G, Pike MC, et al. ABO blood-groups in trophoblastic neoplasia. *Lancet.* 1971;1:553–556.
349. Dawood MY, Teoh ES, Ratnam SS. ABO blood group in trophoblastic disease. *J Obstet Gynaecol Br Commonw.* 1971;78:918–923.
350. Messerli ML, Lilienfeld AM, Parmley T, et al. Risk factors for gestational trophoblastic neoplasia. *Am J Obstet Gynecol.* 1985;153:294–300.
351. Parazzini F, La Vecchia C, Franceschi S, et al. ABO blood-groups and the risk of gestational trophoblastic disease. *Tumori.* 1985;71:123–126.
352. Brinton LA, Wu BZ, Wang W, et al. Gestational trophoblastic disease: a case-control study from the People's Republic of China. *Am J Obstet Gynecol.* 1989;161:121–127.
353. Parazzini F, La Vecchia C, Pampallona S, et al. Reproductive patterns and the risk of gestational trophoblastic disease. *Am J Obstet Gynecol.* 1985;152:866–870.
354. Kashanian M, Baradaran HR, Teimoori N. Risk factors for complete molar pregnancy: a study in Iran. *J Reprod Med.* 2009;54:621–624.
355. La Vecchia C, Franceschi S, Parazzini F, et al. Risk factors for gestational trophoblastic disease in Italy. *Am J Epidemiol.* 1985;121:457–464.
356. Buckley JD, Henderson BE, Morrow CP, et al. Case-control study of gestational choriocarcinoma. *Cancer Res.* 1988;48:1004–1010.
357. Berkowitz RS, Cramer DW, Bernstein MR, et al. Risk factors for complete molar pregnancy from a case-control study. *Am J Obstet Gynecol.* 1985;152:1016–1020.
358. Palmer JR, Driscoll SG, Rosenberg L, et al. Oral contraceptive use and risk of gestational trophoblastic tumors. *J Natl Cancer Inst.* 1999;91:635–640.
359. Parazzini F, Cipriani S, Mangili G, et al. Oral contraceptives and risk of gestational trophoblastic disease. *Contraception.* 2002;65:425–427.
360. Ho YB, Burch P. Relationship of oral contraceptives and the intrauterine contraceptive devices to the regression of concentrations of the beta subunit of human chorionic gonadotropin and invasive complications after molar pregnancy. *Am J Obstet Gynecol.* 1983;145:214–217.
361. Stone M, Dent J, Kardana A, et al. Relationship of oral contraception to development of trophoblastic tumour after evacuation of a hydatidiform mole. *Br J Obstet Gynaecol.* 1976;83:913–916.
362. Curry SL, Schlaerth JB, Kohorn EI, et al. Hormonal contraception and trophoblastic sequelae after hydatidiform mole (a Gynecologic Oncology Group Study). *Am J Obstet Gynecol.* 1989;160:805–809.
363. Morrow P, Nakamura R, Schlaerth J, et al. The influence of oral contraceptives on the post-molar human chorionic gonadotropin regression curve. *Am J Obstet Gynecol.* 1985;151:906–914.
364. La Vecchia C, Parazzini F, Decarli A, et al. Age of parents and risk of gestational trophoblastic disease. *J Natl Cancer Inst.* 1984;73:639–642.
365. Hoffner L, Surti U. The genetics of gestational trophoblastic disease: a rare complication of pregnancy. *Cancer Genet.* 2012;205:63–77.

Molecular Pathogenesis of Gynecologic Cancers

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INTRODUCTION

An overview of the molecular pathogenesis of cancer is presented in the initial sections of this chapter. A more comprehensive discussion of this topic can be found in Part I of *DeVita Hellman and Rosenberg's Cancer: Principles and Practice of Oncology* (1). Genetic alterations involved in the development of gynecologic cancers are covered in more detail in the latter sections of this chapter.

The causes of human cancers are diverse, but malignant transformation is invariably caused by the development of genetic alterations that disrupt cell growth (Table 2.1). Several classes of genetic alterations are involved in carcinogenesis, including changes in the sequence of genes (mutations), gains (amplifications) or losses (deletions) in the number of copies of genes and rearrangement and translocation of genes from their normal chromosomal locations (2). These alterations lead to activation of genes that stimulate proliferation (oncogenes) and inactivation of genes that inhibit proliferation (tumor-suppressor genes). Disruption of DNA-repair systems also often occurs in the process of malignant transformation and may lead to accelerated accumulation of genetic alterations. Because repair of genetic damage inhibits carcinogenesis, DNA-repair genes are also considered tumor suppressors.

Most transforming mutations in oncogenes alter a single amino acid at specific codons that produce overactive protein products (e.g., *KRAS*, *BRAF*), and only one allele need be mutated. In contrast, inactivation of tumor suppressors (e.g., *RB1*, *BRCA1*) requires loss of both copies of the gene (two hits). Mutations in tumor suppressors occur throughout the gene, and are usually small insertions, deletions or base substitutions that result in truncated protein products. Loss of the second nonmutated allele generally occurs due to chromosomal deletion, leading to abrogation of tumor-suppressor activity.

Cancers may have many genetic alterations, but only a small fraction of these are “driver” mutations responsible for malignant transformation. The majority are “passenger” mutations that arise secondarily due to genetic instability. Although not involved in the initial monoclonal development of a cancer, passenger mutations may play a role in clonal evolution and progression of the malignant phenotype. This may alter proteases involved in invasion and metastasis and caspases that regulate cell death in response to therapy.

Changes in gene expression due to epigenetic alterations (DNA methylation and acetylation), aberrant gene splicing, noncoding microRNAs, and other mechanisms also contribute to the malignant phenotype, but sequential genetic alterations leading to outgrowth of a clonal population of cells is the major determinant of whether a cancer develops as well as the time

Table 2.1 Molecular Alterations in Cancer

Genetic changes

Mutations

Mutations in oncogenes change a single amino acid and lead to gain of activity that stimulates proliferation (e.g., *KRAS*). These mutations are dominant and not dependent on changes in the other copy of the gene.

Mutations in tumor-suppressor genes (e.g., *PTEN*) and DNA repair genes (e.g., *BRCA1*) generally are small base insertions/deletions or single base changes that cause stop codons. These lead to truncated protein products that are nonfunctional. Loss of tumor-suppressor activity is usually dependent on deletion of the other copy of the gene.

Driver mutations play a critical role in the process of malignant transformation

Passenger mutations occur due to generalized genomic instability. Although not involved in malignant transformation, they may contribute to cancer phenotypes (e.g., metastatic potential, response to therapy)

DNA copy number changes

Deletion of one or both copies of a tumor-suppressor gene due to genomic instability leads to loss of a gene product (e.g., *RB1*)

Gain of additional copies of an oncogene leads to increased activity (e.g., *HER-2/neu*)

Gene rearrangements and translocations

When a gene is moved from its normal location to another chromosomal location, its expression may be increased due to proximity to a gene promoter (e.g., *ALK* in lung cancer)

Aneuploidy

Aneuploidy with gain or loss of complete chromosomes is common in many cancers (e.g., high-grade serous ovarian cancer) and likely plays a role in their development and progression.

Other biological processes

Epigenetic alterations

Hypermethylation of CpG islands in the promoter regions of tumor-suppressor genes may lead to gene inactivation (e.g., *MLH1*).

Loss of promoter methylation in genes that stimulate proliferation may provide an oncogenic stimulus (e.g., *IGF2*).

Changes in acetylation of histone proteins that coat DNA may also play a role in carcinogenesis.

Aberrant gene splicing

Genes may have alternative splice forms that produce messenger RNAs and proteins that have altered activity.

MicroRNAs

These small noncoding RNAs can affect gene expression by binding to messenger RNAs and blocking their translation. Altered miRNA expression plays a role in the development and behavior of some cancers.

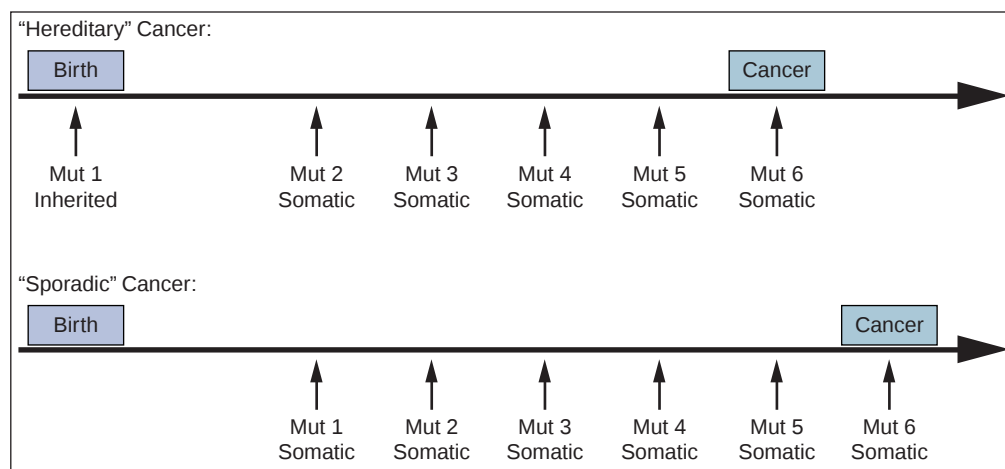


FIGURE 2.1. All cancers are genetic. "Hereditary" cancers differ from "sporadic" cancers by virtue of association with a predisposing mutation inherited through the germ line. In contrast, all of the mutations in sporadic cancers are acquired somatically.

required for its development and progression. The histopathologic progression through hyperplasia, dysplasia, *carcinoma in situ*, and invasive carcinoma, reflects the multistep, multigenic nature of malignant transformation. Cancers may arise through the accumulation of acquired (somatic) alterations or through the inheritance of an alteration in the germline followed by the acquisition of additional somatic alterations (Fig. 2.1). Hereditary cancers are discussed in detail in Chapter 3.

The techniques used to study genetic alterations have evolved dramatically. Advances in the 1980s and 1990s enabled the discovery of several genes that frequently play a role in the development of cancers, including the *KRAS* and *HER-2/neu* oncogenes and the *TP53* and *RB1* tumor-suppressor genes. It became apparent that the spectrum of driver alterations varies considerably between cancer types, and among cancers of the same type. More recently, powerful new technologies have enabled comprehensive genomic studies. The Human Genome Project was completed in 2004 and provided a road map of the entire genome, including the approximately 18,000 protein-encoding genes. The HapMap project then catalogued the millions of common single nucleotide polymorphisms (SNPs) in the genome that change a single base in the DNA sequence. More recently the 1000 Genomes Project has characterized rarer germline genetic variants. A road map of normal human genetic variation and the development of faster and cheaper "next generation" DNA sequencing has allowed mutational analysis of complete cancer genomes. It has been shown that cancers typically have about 30 to 100 acquired mutations. However, cancers are continually evolving due to genetic instability and contain subclones that differ with respect to their mutational profile. A small number of genes are mutated in a high fraction of cancers (e.g., *KRAS*, *TP53*) likely reflecting the strong selective advantage these alterations confer. A much larger number of genes are mutated at considerably lower frequencies. The terms "mountains" and "hills" have been used to describe genes that are commonly versus rarely mutated. Mutations in cancers typically target multiple biological pathways (3). Several genes in a pathway may be mutated, but driver mutations in a pathway often are mutually exclusive when they involve the same pathway (e.g., *KRAS* and *BRAF*).

The Cancer Genome Atlas (TCGA) Project sponsored by the National Cancer Institute is performing a comprehensive genomic characterization of all common forms of human cancer. Ovarian and endometrial cancers were among the first to be studied by

TCGA and these findings have been incorporated into this chapter. The International Cancer Genome Consortium (ICGC) is performing similar genomic analyses of human cancers. Both TCGA and ICGC are depositing their data online in the public domain to stimulate further research. The full spectrum and complexity of the genomic alterations in a single cancer can be best captured in a Circos plot (Fig. 2.2), which uses a circular ideogram layout to facilitate the display of changes across the genome.

An understanding of the molecular pathogenesis of cancer provides the opportunity to better define subgroups within a given type of cancer that may differ with respect to clinical behavior or outcome. In addition, the identification of specific mutations has facilitated the development of therapies that target these alterations (4,5). In this regard, monoclonal antibodies and small molecules targeting aberrantly expressed cellular proteins that drive malignant growth have been successful in treating some cancers (e.g., trastuzumab targets *HER-2/neu* in breast cancer, gefitinib, and erlotinib target EGFR in lung and other cancers). However, resistance to therapy often occurs due to mutational heterogeneity both within the primary tumor and in metastases as clonal evolution develops over time. Unfortunately, many cancers, including most gynecologic cancers, have not proven easily amenable to targeted therapy, perhaps because their growth is not driven by a single altered gene or pathway. Successful therapy may require the use of multiple agents that target more than one gene or pathway.

In several types of common cancers, analysis of known "druggable" molecular targets has become part of the standard of care. Companion molecular diagnostic tests are often requisite to guide selective use of expensive targeted agents in patients most likely to benefit. As the cost of genomic analyses of cancers continues to fall, it will be increasingly feasible to perform full sequencing of cancers to look for less commonly mutated targets. This has the potential to facilitate even greater individualization of therapy based on the unique profile of alterations in a cancer, but the utility of this approach remains unproven.

Finally, an increased understanding of the molecular pathogenesis provides the opportunity to explore new approaches to early detection and prevention. This has been realized for cervical cancer with the identification of the human papilloma virus leading to creation of a vaccine. In ovarian and endometrial cancers, genetic changes that occur early in the development of cancers have the potential to serve as biomarkers for early detection and as surrogate endpoints in prevention studies.

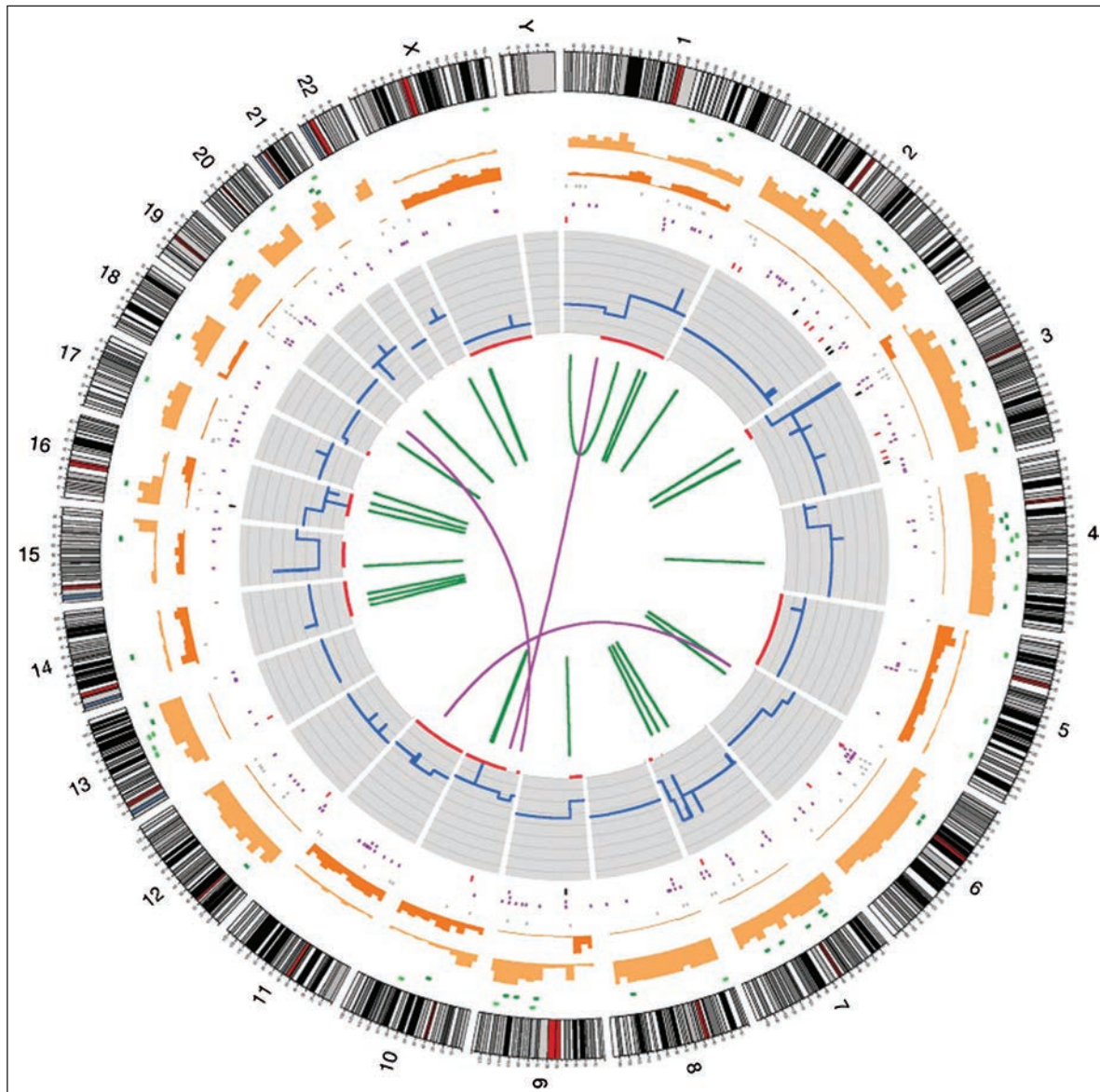


FIGURE 2.2. Circos plot of somatic mutations in COLO-829. Chromosome ideograms are shown around the outer ring and are oriented pter–qter in a clockwise direction with centromeres indicated in red. Other tracks contain somatic alterations (from outside to inside): validated insertions (light green rectangles); validated deletions (dark green rectangles); heterozygous (light orange bars), and homozygous (dark orange bars) substitutions shown by density per 10 megabases; coding substitutions (colored squares: silent in gray, missense in purple, nonsense in red, and splice site in black); copy number (blue lines); regions of loss of heterozygosity (LOH) (red lines); validated intrachromosomal rearrangements (green lines); validated interchromosomal rearrangements (purple lines).

Source: Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* 2010;463(7278):191. [PMID: 20016485]

CELLULAR GROWTH AND DEATH

Proliferation

The number of cells in normal tissues is tightly regulated by a balance between cellular proliferation and death. The final common pathway for cell division involves distinct molecular switches that control cell cycle progression from G1 to the S phase of DNA synthesis (6). These include the Rb and E2F proteins and their various regulatory cyclins, cyclin dependent kinases (cdks) and cdk inhibitors. The events that facilitate progression from G2 to mitosis and cell division are regulated by other cyclins and cdks (Fig. 2.3), as well as by molecules involved in chromosomal segregation such as microtubules. When the chromosomes do not separate properly, aneuploidy may occur

with gain or loss of complete chromosomes (7). Aneuploidy is a hallmark of many cancers and likely plays a role in their development and progression.

Cell cycle progression is also dependent on ubiquitin-mediated proteolysis of molecules involved in cell cycle arrest (6). Ubiquitin is a 76 amino acid polypeptide that can be linked to lysine residues of proteins, and ubiquitination marks proteins for proteolysis and destruction by the proteasome complex. Proteasome inhibitors have been successfully employed to treat some hematologic malignancies, and the *FBXW7* (*CDC4*) ubiquitin ligase has been shown to be mutated in some serous uterine cancers.

In some tissues—such as the bone marrow, epidermis, and gastrointestinal tract—the life span of mature cells is relatively short and high rates of proliferation are required to maintain the population; while in other tissues—such as liver, muscle

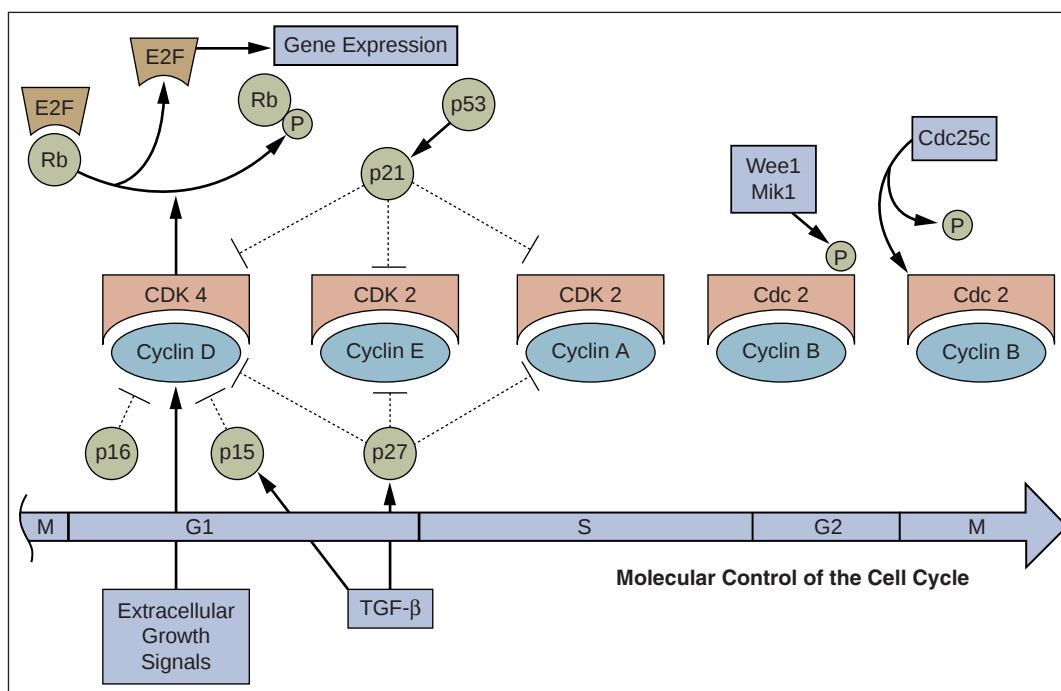


FIGURE 2.3. Molecular control of cell-cycle progression. A linear version of the various stages of the cell cycle is shown with the various cyclin/cyclin-dependent kinase complexes corresponding to the stages that they control.

and brain—cells are long lived and proliferation rarely occurs. Complex molecular mechanisms have evolved to closely regulate proliferation. These involve a finely tuned balance between growth stimulatory and inhibitory signals.

Increased proliferation is one of the hallmarks of cancer. There may be increased activity of genes involved in stimulating proliferation (oncogenes) and/or loss of growth-inhibitory (tumor-suppressor) genes. In the past, it was thought that cancer might arise solely because of more rapid proliferation or a higher fraction of cells proliferating. It is now clear that this was an overly simplistic view. Although increased proliferation is a characteristic of many cancers, the fraction of cancer cells actively dividing and the time required to transit the cell cycle is not always strikingly increased. Altered regulation of proliferation is only one of several factors that contribute to malignant transformation.

Cell death

In addition to being driven by increased proliferation, growth of a cancer may be attributable to cellular resistance to death. At least three distinct types of cell death pathways have been characterized, including apoptosis, autophagy, and necrosis (8).

Apoptosis

The term “apoptosis” derives from Greek and alludes to a process akin to leaves dying and falling off a tree. Apoptosis is an active energy-dependent process that involves cleavage of the DNA by endonucleases and proteins by proteases called caspases. Morphologically, apoptosis is characterized by condensation of chromatin, nuclear and cytoplasmic blebbing, and cellular shrinkage. The molecular events that effect apoptosis in response to various stimuli are complex and have only been partially elucidated, but several reliable markers of apoptosis have been discovered including annexin V, caspase-3 activation, and DNA fragmentation.

External stimuli such as TNF, TRAIL, Fas and other death ligands that interact with cell surface receptors can induce

activation of caspases and lead to apoptosis via the extrinsic pathway. The intrinsic apoptosis pathway is activated in response to a wide range of stresses including DNA damage and deprivation of growth factors. The intrinsic apoptosis pathway is regulated by a complex interaction of pro- and antiapoptotic proteins in the mitochondrial membrane that affect its permeability. Proteins that increase permeability allow release of cytochrome *c*, which activates the apoptosome complex leading to activation of caspases that effect apoptosis. Conversely, proteins that stabilize mitochondrial membranes inhibit apoptosis. The first major insight that led to the understanding of the intrinsic apoptosis pathway was the finding that an activating translocation of the *BCL-2* gene in B-cell lymphomas results in essentially complete inhibition of apoptosis (9). Subsequent studies demonstrated that the antiapoptotic effect of *BCL-2* is attributable to stabilization of the mitochondrial membrane. Additional genes related to *BCL-2*, such as *BAD*, *BCL-XL* and others, also block apoptosis by inhibiting membrane permeability. Other genes in the *BCL* family, such as *BAX* and *BAK*, increase membrane permeability and are pro-apoptotic. An understanding of the complex system of checks and balances involved in regulation of apoptosis provides opportunities for the development of targeted therapies (10).

In addition to restraining the number of cells in a population, apoptosis serves an important role in preventing malignant transformation by allowing for elimination of cells that have undergone genetic damage. Following exposure of cells to mutagenic stimuli, including radiation and carcinogenic drugs, the cell cycle is arrested so that DNA damage may be repaired. If DNA repair is not sufficient, apoptosis occurs so that damaged cells do not survive. This serves as an anticancer surveillance mechanism by which mutated cells are eliminated before they become fully transformed. The *TP53* tumor-suppressor gene is a critical regulator of cell cycle arrest and apoptosis in response to DNA damage. Many of the molecules involved in apoptosis reside in the mitochondria and are encoded by mitochondrial DNA. Mutations in mitochondrial DNA have been shown to be frequent in cancer and may play a role in evasion of apoptosis (11).

Necrosis

Necrosis is a type of cell death that is distinct from apoptosis and is the result of bioenergetic compromise (12). Morphologic changes include swollen organelles and rupture of the cell membrane leading to loss of osmoregulation and cellular fragmentation. Necrosis is a less well-regulated process that leads to spillage of protein contents and this may incite a brisk immune response. This is in contrast to the silent elimination of cells by apoptosis, which typically elicits a minimal immune response. There is evidence that some drugs may enhance necrotic death in tumors and this may stimulate a beneficial antitumor immune response.

Autophagy

Autophagy is a potentially reversible process in which a cell that is stressed “eats” itself (13). A wide range of stresses have been identified that may elicit autophagy (some of which may also elicit apoptosis), including growth factor deprivation and accumulation of reactive oxygen species. Unlike necrosis and apoptosis, in which loss of integrity of the cytoplasmic and nuclear membranes respectively are defining events, autophagy is characterized by the formation of cytoplasmic autophagic vesicles into which cellular proteins and organelles are sequestered. This may allow for cell survival if damaged organelles can be repaired. Conversely, the process may lead to cell death if these vesicles fuse with lysosomes with resultant degradation of their contents. Several cancer therapeutic agents have been shown to induce autophagy, while targeted disruption of genes such as *ATG5* that are involved in autophagy can inhibit cell death.

Cellular Senescence

Normal cells are only capable of undergoing division a finite number of times before becoming senescent and this represents a barrier to immortality (14). Senescence can also be triggered by stresses such as oncogene activation. Induction of senescence is mediated by persistent p16 and p53 activation leading to permanent cell cycle arrest. Cellular senescence is regulated by a biological clock related to progressive shortening of repetitive DNA sequences (TTAGGG) called telomeres that cap the ends of chromosomes. Telomeres are involved in chromosome stabilization and in preventing recombination and chromosomal translocations and aneuploidy during mitosis (15). At birth, chromosomes have long telomeric sequences (150,000 bases) that become progressively shorter by 50 to 200 bases each time a cell divides. Telomerase is a ribonucleoprotein complex. The RNA component serves as a template for telomere extension and the protein subunit acts to catalyze the synthesis of new telomeric repeats.

Replicative senescence serves as a defense against immortalization and malignant transformation by placing limits on proliferation of cells that have accumulated genetic damage. Reactivation of telomerase is critical to the emergence of cancers (16), but early in the process of malignant transformation telomere shortening and dysfunction may promote the carcinogenic process through the generation of chromosomal rearrangements and aneuploidy (17). Progressive telomere shortening during adulthood may explain the association between advancing age and increased cancer risk, particularly for epithelial malignancies. This risk has been mainly attributed to progressive accumulation of mutations with aging, but this theory does not explain the marked aneuploidy of most epithelial cancers.

Telomerase activity is present in a high fraction of many cancers, including ovarian (18), cervical (19) and endometrial cancers (20). It has been suggested that detection of telomerase might be useful for early diagnosis of cancer, but lack of specificity is a significant issue. In this regard, endometrium is one of

the normal adult tissues in which telomerase expression is most common (21). Perhaps this relates to the need for a large number of lifetime cell divisions because of rapid growth and shedding of this tissue each month during the reproductive years. Therapeutic approaches to inhibiting telomerase are under development that would reverse their immortalized state and render them susceptible again to normal replicative senescence (22).

Stem Cells

Stem cells in normal tissues have the capacity to undergo asymmetric division to produce daughter cells that undergo differentiation and eventually senescence, and can self-renew to produce more stem cells (23). Stem cells have been most easily identifiable in tissues that normally are highly proliferative, such as the bone marrow, skin and intestine, in which a constant stream of cells are being born to replace those that are differentiating and dying. It has been theorized that stem cells may exist in cancers and that these have the capacity for self-renewal and differentiation into populations of cells that recapitulate tumor heterogeneity (24). Stem cells are also referred to as tumorigenic cells because of their capacity to regenerate tumors. The stem cell theory suggests that less than 1% of cells in a cancer are stem cells and that by virtue of being dormant or quiescent, they may be relatively resistant to chemotherapy and radiation. It is postulated that cancer stem cells may persist as microscopic disease after eradication of most cancer cells and give rise to recurrent disease. There has been a great deal of interest in identifying and characterizing cancer stem cells, as this could facilitate development of therapies that specifically target these resistant cells.

Several molecular markers have been identified that define cancer stem cells (25), including the cell membrane glycoprotein CD133 (Prominin). Expression of CD133 has been associated with greater proliferative potential and ability to form tumors in animal models. CD44 is the receptor for hyaluronic acid and has been identified as a stem cell marker in several cancer types. CD117, also known as c-kit, is another well-characterized stem cell marker that has been implicated in several solid tumors (25). CD24 is a mucin-like cell surface glycoprotein marker that has been identified as a stem cell marker. The Sonic Hedgehog and WNT pathways also have been implicated in stem cell behavior.

Although expression of the markers and pathways described above in cancers have been associated with stem cell characteristics, the existence of discrete cancer stem cell populations has not been definitively proven. It is possible that the genes and pathways involved in cellular renewal are simply more highly expressed in a fraction of cells within heterogeneous tumors (26). Cancer stem cells may exist in some malignancies but not others. In this regard, demonstration of progenitor stem cells has been more robust in leukemias than in solid tumors.

ORIGINS OF GENETIC ALTERATIONS

Human cancers arise due to a series of genetic alterations that lead to disruption of normal mechanisms that govern cell growth, death, and senescence (2). Genetic damage may be inherited or arise after birth due to various exposures including those related to carcinogenic substances such as tobacco and asbestos, physical factors such as ultraviolet radiation, infections such as HPV, dietary factors, obesity, and inflammation. However much of the acquired genetic damage that causes cancer is due to endogenous mutagenic processes within the cell (Table 2.2). The incidence of most cancers increases with aging because the longer a person is alive the higher the likelihood of a cell acquiring sufficient damage to become fully transformed. It is thought that at least three to six alterations are required to

Table 2.2 Origins of Genetic Damage in Human Cancers

Type of genetic damage	Examples
<i>Germline alterations</i>	
High-penetrance genes	<i>BRCA1</i> , <i>BRCA2</i> (breast, ovarian cancers) <i>MLH1</i> , <i>MSH2</i> (Lynch syndrome)
Low-penetrance genes	SNPs associated with various cancers
<i>Exogenous carcinogens</i>	
Ultraviolet radiation	<i>TP53</i> mutations in skin cancers
Tobacco	<i>TP53</i> mutations in lung cancers
Viruses	HPV inactivation of <i>RB</i> and <i>TP53</i> in cervical cancers
<i>Endogenous DNA damage</i>	
Cytosine methylation and deamination	<i>TP53</i> mutations in many cancer types
DNA Hydrolysis	various genes
Spontaneous errors in DNA synthesis	various genes
Free radical production due to oxidative stress	various genes

fully transform a cell. Many cancers are genetically unstable and this leads to accumulation of a substantial number of secondary changes and the development of subclones that play a role in evolution of the malignant phenotype.

Inherited Cancer Susceptibility

Although most cancers arise sporadically due to acquired genetic damage, inherited mutations in cancer susceptibility genes are responsible for some familial cases. The age of cancer onset is younger in these families and it is not unusual for some individuals to be affected with multiple primary cancers. Tumor-suppressor genes and DNA repair genes have been implicated most frequently in hereditary cancer syndromes. The most common forms of hereditary cancer syndromes predispose to breast/ovarian (*BRCA1/2* genes) and colon/endometrial (DNA mismatch repair genes) cancers. Although affected individuals carry the germline alteration in every cell of their bodies, paradoxically, cancer susceptibility genes are characterized by a limited repertoire of cancers. The penetrance of cancer susceptibility genes is incomplete, as all individuals who inherit a mutation do not develop cancer. The emergence of cancers is dependent on the occurrence of additional genetic alterations. Hereditary cancer syndromes are covered in detail in Chapter 3.

In addition to the high-penetrance mutations noted above that cause familial cancer syndromes, low-penetrance genetic variants may also affect cancer susceptibility, albeit less dramatically (27). There are over 10 million polymorphic genetic loci in the human genome, most of which are SNPs (e.g., CCA to CAA). Many of these SNPs are common, with the rarer of the two alleles occurring in more than 5% of individuals. Genome wide association studies have discovered a number of SNPs that affect the risk of ovarian cancer by 10% to 20% per rare allele copy (27). A more complete understanding of the genetic factors that affect cancer susceptibility could facilitate implementation of screening and prevention approaches in subsets of the population at increased risk.

Acquired Genetic Damage

The etiology of acquired genetic damage in cancers also has been elucidated to some extent. For example, a strong causal link exists between cigarette smoke and cancers of the aerodigestive tract, between ultraviolet radiation and skin cancer, and between HPV and lower genital tract cancers (Table 2.2). For many common forms of cancer (e.g., colon, breast, prostate, endometrium, ovary), there is not a strong association with specific carcinogens. It is thought that the genetic alterations responsible for these cancers may arise mainly due to endogenous mutagenic processes. This includes methylation and deamination of cytosine residues leading to transition mutations to thymidine. In this regard, in most types of cancers that are not associated with a specific carcinogen, transition mutations from purine to purine or pyrimidine to pyrimidine are much more common than transversion mutations that change purine to pyrimidine or pyrimidine to purine. An additional mechanism of endogenous damage includes spontaneous errors in DNA synthesis that frequently occur during the process of DNA replication associated with normal proliferation. Free radicals generated in response to inflammation and other cellular damage may also cause DNA damage. These endogenous processes are thought to produce mutations on an ongoing basis. Several networks of highly effective DNA damage surveillance and repair genes exist, but some mutations may elude them. The efficiency of these DNA damage response systems varies between individuals due to genetic and other factors and may affect susceptibility to cancer.

Epigenetic Changes

Epigenetics comprises heritable changes that are not due to alterations in DNA sequence (28,29). Methylation of cytosine residues that reside next to guanine residues (CpG dinucleotides) is the primary mechanism of epigenetic regulation, and this process is regulated by a family of DNA methyltransferases. CpG dinucleotides are asymmetrically distributed with about half of human genes containing CpG-rich regions termed “CpG islands” at their transcriptional start sites. Most genes are regulated without changing the methylation status of the CpG sites, but permanent silencing of genes associated with X-chromosome inactivation and genomic imprinting is due to heritable methylation of CpG islands.

Most cancers have globally reduced DNA methylation, which may lead to activation of some genes. Conversely, selective hypermethylation of CpG islands in the promoter regions of tumor-suppressor genes may lead to gene inactivation (e.g., *BRCA1*, *MLH1*). In addition, loss of silencing of imprinted genes that stimulate proliferation, such as *IGF2*, may provide an oncogenic stimulus. Acetylation and methylation of the histone proteins that coat DNA represent another level of epigenetic regulation that is altered in cancer. The underlying cause of epigenetic alterations in cancer remains poorly understood.

Alterations in Signal Transduction Pathways in Malignant Transformation

Alterations in genes that stimulate cellular growth (oncogenes) can cause malignant transformation when they become overactive (2). In some cancers, amplification of oncogenes occurs with resultant overexpression of the corresponding protein. Instead of two copies of one of these genes, there may be many additional copies. Some oncogenes may become overactive when affected by gain of function point mutations. Finally, oncogenes may be translocated from one chromosomal location to another and come under the influence of gene promoters that cause overexpression. This latter mechanism frequently occurs as a driving

event in the development of leukemias and lymphomas, but is infrequent in gynecologic cancers. However, some other types of solid tumors may have translocations that represent significant driver events, such as those involving the *ALK* receptor gene in lung cancer. These have been targeted successfully with the monoclonal antibody crizotinib (30).

Loss of tumor-suppressor gene function also plays a role in the development of most cancers. This usually involves a two-step process in which both copies of a tumor-suppressor gene are inactivated. This often involves mutation of one copy of a tumor-suppressor gene and loss of the other copy due to deletion of a segment of the chromosome where the gene resides (e.g., *RB1*). There is also evidence that some tumor-suppressor genes may be inactivated due to methylation of the promoter region of the gene (e.g., *MLH1*, *BRCA1*). The promoter is an area proximal to the coding sequence that binds transcription factors that regulate whether or not the gene is transcribed from DNA into RNA. When the promoter is methylated, it is resistant to activation and the gene is essentially silenced despite remaining structurally intact. This two-hit paradigm of tumor-suppressor gene inactivation is relevant to both hereditary cancer syndromes, in which one mutation is inherited and the second acquired, and to sporadic cancers, in which both hits are acquired. Tumor-suppressor gene products are found throughout the cell, reflecting their diverse functions.

The sections below will review the role of oncogenes and tumor-suppressor genes in signal transduction pathways that regulate cellular growth and metabolism (3). These pathways are complex and have considerable overlap and redundancy (31), and an exhaustive discussion is beyond the scope of this book. Pathways for which there is less evidence of a role in driving the development of gynecologic cancers, such as the Hedgehog, Notch, and cytokine pathways, are not covered.

Peptide Growth Factors and Receptor Tyrosine Kinases

Peptide growth factors in the extracellular space, such as those of the EGF, PDGF, and FGF families, stimulate a cascade of molecular events that leads to proliferation by binding to high affinity cell membrane receptors (Fig. 2.4). Growth factors are involved in normal cellular processes such as stromal-epithelial communication, tissue regeneration, and wound healing. The concept that

autocrine growth stimulation might be a key strategy by which cancer cell proliferation becomes autonomous has received considerable attention. In this model, it is postulated that cancers secrete stimulatory growth factors that then interact with receptors on the same cell. Although peptide growth factors provide a growth stimulatory signal, there is little evidence to suggest that overproduction of growth factors is a precipitating event in the development of most cancers. Increased expression of peptide growth factors likely facilitates, rather than drives, malignant transformation.

Cell membrane receptors that bind peptide growth factors are composed of an extracellular ligand binding domain, a membrane-spanning region, and a cytoplasmic tyrosine kinase domain (31,32). Binding of a growth factor to the extracellular domain results in dimerization and conformational shifts in the receptors and activation of the inner tyrosine kinase. The kinase transfers a phosphate group from ATP to specific tyrosine residues both on the growth factor receptor itself (autophosphorylation) and on molecular targets in the cell interior leading to activation of secondary signals that stimulate proliferation. Growth of some cancers is driven by overexpression of receptor tyrosine kinases. The epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases plays a significant role in the development of several types of cancers, and includes ErbB-1 (EGFR), ErbB-2 (*HER-2/neu*), ErbB-3, and ErbB-4. These receptors are activated by binding of ligands, including EGF, transforming growth factor- α , amphiregulin, and the neuregulins.

Because receptor tyrosine kinases are located on the cell surface, they are appealing therapeutic targets. A number of agents that target the EGFR family have been developed and translated into clinical practice. Trastuzumab is a monoclonal antibody that binds to *HER-2/neu*, and it is widely used in the treatment of breast cancers that overexpress this receptor (33). Cetuximab is a monoclonal antibody that targets the extracellular domain of EGFR, whereas gefitinib is a direct inhibitor of the EGFR tyrosine kinase (34). Lapatinib is a dual EGFR/HER-2 kinase inhibitor. Likewise, therapeutic approaches have been developed that target other receptor tyrosine kinases. Imatinib antagonizes the activity of the BCR-ABL, c-kit, and platelet-derived growth factor (PDGF) receptor tyrosine kinases and has proven highly effective in treatment of chronic myelogenous leukemias and gastrointestinal stromal tumors.

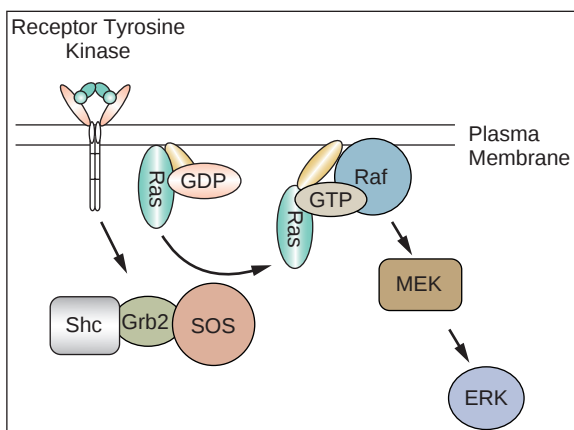


FIGURE 2.4. Receptor tyrosine kinase pathway. Most receptor tyrosine kinases stimulate the activity of the Ras guanine nucleotide exchange factor son of sevenless (SOS), which associates with the linker proteins Shc and Grb2. The activation of Ras by SOS stimulates a protein serine kinase cascade initiated by Raf, which stimulates MEK. MEK then activates the extracellular signaling-regulated kinases (ERKs). ERKs phosphorylate transcription factors to regulate gene expression.

Nonreceptor Kinases and Phosphatases

Following interaction of growth factors with cell membrane receptors, secondary molecular signals are generated to transmit the growth stimulus to the nucleus. This function is served by a multitude of complex and overlapping signal transduction pathways that occur in the inner cell membrane and cytoplasm. Many of these signals involve phosphorylation of proteins by enzymes known as nonreceptor kinases. The kinases that are involved in growth regulation are of two types, those that phosphorylate tyrosine residues of target proteins, including those of the *SRC* family (35), and others that are specific for serine and/or threonine residues such as *AKT* (36). The activity of kinases is opposed by phosphatases such as *PTEN*, which act in opposition to the kinases by removing phosphates from the target proteins. The *PTEN* gene is among the most frequently mutated tumor-suppressor genes in human cancers.

RAS/RAF, Mitogen-Activated Protein Kinase (MAPK) Pathway

Guanosine-triphosphate-binding proteins (G proteins) such as RAS represent another class of molecules involved in transmission of growth signals (Figs. 2.4 and 2.5A). They are located on

the inner aspect of the cell membrane and are positively regulated by Grb and SOS in response to receptor tyrosine kinases and other signals. They have intrinsic GTPase activity that catalyzes the exchange of GTP (guanine-tri-phosphate) for GDP (guanine-di-phosphate). In their active GTP bound form, G proteins interact with kinases that are involved in relaying the mitogenic signal, such as those of the MAP kinase family. Conversely, hydrolysis of GTP to GDP, which is stimulated by GTPase activating proteins (GAPs), leads to inactivation of G proteins. The RAS family of G proteins is among the most frequently mutated oncogenes in human cancers. Activation of RAS genes usually involves point mutations in codons 12, 13, or 61 that result in constitutively activated molecules (37).

The RAF family of genes encode serine-threonine kinases that interact with RAS proteins and propagate signaling by

activating MAP kinases (MEK) which translocate to the nucleus. Mutations in the *BRAF* gene occur in many cancers that lack RAS mutations and most of these mutations involve codon 599 in the kinase domain (38). The mutual exclusivity of *KRAS* and *BRAF* mutations is consistent with the need to only activate one gene in a pathway. Melanomas often have mutations in codon 600 of *BRAF*. The *BRAF* kinase inhibitor vemurafenib has been shown to be highly active in melanomas with the *BRAF* V600E mutation (39).

The RAF serine/threonine kinase is downstream of RAS, and its activation leads to signaling via mitogen-activated protein kinase kinase (MAPKK), also called MEK, which activates mitogen-activated protein (MAP) kinase or extracellular regulated kinase (ERK). MAP kinase activation results in phosphorylation and activation of nuclear factors such as ribosomal S6 kinase

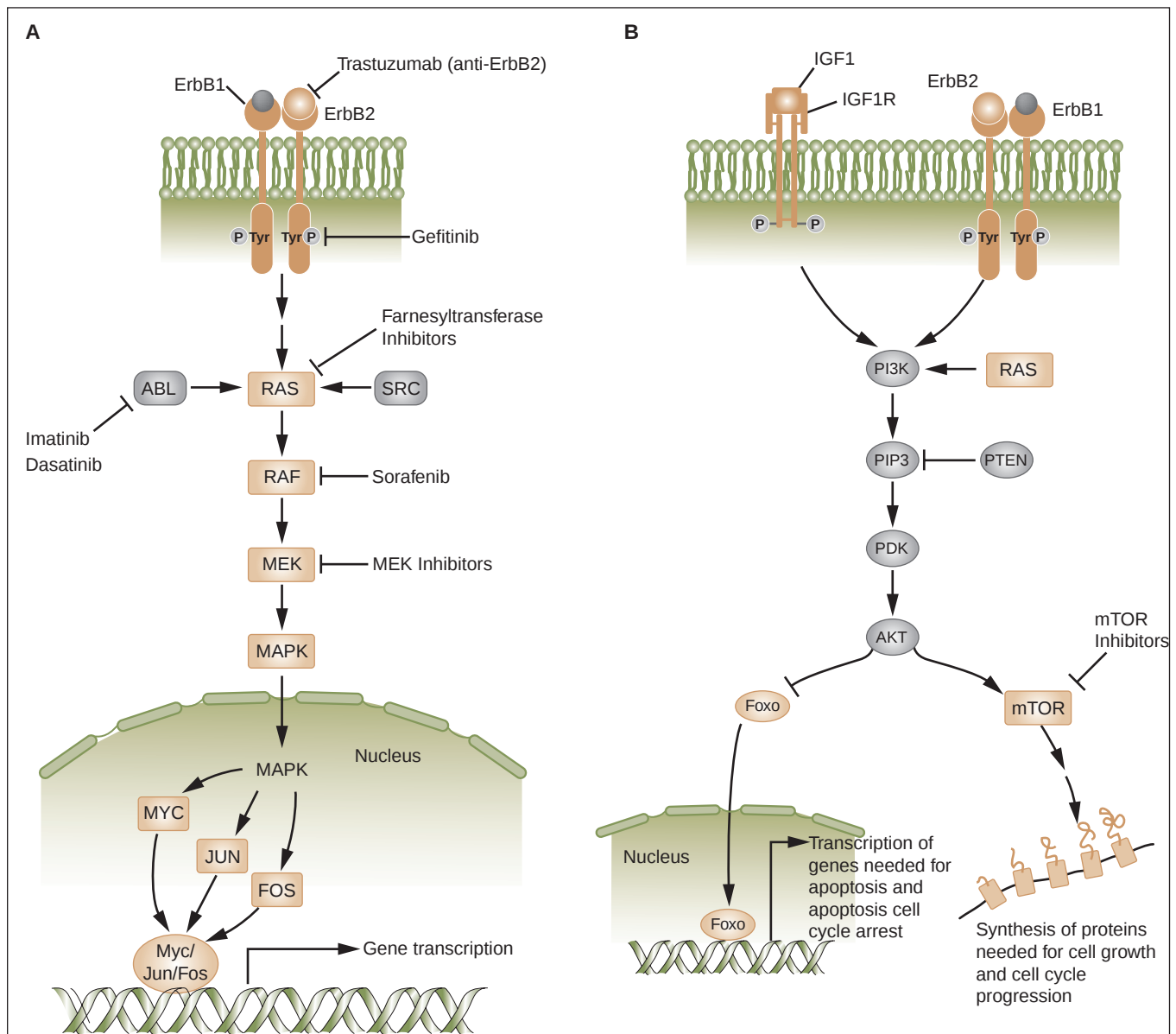


FIGURE 2.5. A: The ras/raf/MEK/MAPK pathway is activated by multiple growth factor receptors (here exemplified by ErbB1 and ErbB2) as well as several intracellular tyrosine kinases such as SRC and ABL. Activated RAS stimulates a sequence of phosphorylation events mediated by RAF, MEK, and ERK (MAP) kinases. Activated MAP kinase (MAPK) translocates to the nucleus and activates proteins such as MYC, JUN, and FOS that promote the transcription of numerous genes involved in tumor growth. **B:** The phosphatidylinositol 3-kinase (PI3K) pathway is activated by RAS and by a number of growth factor receptors (here exemplified IGF1R and the ErbB1/ErbB2 heterodimer). Activated PI3K generates phosphatidylinositol-3,4,5-triphosphate (PIP3), which activates phosphoinositide-dependent kinase-1 (PDK). In turn, PDK phosphorylates AKT. PTEN is an endogenous inhibitor of AKT activation. Phosphorylated AKT transduces multiple downstream signals, including activation of the mTOR and inhibition of the FOXO family of transcription factors. mTOR activation promotes the synthesis of proteins required for cell growth and cell cycle progression.

and transcription factors *JUN*, *MYC* and *FOS*, resulting in the switching on of a number of genes associated with proliferation.

PI3K/AKT/mTOR Pathway

Phosphatidylinositol 3-kinases (PI3Ks) are a class of lipid kinases that phosphorylate phosphoinositides (PIs) at the position D3 of the inositol ring (40). Extracellular molecules such as growth factors are the main effectors for PI3K pathway activation through the interaction with receptor tyrosine kinases and G protein-coupled receptors (Fig. 2.5B). Phosphorylated PIs serve as plasma docking sites for the recruitment of pleckstrin-homology domain containing proteins such as AKT and its upstream activator PDK1. PI3K activation is one of the main causes of increased proliferation and resistance to apoptosis. The *PIK3CA* gene is one of the most frequently mutated oncogenes in human cancers.

Alterations in PI3Ks and downstream effectors, including AKT and mTOR, frequently are involved in initiation and maintenance of the tumorigenic phenotype. The PI3K-AKT pathway promotes cell growth and survival and inhibits apoptosis and autophagy through several mechanisms. AKT activates the mammalian target of rapamycin (mTOR) pathway (Fig. 2.5B) and modulates genes that inhibit cell cycle progression (e.g., *cdks*, *CHK1*, and *MDM2*). AKT targets include the pro-apoptotic effectors *BAD* and *BAX*, which are inhibited by phosphorylation respectively at Ser136 and Ser184, resulting in inhibition of the apoptotic response. AKT also inhibits the expression of BH3-only proteins such as *BAD* and *BIM* through effects on transcription factors, such as Forkhead family proteins (e.g., *FOXO3a*) and *p53*. AKT also influences *p53* activity through *MDM2* phosphorylation at Ser166 and Ser186, which promotes its translocation to the nucleus, with subsequent destabilization. AKT can phosphorylate and activate I κ B kinase- α , which in turn phosphorylates I κ B, targeting it for degradation. This leads to nuclear translocation and activation of the transcription factor NF- κ B and transcription of NF- κ B-dependent pro-survival genes.

The *PTEN* tumor suppressor is the most important negative regulator of the PI3K signaling pathway (41). It is a lipid and protein phosphatase that removes phosphates in opposition to PI3K tyrosine kinases. Its ability to dephosphorylate phosphatidylinositol 3,4,5-trisphosphate (PIP3) resulting in phosphatidylinositol 4,5-bisphosphate (PIP2) inhibits oncogenic PI3K-dependent signaling. Although *PTEN* is a tumor suppressor and may be completely lost due to mutation and deletion of the two copies of the gene, mutational inactivation of one copy of the gene (haploinsufficiency) also appears to facilitate malignant transformation.

Both genetic and epigenetic alterations affect the activity of this pathway (40). Mutations in the *PIK3CA* gene that lead to increased activity frequently occur in human cancers, including ovarian and endometrial cancers. *PTEN* is frequently targeted by either germline or somatic mutation, and is the second most frequently mutated gene in human cancers. In addition, loss of heterozygosity or promoter hypermethylation occurs in a broad range of cancers including endometrioid ovarian and endometrial cancers. Inhibition of the PI3K/Akt/mTOR pathway represents an attractive therapeutic approach (42).

WNT Pathway

β -catenin (*CTNNB1*) is involved along with cadherins in cell-cell adhesion junctions and may play a role in inhibition of excessive growth when cells come in contact with each other. β -catenin also may be translocated to the nucleus and play a role in regulating transcription of genes involved in embryonic

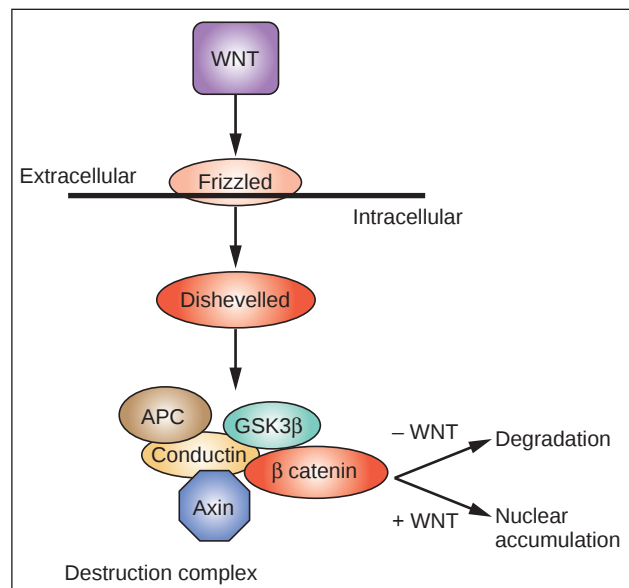


FIGURE 2.6. Wingless (WNT)/ β -catenin signaling. WNT extracellular ligands bind Frizzled receptors and regulate the phosphorylation status of axin. Axin functions as part of the destruction complex that regulates the stability of β -catenin, a transcriptional regulator.

development, cell differentiation, and cell polarity (Fig. 2.6). β -catenin activity is regulated by the WNT pathway (31). The WNT family of genes encodes secreted peptides that interact with Frizzled family cell surface receptors. Frizzled activates the intracellular Dishevelled protein resulting in an increase in the amount of β -catenin translocated to the nucleus. Dishevelled accomplishes this by inhibiting a complex of proteins that includes axin, GSK-3 β , and APC that normally promote proteolytic degradation of β -catenin. This allows β -catenin to enter the nucleus and interact with TCF/LEF family transcription factors to promote gene expression.

Genes encoding WNT signaling inhibitors are often down-regulated during carcinogenesis and driver mutations in several of these genes (*APC*, *Axin*, *GSK-3 β* , *β -catenin*) occur frequently in human cancers, including endometrial cancers. Germline mutations in the *APC* gene are responsible for familial adenomatous polyposis of the colon.

Nuclear Oncogenes

If proliferation is to occur in response to signals generated in the cell membrane and cytoplasm, these events must lead to activation of nuclear transcription factors and other gene products responsible for stimulating DNA replication and cell division (Fig. 2.5A). Expression of several genes that encode nuclear proteins increases dramatically within minutes of treatment of cells with peptide growth factors. Once induced, the products of these genes bind to specific DNA regulatory elements and induce transcription of genes involved in DNA synthesis and cell division. Examples include the *FOS* and *JUN* genes, which dimerize to form the AP1 transcription complex. When inappropriately overexpressed these transcription factors can act as oncogenes. The *MYC* family of nuclear transcription factors is often involved in the development of human cancers, including some ovarian cancers, due to amplification/overexpression. Many of the nuclear regulatory genes such as *MYC* that control proliferation also impact the threshold for apoptosis. Thus, there is overlap in the molecular pathways that regulate the opposing processes of proliferation and apoptosis.

Genes involved in chromatin remodeling also that have been implicated as oncogenes (e.g., ARID1A). Finally, genes that positively regulate cell cycle progression may be amplified and/or overexpressed in some cancers leading to unrestrained proliferation (e.g., cyclin D1 [CCND1] and cyclin E1 [CCNE1]).

Nuclear Tumor-Suppressor Genes

The retinoblastoma gene (*RB*) was the first tumor-suppressor gene discovered and is frequently mutated in human cancers (43,44). It was named based on its discovery in the context of a rare hereditary cancer syndrome, as have many other tumor-suppressor genes. The *RB* gene plays a key role in regulation of cell cycle progression. In the G1 phase of the cell cycle RB protein binds to the E2F family of transcription factors and prevents it from activating transcription of other genes involved in DNA replication and cell cycle progression. This serves as an important restriction point that can protect genomic integrity if DNA damage is present. G1 arrest is maintained by cyclin dependent kinase (cdk) inhibitors such as p16, p21, and p27 that prevent phosphorylation of RB (45). When RB is phosphorylated by cyclin/cdk complexes, E2F is released and stimulates entry into the DNA synthesis phase of the cell cycle. Other cyclins and cyclin dependent kinases are involved in progression from G2 to mitosis. Mutations in the *RB* gene have been noted primarily in retinoblastomas and sarcomas, but less frequently in other types of cancers. By maintaining G1 arrest, the cdk inhibitors p16, p21, p27, and others act as tumor-suppressor genes. Loss of p16 (*CDKN2A*) tumor-suppressor function due to genomic deletion or promoter methylation occurs in some cancers. Likewise, loss of p21 and p27 has been noted in some cancers as well.

Mutation of the *TP53* tumor-suppressor gene is the most frequent genetic event described thus far in human cancers (46,47). The *TP53* gene encodes a 393 amino acid protein that plays a central role in the regulation of both proliferation and apoptosis. In normal cells, p53 protein resides in the nucleus and exerts its tumor-suppressor activity by binding to transcriptional regulatory elements of genes, such as the cdk inhibitor p21, that act to arrest cells in G1. The *MDM2* gene product degrades p53 protein when appropriate, whereas p14ARF down-regulates *MDM2* when up-regulation of p53 is needed to initiate cell cycle arrest.

Many cancers have missense mutations in one copy of the *TP53* gene that result in substitution of a single amino acid in exons 5 through 8, which encode the DNA binding domains that are involved in regulating transcription (Fig. 2.7). Although these mutant *TP53* genes encode full-length proteins, they are unable to bind to DNA and regulate transcription of other genes. Mutation of one copy of the *TP53* gene often is accompanied by deletion of the other copy, leaving the cancer cell with only mutant p53 protein. If the cancer cell retains one normal copy of the *TP53* gene, mutant p53 protein can complex with

wild-type p53 protein and prevent it from oligomerizing and interacting with DNA. Because inactivation of both *TP53* alleles is not required for loss of p53 function, mutant p53 is said to act in a “dominant negative” fashion. While normal cells have low levels of p53 protein because it is rapidly degraded, missense mutations encode protein products that are resistant to degradation. The resultant overaccumulation of mutant p53 protein in the nucleus can be detected immunohistochemically. A smaller fraction of cancers have mutations in the *TP53* gene that encode truncated protein products. In these cases, loss of the other allele occurs as the second event as is seen with other tumor-suppressor genes.

Beyond simply inhibiting proliferation, normal p53 is thought to play a role in preventing cancer by stimulating apoptosis of cells that have undergone excessive genetic damage. In this regard, p53 has been described as the “guardian of the genome” because it delays entry into S phase until the genome has been cleansed of mutations. If DNA repair is inadequate, p53 may initiate apoptosis, thereby eliminating cells with genetic damage (Junttila and Evan, 2009).

TGF- β Pathway

The transforming growth factor-beta (TGF- β) family of growth factors inhibits proliferation (48). It is thought that TGF- β causes G1 arrest by inducing expression of cyclin dependent kinase inhibitors such as p27. Three closely related forms of TGF- β have been discovered that are encoded by separate genes (*TGF- β 1*, *TGF- β 2*, *TGF- β 3*). TGF- β is secreted in an inactive form bound to a portion of its precursor molecule from which it must be cleaved to release biologically active TGF- β . Active TGF- β interacts with type I and type II cell surface TGF- β receptors and initiates serine/threonine kinase activity (49). Prominent intracellular targets include a class of molecules called SMADs that translocate to the nucleus upon TGF- β receptor mediated phosphorylation and act as transcriptional regulator. In the nucleus, the SMAD complex interacts with other DNA-binding transcription factors and co-factors to regulate the transcription of TGF- β target genes to initiate growth arrest. Typical events include the upregulation of cyclin-dependent kinase inhibitors (p16, p15, p21, and p27) and translation-inhibitory protein 4eBP1 as well as the down regulation of MYC. In addition to growth arrest, TGF- β also limits tumor progression through the induction of apoptosis.

MicroRNA

MicroRNAs (miRNA) consist of single RNA strands of about 21 to 23 nucleotides that do not encode proteins (Fig. 2.8). They bind to messenger RNAs that contain complementary sequences and can block protein translation. In addition to regulation of normal biological processes, dysregulation of miRNA

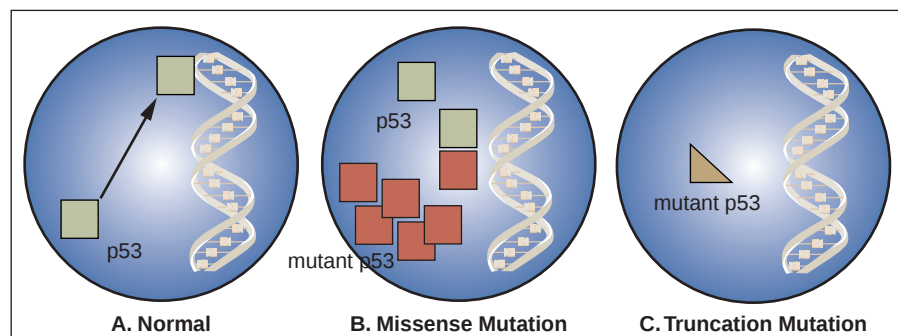


FIGURE 2.7. Inactivation of the p53 gene. **A:** Normal p53 protein binds to transcriptional regulatory elements in DNA. **B:** p53 missense mutations encode proteins that no longer bind to DNA and the mutant protein complexes with and inactivates any remaining normal p53 in the nucleus. **C:** p53 mutations that encode truncated protein products result in proteins that no longer bind to DNA, and these mutations usually are accompanied by deletion of the wild-type p53 allele.

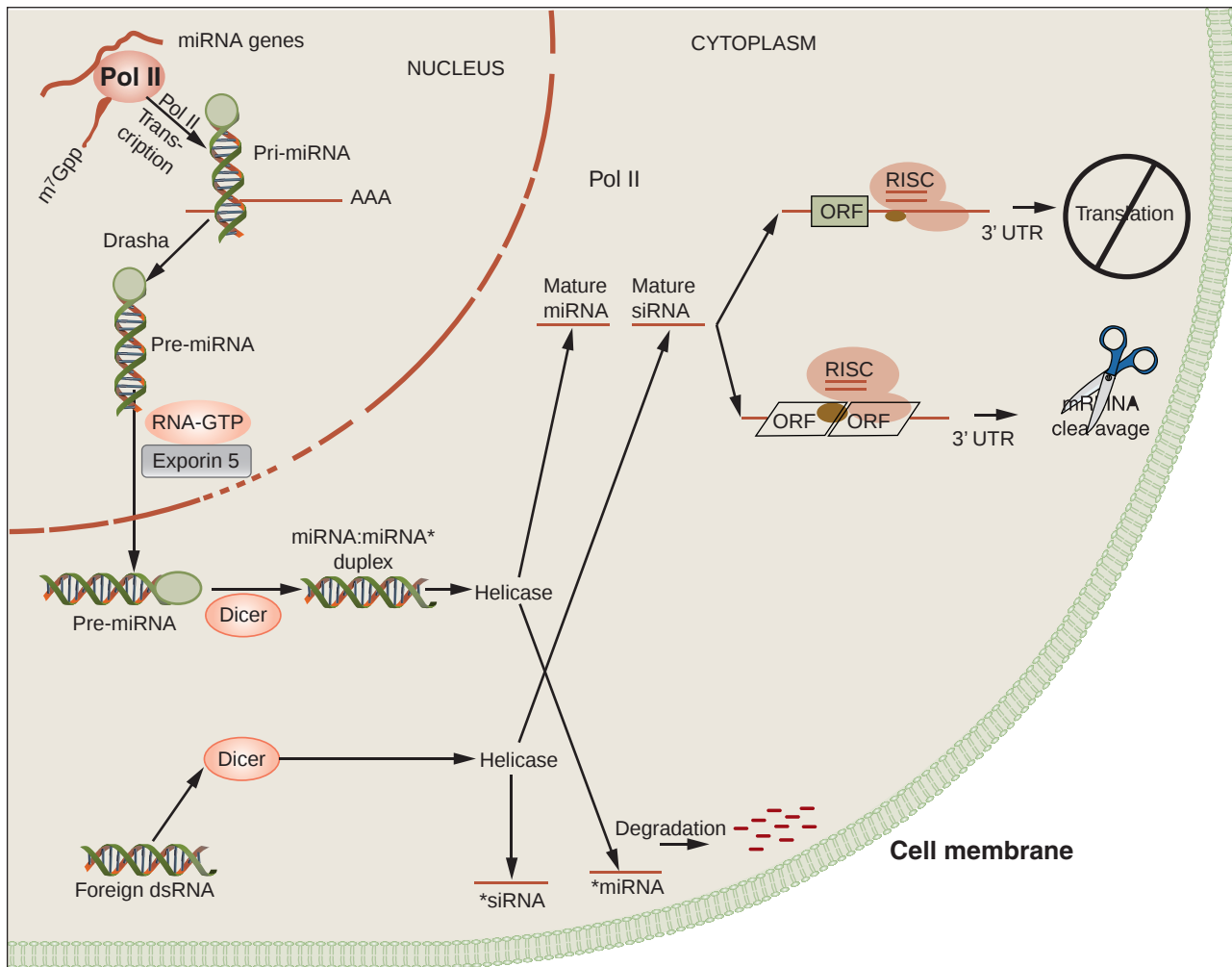


FIGURE 2.8. MicroRNA pathways.

expression appears to play a role in the development and behavior of human cancers (50).

MiRNA production begins in the nucleus from several kilobase-long primary miRNAs (pri-miRNA). These pri-miRNAs undergo cleavage to produce short hairpin-shaped intermediates known as precursor miRNAs (pre-miRNA), which are approximately 70 nucleotides in length.

Drosha, a RNase III enzyme, along with the DiGeorge syndrome critical region gene 8 (DGCR8), processes the precursors prior to translocation to the cytoplasm via Exportin-5. Subsequently, pre-miRNAs are cleaved by Dicer, also an RNase III enzyme, resulting in mature miRNAs. SiRNA, an approximately 21-nucleotide single-stranded sequence, is derived within the cytoplasm and does not require processing by the Drosha-DGCR8 complex. Mature miRNAs and siRNAs are then activated through the RNA-induced silencing complex, which produces host mRNA degradation and/or translational repression upon binding to the target. High Dicer and Drosha expression have been shown to be associated with increased median survival in ovarian cancer (>11 years, vs. 2.7 years) (51).

Exogenous constructs of either siRNAs or short hairpin RNAs (shRNA) can also be introduced into cells through transfection. ShRNAs are introduced through viral vectors to produce stable gene silencing, whereas siRNA transfections are more transient. RNAi technology has been used as a research tool to study the effect of turning off various genes and also potentially has therapeutic applications.

Energy Metabolism

Cancer cells uptake increased amounts of glucose to satisfy their metabolic demands (52), and this is the basis of fluorodeoxyglucose (FDG)-PET imaging. Normal tissues generate energy using mitochondrial oxidative phosphorylation and only switch to breaking down glucose to derive energy in the absence of oxygen, which leads to the accumulation of lactate. In contrast, glycolysis of glucose to lactate occurs in cancers even in the presence of oxygen, a phenomenon called 'aerobic glycolysis.' This is referred to as the Warburg effect, in honor of its discoverer (53). Because cancers often outgrow their blood supply and become hypoxic, the ability to survive using aerobic glycolysis instead of oxidative phosphorylation may be selected for during malignant transformation. Lactate production by cancers may also promote invasion and metastasis by acidifying the microenvironment. Aerobic glycolysis also may serve the increased metabolic requirement for carbon atoms to produce the macromolecules needed to build new cancer cells. If glucose is completely broken down to carbon dioxide via the citric acid cycle, these carbon building blocks are lost.

The hypoxia-inducible transcription factor-1 α (HIF-1 α) plays an important role in the cellular response to decreased oxygen in the local environment. When oxygen is absent, HIF-1 α accumulates and promotes transcription of pro-angiogenesis genes as well as those involved in glucose transport and glycolysis. HIF-1 α accumulation may be a consequence of loss of the

VHL tumor suppressor gene, providing a link between the loss of a tumor suppressor and the altered metabolic phenotype of malignant cells. Another link between glucose metabolism and cancer is the finding that isocitrate dehydrogenase (IDH), an enzyme involved in glycolysis, is frequently mutated in glioblastomas. The common amino acid changing IDH mutations result in increased production of 2-hydroxyglutarate, which accumulates to high levels and plays a role in the development of these cancers. Activation of the PIK and RAS pathways also regulate glucose uptake and metabolism.

Differences in metabolism between normal and malignant cells represent an appealing therapeutic target. In this regard, there is a suggestion that the diabetic drug metformin may have efficacy in the treatment and prevention of cancer. This appears to be independent of blood glucose level, and the exact mechanism is unclear.

DNA REPAIR

It has been estimated that thousands of mutations occur in humans on a daily basis (54). Cells in many organs such as the skin, gastrointestinal tract, and respiratory tract that are exposed most directly to the environment constantly undergo renewal with shedding of differentiated cells that may contain mutations. Mammalian cells also have highly evolved and complex DNA repair systems to maintain the integrity of the genome. A series of cell cycle checkpoints exist that allow the opportunity to pause for successful DNA repair, or alternatively for cell death if repair cannot be accomplished. DNA damage checkpoints occur at the boundaries between G1/S and G2/M and during S phase and mitotic spindle assembly. These checkpoints serve to protect against genetic damage that can lead to malignant transformation being fixed in the genome.

There are several repair mechanisms that operate on specific types of DNA damage during these checkpoints (55,56), including mismatch repair (MMR), nucleotide excision repair (NER), base-excision repair (BER), homologous recombination (HR)

repair and nonhomologous end joining (NHEJ). Loss of DNA repair activity increases the likelihood of mutations being fixed in the genome and this is a hallmark of many cancers.

DNA Mismatch Repair (MMR)

MMR excises nucleotides that are incorrectly paired with the correct nucleotide on the opposite DNA strand (55). It involves recognition of a base pair mismatch, recruitment of repair enzymes, excision of the incorrect sequence and re-synthesis by DNA polymerase using the parental strand as a template (Fig. 2.9). The recognition of small loops generated by insertion or deletion of nucleotides, as well as single base mismatches is primarily accomplished by a complex called MUTS, which is a heterodimer of MSH2 and MSH6. MLH1 and PMS2 are recruited to the site to initiate the subsequent steps of repair, including excision, DNA synthesis, and ligation.

Loss of mismatch repair leads to a “mutator phenotype” in which there is accumulation of genetic mutations throughout the genome, particularly in repetitive DNA sequences called microsatellites. Examples of microsatellite sequences include mono (AAAA), di (CACACACA), and tri (CAGCAGCAGCAG) nucleotide repeats. Replication errors in these repetitive sequences are common and their inefficient repair leads to the propensity to accumulate mutations, and this is referred to as microsatellite instability (MSI). Some microsatellite sequences are in noncoding areas of the genome while others are within genes. It is thought that accumulation of mutations in microsatellite sequences of tumor suppressor genes may inactivate them and accelerate the process of malignant transformation.

About 3% of endometrial cancers arise due to inherited mutations in MMR genes in the context of Lynch syndrome (57,58). Most cases are due to alterations in MSH2 and MLH1, but MSH6 and PMS1, PMS2, and MSH3 mutations also occur. Lynch syndrome is covered in depth in Chapter 3. More frequently, the MLH1 MMR gene is inactivated due to promoter methylation in sporadic endometrial cancers of the endometrium leading to microsatellite instability.

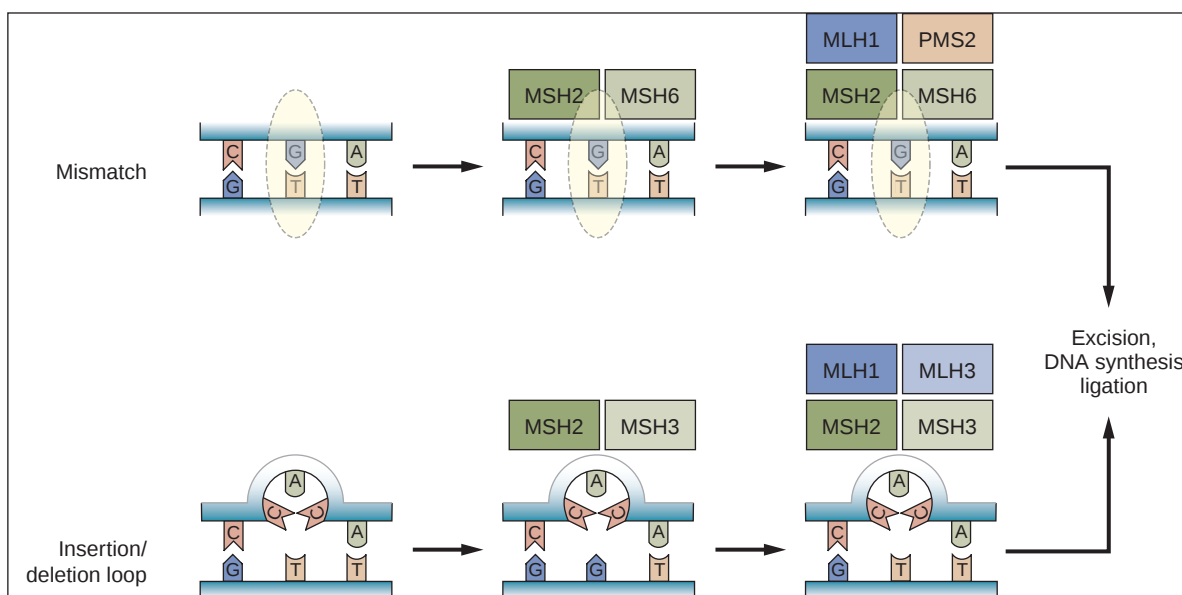


FIGURE 2.9. Mismatch repair pathways. Mismatched bases due to errors in DNA replication or other causes are recognized by the mismatch repair machinery. The initial step involves recognition of simple mismatches by MSH2 and MSH6 (upper panel), or recognition of insertion/deletion loops by MSH2 and MSH3 (lower panel). Subsequent steps involve recruitment of MLH1 and PMS2 to mismatch sites, or MLH1 and MLH3 to insertion/deletion loop sites. This is followed by excision of the respective lesions, DNA synthesis, and ligation to complete the repair.

Nucleotide Excision Repair/Base Excision Repair

The mismatch repair pathway functions primarily in the recognition and repair of replication errors, while the NER and base excision repair (BER) pathways respond to damage caused by DNA damaging agents. NER is an important DNA repair mechanism, as evidenced by the severe human diseases, including Xeroderma pigmentosum, that result from hereditary defects of NER proteins. The NER genes recognize and repair bulky DNA damage caused by environmental carcinogens, ultraviolet light and chemotherapeutic agents such as platinum compounds (Fig. 2.10). Defects in NER proteins predispose to various types of cancer, including skin cancer in Xeroderma pigmentosum (59).

There are two NER pathways: one global pathway involved in scanning the entire genome and another that detects lesions that interfere with elongating RNA polymerases. The proteins required for NER assemble in an ordered stepwise fashion at sites of base damage. This assembly generates a large multiprotein complex namely the “repairosome.” This repair complex can nick the DNA at precise distances on either side of the base damage and these gaps are repaired using the opposite normal DNA strand as a template. There are several proteins involved in NER process including ERCC1, RPA, RAD23A, RAD23B, XPA, XPB, XPC, XPD, XPE, XPF, XPG, CSA, and CSB. *BRCA1* may also play a role in NER. ERCC1 expression may be a marker of cisplatin resistance in cervical cancer, with low expression predicting superior 5-year disease free survival (60).

BER is closely related to NER in that both repair lesions in DNA bases (Fig. 2.10). BER involves repair of small lesions due

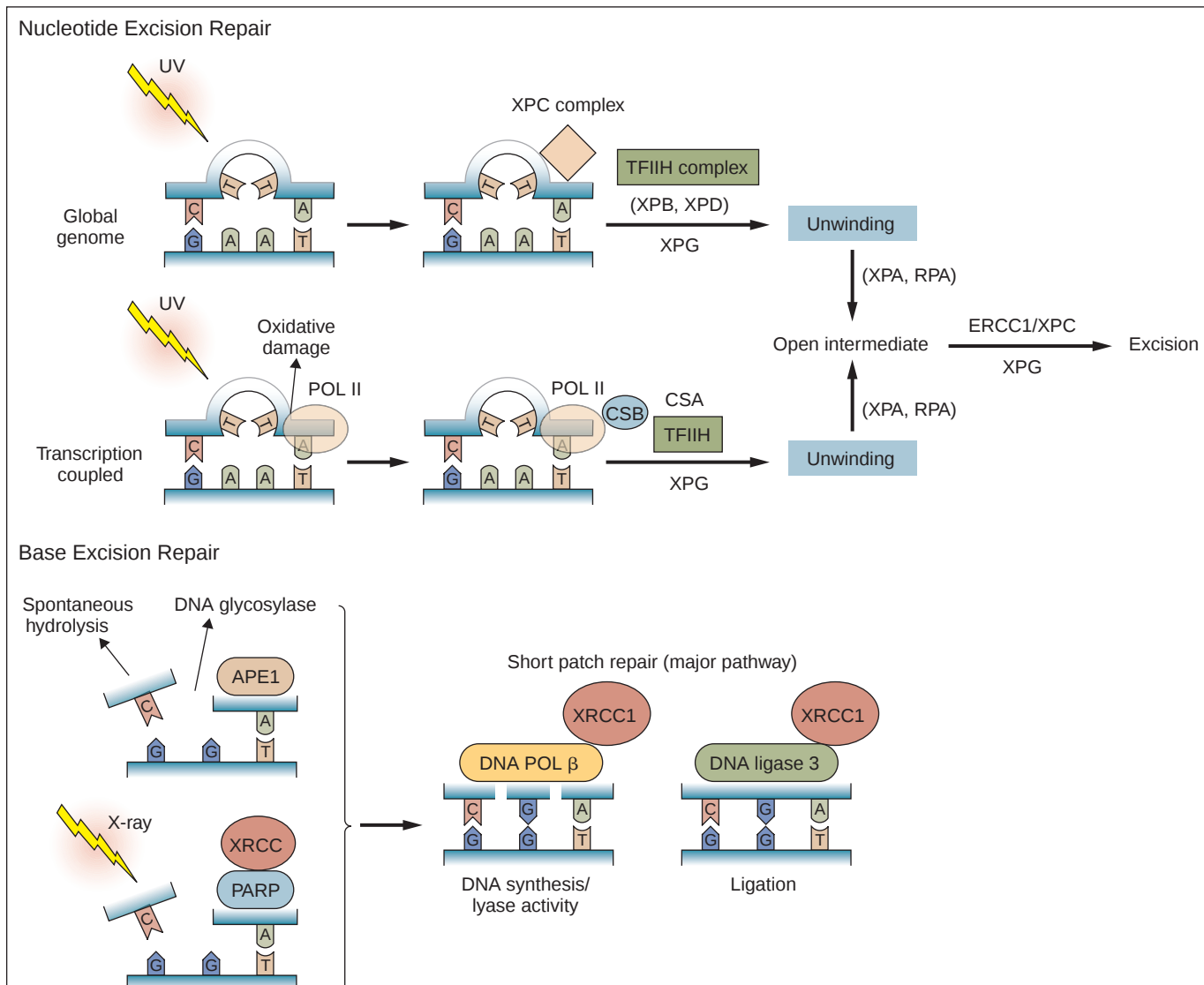


FIGURE 2.10. Nucleotide excision repair and base excision repair: Nucleotide excision repair is activated in response to bulky lesions that are generated, for example, by UV irradiation (upper panels). Global genome repair involves proteins identified by complementation groups in patients with xeroderma pigmentosa (XP proteins). Initial recognition of lesions occurs by a complex containing xeroderma pigmentosa C. Transcription coupled repair also involves proteins identified by mutation in Cockayne syndrome (CS proteins), and occurs when RNA polymerase II stalls at the site of lesions. Stalled RNA polymerase II recruits Cockayne syndrome B to the site of damage. Subsequently, DNA is locally unwound around the injured site by a TFIIH complex containing XPB and XPD. This process also involves XPG, CSA, and other proteins for TCR. Once unwound, XPA and replication protein A contribute to stabilization of an open intermediate and recruitment of the ERCC1 and XPF endonucleases that excise the lesion. Subsequent steps involve DNA synthesis and ligation to complete the repair. In BER (lower panels), abasic sites generated by spontaneous hydrolysis, action of DNA glycosylases, or X-ray-induced single-strand breaks are recognized by the APE1 endonuclease, as well as PARP and XRCC1. Subsequent repair is influenced by PARP-mediated ADP ribosylation of histones and other proteins, while XRCC1 serves as a scaffold for recruitment of DNA polymerase β and DNA ligase 3. These latter enzymes catalyze nucleotide reinsertion and ligation into the injured strand as part of the short patch repair pathway (major BER pathway).

to chemicals and X-rays that do not distort the DNA helix. Single bases in DNA can be damaged by several mechanisms, the most common being deamination, oxidation, and alkylation. BER is initiated by DNA glycosylases that recognize a single or small set of altered or inappropriate bases. BER removes damaged bases that could otherwise cause mutations by mispairing or lead to breaks in DNA during replication. The BER system excises the inappropriate base from the genome as a free base, leaving a site of base loss in the DNA. These sites are further repaired and reconstructed by a series of biochemical events.

Deletion of BER genes increases mutation rates and contributes to the development of various cancers. In this regard, somatic mutations in the DNA polymerase Pol β have been found in some human cancers (61). Mutations in POLE have been found by TCGA in a subset of endometrial cancers with the highest mutation rates. Inherited mutations in the DNA glycosylase MUTYH increase susceptibility to colon cancer (62).

Double Strand Break Repair: Homologous Recombination (HR) Repair and Nonhomologous End Joining (NHEJ)

Double stranded DNA damage can be caused by exogenous factors such as ionizing radiation, ultraviolet rays, alkylating agents, chemotherapeutic drugs or by endogenous factors such as reactive oxygen species or errors in cellular DNA metabolism. Following double stranded DNA damage the ATM (Ataxia telangiectasia mutated) and ATR kinases phosphorylate several proteins including CHK1 and CHK2 that initiate cell cycle arrest by way of p53 and this leads to DNA repair that restores genomic integrity or to apoptosis if DNA repair is inadequate (63).

Homologous recombination (HR) is a process that provides high-fidelity, template dependent repair of complex DNA damage such as DNA cross-links, double strand breaks, single strand DNA

gaps and DNA interstrand cross-links (Fig. 2.11) (55,64). The HR pathway involves the following basic steps. Double stranded breaks are recognized by the MRN complex and checkpoint proteins. A 5'-3' exonuclease generates 3' overhangs, which are then coated with replication protein A (RPA). *BRCA1-BRCA2-RAD51* forms a stable complex, (65) and potentiates HR by promoting assembly of RAD51 onto single the stranded ends. A homology search ensues, followed by strand invasion and DNA synthesis. The links between DNA strands (double Holliday junctions) can be resolved to produce exchange between chromosomes (crossovers) or no exchange (noncrossovers). This is a precise repair mechanism that restores the original sequence. If double stranded breaks are not repaired precisely, this can cause deletions, translocations, and fusions in the DNA, producing genomic rearrangements.

Fanconi anemia is an inherited disease characterized hypersensitivity to DNA cross-linking agents and predisposition to cancer. There are over a dozen genes in the Fanconi anemia pathway that cooperate in HR repair of DNA cross-links. Mutations of several of these, including *BRCA1* and *BRCA2*, increase the risk of breast and ovarian cancer. Inherited mutations in other genes involved in HR are associated with predisposition to these cancers, including *RAD51C* (66) and *RAD51D* (67). The relative risk of ovarian cancer for *RAD51D* mutation carriers was estimated to be 6.30. *PALB2* plays a critical role in HR repair through its ability to recruit *BRCA2* and *RAD51* to DNA breaks. This serves as the molecular scaffold in the formation of the *BRCA1-PALB2-BRCA2* complex. *PALB2* confers breast cancer susceptibility and may also play a role in ovarian cancer susceptibility (68). The *BRIP1* gene is involved in the repair of DNA double-strand breaks by HR in a manner that depends on its association with *BRCA1* and rare germline mutations are estimated to increase ovarian cancer risk by about eightfold (69).

DNA double strand breaks may also be repaired through a nonhomologous end joining (NHEJ) repair mechanism, wherein the break ends are directly ligated without the need for a homologous template (Fig. 2.11). Proteins associated with NHEJ include DNA-PKcs, MRE11, RAD50, XRCC4, and DNA ligase IV.

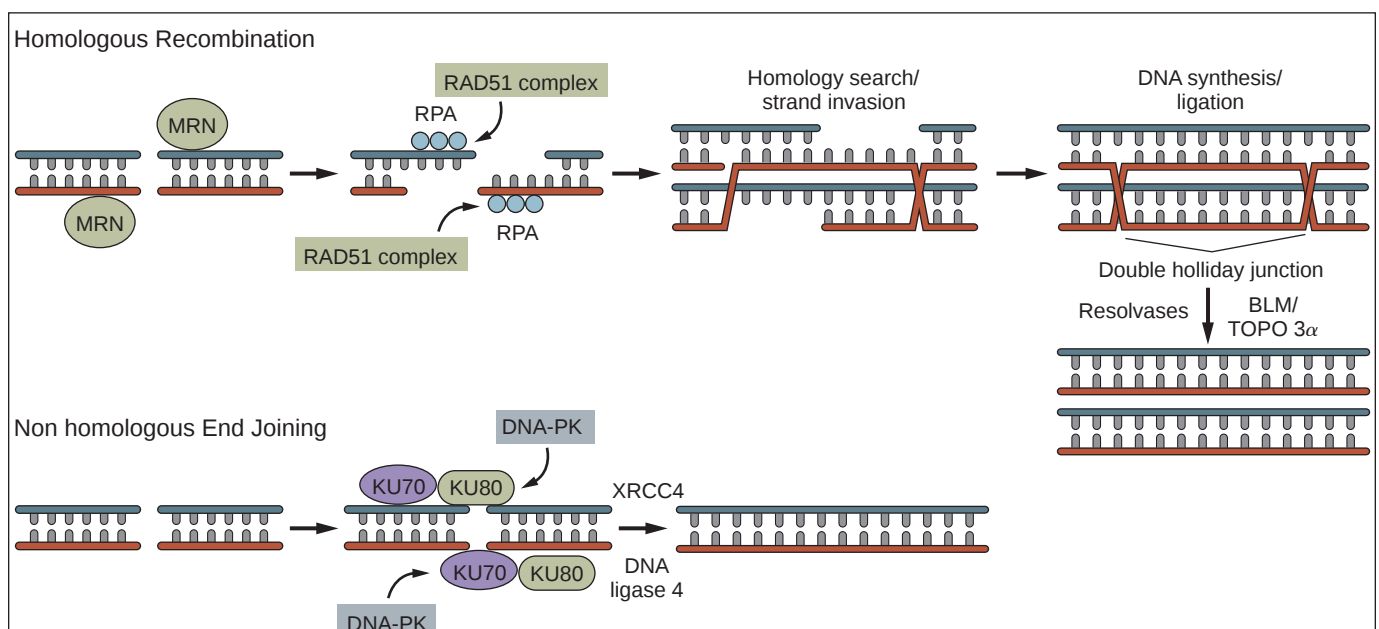


FIGURE 2.11. Double-strand break repair by homologous recombination and nonhomologous end-joining. In homologous recombination (HR), DSBs are recognized by the MRN (Mre11, Rad50, and Nbs1) complex, among other proteins. 5'-3' exonuclease activity results in the generation of single-strand overhangs that are coated with RPA. Mediator proteins such as *BRCA2* and *RAD52* stimulate assembly of a *RAD51* nucleoprotein filament complex that guides subsequent homology search and strand invasion into the homologous strand (e.g., the identical sister chromatid in late S/G2 phase and mitosis). Subsequent DNA synthesis and ligation results in the formation of recombination intermediates that contain double Holliday junctions. These are resolved by resolving enzymes such as the RecQ helicase BLM, in conjunction with topoisomerase 3α. The process of NHEJ involves recognition of DSB ends by the Ku70-Ku80 heterodimer; with subsequent recruitment of DNA-dependent protein kinase. DNA ends are then ligated following recruitment of XRCC4 and DNA ligase 4.

GYNECOLOGIC MALIGNANCIES

Gynecologic cancers vary with respect to grade, histology, stage, response to treatment and survival. It is now appreciated that this clinical heterogeneity is attributable to differences in underlying molecular pathogenesis. Some cancers arise in a setting of inherited mutations in cancer susceptibility genes, but most occur sporadically in the absence of a strong hereditary predisposition. The spectrum of genes that are mutated varies between cancer types. For each type of cancer, there are a few genes that are frequently mutated, while a wider spectrum are altered in a small fraction of cases (70). There also is significant variety with respect to the spectrum of genetic changes within a given type of cancer. Cancers with a similar microscopic appearance may differ considerably at the molecular level. In some instances, molecular features may be predictive of clinical phenotypes such as stage, histologic type, and survival. An understanding of the clinical phenotypes associated with various genetic alterations in gynecologic cancers has the potential to inform prognosis and prediction of response to therapy.

ENDOMETRIAL CANCER

Etiology

Epidemiologic and clinical studies of endometrial cancer have suggested that there are two distinct types of endometrial cancer (71). “Type I” cases are associated with unopposed estrogen stimulation and often develop in a background of endometrial hyperplasia. Obesity is the most common cause of unopposed estrogen and is part of a metabolic syndrome that also includes insulin resistance and overexpression of insulin-like growth factors that may also play a role in carcinogenesis. Type I cancers typically are well differentiated, endometrioid, early stage lesions and have a favorable outcome. In contrast, “Type II” cancers are poorly differentiated and/or nonendometrioid and are more virulent. The prototype Type II tumor is serous but other histologic subtypes such as clear cell and carcinosarcoma are generally included. They often present at an advanced stage and survival is relatively poor. In practice, not all endometrial cancers can be neatly characterized as either type I or type II. However, as the genetic events involved in the development of endometrial cancer have been elucidated, it has been found that alterations often, but not always, are seen primarily in either type I or II cases (72) (Table 2.3).

Similar to other human cancers, endometrial cancers are believed to arise due to a series of genetic alterations. For Type I tumors, it has long been thought that estrogens contribute to the development of endometrial cancer by virtue of their mitogenic effect on the endometrium. A higher rate of proliferation in response to estrogens may lead to an increased frequency of spontaneous mutations. In addition, when genetic damage occurs, regardless of the cause, the presence of estrogens may facilitate clonal expansion. It also has been postulated that estrogens may act as “complete carcinogens” that both promote carcinogenesis by stimulating proliferation and act as initiating agents by virtue of their carcinogenic metabolites. Unopposed menopausal estrogen replacement therapy was reported in the 1970s to increase the risk of endometrial cancer by four- to five-fold. Estrogen has been listed as a known carcinogen by the U.S. Department of Health and Human Services since 1985. In contrast, progestins oppose the action of estrogens both by down

Table 2.3 Characteristics of Type I versus Type 2 Endometrial Adenocarcinomas

	Type 1	Type 2
<i>Clinical features</i>		
Risk factors	Obesity, unopposed estrogen	Older age
Race	White > Black	White = Black
Precursor	Atypical endometrial hyperplasia	none or <i>in situ</i> carcinoma
Histology	Endometrioid	Serous/clear cell
Grade	1, 2	3
Stage	I/II	III/IV
Survival	Favorable	Poor
<i>Molecular features^a</i>		
Ploidy	Diploid	Aneuploid
MSI	35%	Rare
<i>Tumor-suppressor genes</i>		
TP53 mutation	15%	90%
HER-2/ <i>neu</i> amplification	Rare	30%
FBXW7 mutation	10%	30%
PPP2R1A mutation	Rare	25%
ARID1A mutation	40%	10%
PTEN mutation	80%	Rare
MLH1 methylation	35%	None
POLE mutation	10%	Rare
CTCF mutation	25%	None
<i>Oncogenes</i>		
MYC amplification	Rare	25%
FGFR2 mutation	15%	10%
PIK3CA mutation	55%	40%
PIK3R1 mutation	40%	Rare
CTNNB1 (β -catenin) mutation	40%	None
KRAS mutation	25%	Rare

^aMutation frequencies obtained from TCGA data.

regulating estrogen receptor levels and by decreasing proliferation and increasing apoptosis.

Lynch Syndrome and Microsatellite Instability

About 3% of endometrial cancers occur in women with a strong hereditary predisposition due to germline mutations in DNA mismatch repair genes in the context of Lynch syndrome. First described by Henry Lynch, this syndrome commonly includes malignancies of the colon, endometrium, stomach, and ovary (57). Less frequent malignancies that are part of this syndrome include those arising in the small bowel, upper urinary tract,

brain, and biliary tract. Colorectal cancer is the most common malignancy in Lynch syndrome, which also is sometimes called hereditary non-polyposis colorectal cancer syndrome (HNPCC). The lifetime cancer risks in Lynch syndrome are about 70% for colon cancer, 40% for endometrial cancer, and 10% for ovarian cancer (Lynch syndrome is covered in more detail in Chapter 3).

Lynch syndrome is caused by inherited germline mutations in one of several DNA mismatch repair (MMR) genes—*MLH1*, *MSH2*, and less often *MSH6*, *MSH3*, *PMS1*, and *PMS2*. These defects lead to faulty DNA repair and increased risk of malignancy (57). A hallmark of MMR deficiency is microsatellite instability. Microsatellites are short repetitive regions of DNA that become unstable during replication in the setting of defective MMR. In addition to germline mutations in the MMR genes, epigenetic silencing through promoter methylation, specifically in *MLH1*, is the most common mechanism of microsatellite instability in endometrial cancer (73,74). Methylation of *MLH1* is not a heritable condition associated with Lynch syndrome. Microsatellite instability is found in up to 35% of endometrial carcinomas and is generally restricted to Type I cases (75,76). Methylation of the *MLH1* promoter also has been noted in endometrial hyperplasias (76,77) and normal endometrium adjacent to cancers, suggesting that this is an early event in the development of some of these cancers (78). The clinical significance of microsatellite instability is unclear, but it may be associated with a more or less favorable outcome.

The Cancer Genome Atlas Project (TCGA)

In 2006, TCGA began with studies in glioblastoma and high-grade serous ovarian cancer. The TCGA pilot project confirmed that an atlas of changes could be created for specific cancer types. It also showed that a national network of research and technology teams working on distinct but related projects could pool the results of their efforts, create an economy of scale, and develop an infrastructure for making the data publicly accessible (<http://cancergenome.nih.gov>). The National Institutes of Health has committed major resources to TCGA to collect and characterize more than 20 cancer types. The ovarian cancer project is complete and is discussed below. The endometrial cancer project is nearing completion as this chapter is being written and will be discussed in this section. Each cancer undergoes comprehensive genomic characterization and analysis. The comprehensive data generated by TCGA are available and widely used by the cancer research community through the TCGA Data Portal. The analyses include sequencing of the entire coding regions of each cancer. Additionally, levels of gene expression, including mRNA and microRNA, are measured either through microarray based platforms or using second generation sequencing techniques to sequence the RNA transcriptome. Copy number alterations and methylation events are also assessed through microarray platforms. Some cancers are also hybridized to reverse phase protein arrays when sufficient biomaterial is available.

Inherent in the design of the TCGA program are methodological aspects to be considered when interpreting the data. Only serous and endometrioid subtypes were accrued in the endometrial cancer project. Furthermore, most of the frozen tumor specimens used were collected and banked previously. Thus, larger tumors undoubtedly are overrepresented, because smaller ones are less likely to be banked. There is also an overrepresentation of serous and high grade endometrioid cancers, with underrepresentation of the more common low-grade cancers. This was to assure adequate numbers of the former groups.

TCGA has reclassified endometrioid and serous endometrial cancers in four broad categories using comprehensive genomic approaches (79). One-third of the cancers are characterized by

microsatellite instability (MI) and associated hypermutation. These cancers have a background mutation rate (BMR) that is approximately ten-fold greater than non-MI tumors. These tumors are exclusively Type I endometrioid and have few DNA copy number alterations. The cancers without MI can be further separated into two groups. Serous cases with extensive DNA copy number alterations and genomic instability (similar to that seen in high-grade serous ovarian carcinoma) constitute one group, and endometrioid cases with few or only focal copy number alterations constitute the other. A smaller fourth subgroup contains samples with very high mutation rates (~100-fold or greater than MSS tumors) and is characterized by mutations in *POLE*, a DNA polymerase involved with repairing errors in transcription. Molecular features can be distinctly overlaid onto these four subclassifications and are discussed below.

DNA Copy Number

Early cytogenetic studies described gross chromosomal alterations in endometrial cancers, including changes in the number of copies of specific chromosomes (80). Comparative genomic hybridization studies have also demonstrated areas of chromosomal loss and gain in both endometrial cancers and atypical hyperplasias (81,82). Uterine serous carcinomas are aneuploid and have copy number alterations in nearly every chromosomal arm across the genome. The copy number alterations are similar to those seen in high-grade serous ovarian carcinoma. However, as discussed below, the mutation spectrum of uterine and ovarian serous cancers differs considerably. Endometrioid endometrial cancers with MI have few copy number alterations. The endometrioid cases lacking MI have some focal copy number alterations and can be subdivided into a group with absolutely no copy number alterations and a second group with focal copy number alterations. A subset of samples also has amplification of chromosome 1q. A more global and specific approach, called GISTIC, can be used to identify recurrent focal copy number alterations. TCGA data suggests that this approach identifies approximately 81 focal copy number events including 38 amplifications and 43 deletions (79). Amplifications occur in many oncogenes, including *KRAS*, *PIK3CA*, *PAX8*, *ESR1*, *MYC*, *FGFR1*, *FGFR3*, *ERBB2*, *ERBB3*, and *CCNE1*. Deletions occur in tumor suppressors, including *PTEN*, *RB1*, *NF1*, *WWOX*, and *PARK2*.

Gene Expression

Microarray analysis and other techniques have been developed that allow analysis of mRNA expression of thousands of genes in a tissue sample. Patterns of gene expression have been described using microarrays that distinguish between normal and malignant endometrium and between various histologic types of cancer (83–85). Global gene expression profiles associated with both lymph node metastasis (86) and recurrence (87) also have been identified in endometrial cancer.

TCGA identified three gene expression subtypes in endometrial cancer (79). One subtype contained most of the uterine serous cases and some grade 3 cases thought to be serous-like. One subtype was enriched for hormonally responsive genes and had higher expression of *ESR1* (estrogen receptor) and *PGR* (progesterone receptor). The third subtype was enriched for genes involved in immune regulation. Though these subgroups were associated with clinical outcome, at present it is unclear if they are independent of other known prognostic factors such as stage, grade, and histology. Studies to validate these biomarker panels and molecular-based prediction models are ongoing. These findings will further increase our understanding of the molecular pathogenesis of endometrial cancer and may help predict clinical phenotypes.

Tumor-Suppressor Gene Alterations

TP53

Inactivation of the *TP53* tumor suppressor gene is among the most frequent genetic events in endometrial cancers (46). *TP53* mutation occurs in about 20% to 30% of all endometrial adenocarcinomas and is associated with several known prognostic factors including advanced stage, poor grade, and nonendometrioid histology (88,89). *TP53* missense mutations are more common (~75%) and generally result in overexpression and accumulation of mutant p53 protein, whereas *TP53* truncating mutations (~25%; nonsense and frameshift) result in complete absence of p53 protein. Endometrial cancers that overexpress p53 protein usually harbor missense mutations in exons 5 through 8 of the gene that result in amino acid substitutions in the protein (Fig. 2.12) (88,90–93). These mutations lead to loss of DNA binding activity. Hotspots or areas of very frequent mutation exist at codons 248 and 273. Numerous studies have confirmed the strong association between p53 overexpression and poor prognostic factors and decreased survival (94–98). This is predominantly due to the disproportional frequency of *TP53* mutations in serous and high-grade endometrioid cancers. Nearly 90% of uterine serous carcinomas have *TP53* mutations as do one-third of high-grade endometrioid cases (79). Lower *TP53* mutation frequencies are seen in grade 2 (~10%) and grade 1 (~5%) endometrioid cases.

Although little is known regarding molecular alterations in uterine sarcomas, overexpression of mutant *TP53* occurs in a majority of mixed mesodermal sarcomas of the uterus (74%) and in some leiomyosarcomas (99,100).

PTEN

The *PTEN* tumor suppressor gene encodes a phosphatase that opposes the activity of cellular kinases that stimulate proliferation. *PTEN* is the most commonly mutated gene in endometrial carcinomas (101–103). Deletion of both copies of the gene had previously been thought to be a frequent event, resulting

in complete loss of *PTEN* function. However, the TCGA data suggest that homozygous deletion and mutation infrequently co-occur, as would be expected mechanistically, and homozygous deletion in the absence of mutation is also uncommon (79). More recent data suggest that single copy loss of *PTEN* is uncommon, and most tumors are diploid at this locus. *PTEN* mutations may be deletions, insertions, and nonsense mutations throughout the gene that lead to truncated protein products. In addition, missense mutations in the phosphatase domain can also inactivate *PTEN* function (Fig. 2.13). Loss of *PTEN* in endometrial cancers is associated with increased activity of the PI3 kinase with resultant phosphorylation of its downstream substrate AKT (104). The *PTEN*/AKT pathway is frequently activated in many solid tumors and endometrial cancer appears to be the tumor type with the greatest pathway activation.

Mutations in the *PTEN* gene are associated with endometrioid histology, early stage, and favorable clinical behavior (105). Well-differentiated, noninvasive cases have the highest frequency of mutations. In grade 1 and 2 endometrioid cancers, *PTEN* mutations are found in more than 80% of cases when second generation sequencing is performed. *PTEN* mutations are virtually nonexistent in serous cases with an estimated frequency of 2% to 3%. In addition, *PTEN* mutations have been observed in 20% of endometrial hyperplasias, suggesting that this is an early event in the development of some endometrioid “Type I” endometrial cancers (106). It has been reported that loss of *PTEN* may occur in normal appearing endometrial glands, and it is proposed that this may represent the earliest event in endometrial carcinogenesis (107,108).

Other Mutated Tumor Suppressor Genes

TP53 and *PTEN* were both found to be significantly mutated genes (SMG) in the TCGA project, as evidence by a statistically increased mutation rate compared with an expected base-line mutation rate (BMR) when corrected for the size of the coding region (79). Other noteworthy SMGs in endometrial cancer include *FBXW7*, *ARID1A*, and *PPP2R1A*.

FBXW7 (CDC4) mediates ubiquitin-dependent proteolysis of phosphorylation-dependent ubiquitination and ubiquitin-mediated degradation of *CCNE1* and other putative oncogenes. *FBXW7* has also been reported to regulate *mTOR* signaling and depletion of *FBXW7* results in increased levels of both *mTOR* and phospho-*mTOR*. Data from TCGA and other studies suggests that *FBXW7* is mutated in a substantial fraction (~30%) of uterine serous carcinomas.

ARID1A is a large nuclear protein that participates in chromatin remodeling. It was first reported to be mutated in ovarian endometrioid and clear cell tumors, and subsequently was found to be mutated in approximately 40% of endometrioid endometrial carcinomas. Recent functional studies have demonstrated that *ARID1A* is a tumor suppressor with the ability to inhibit tumor growth.

PPP2R1A is the constant regulatory subunit of the protein phosphatase 2A, a serine threonine/phosphatase, and functions in control of cell growth and division. It is mutated in 20% to 30% of uterine serous carcinomas, but not in ovarian serous carcinomas. *PPP2R1A* mutations are seen in uterine endometrioid tumors at relatively low frequency.

CTCF is a transcription factor that functions as a negative regulator of both *MYC* and *IGF2* suggesting a role as a tumor suppressor. TCGA found *CTCF* to be mutated in nearly 25% of endometrioid cancers, but mutations were not seen in serous cases. These findings suggest varied regulation of *MYC* with direct amplification occurring in serous tumors and loss of inhibition through *CTCF* mutation occurring in endometrioid tumors.

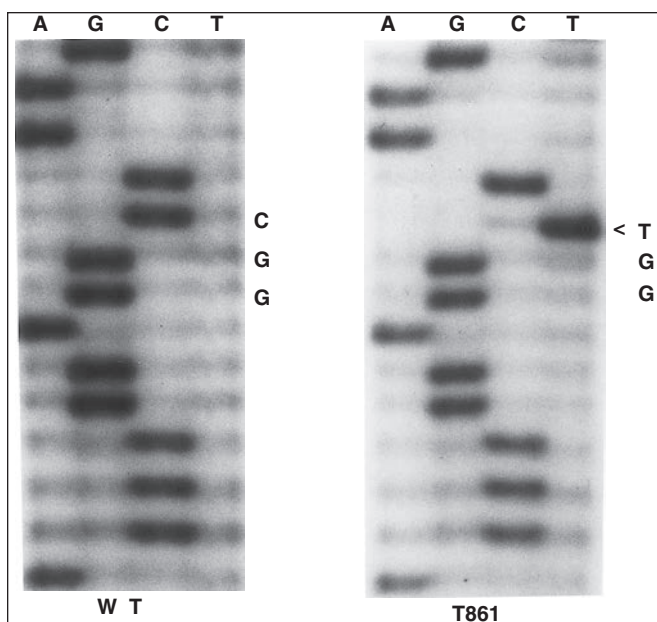


FIGURE 2.12. Mutation of the p53 gene. Endometrial cancer T861 has a missense mutation in codon 248 of the p53 gene that changes the sequence from CGG to TGG and results in the substitution of tryptophan for arginine. On the left is the normal wild-type (WT) sequence.

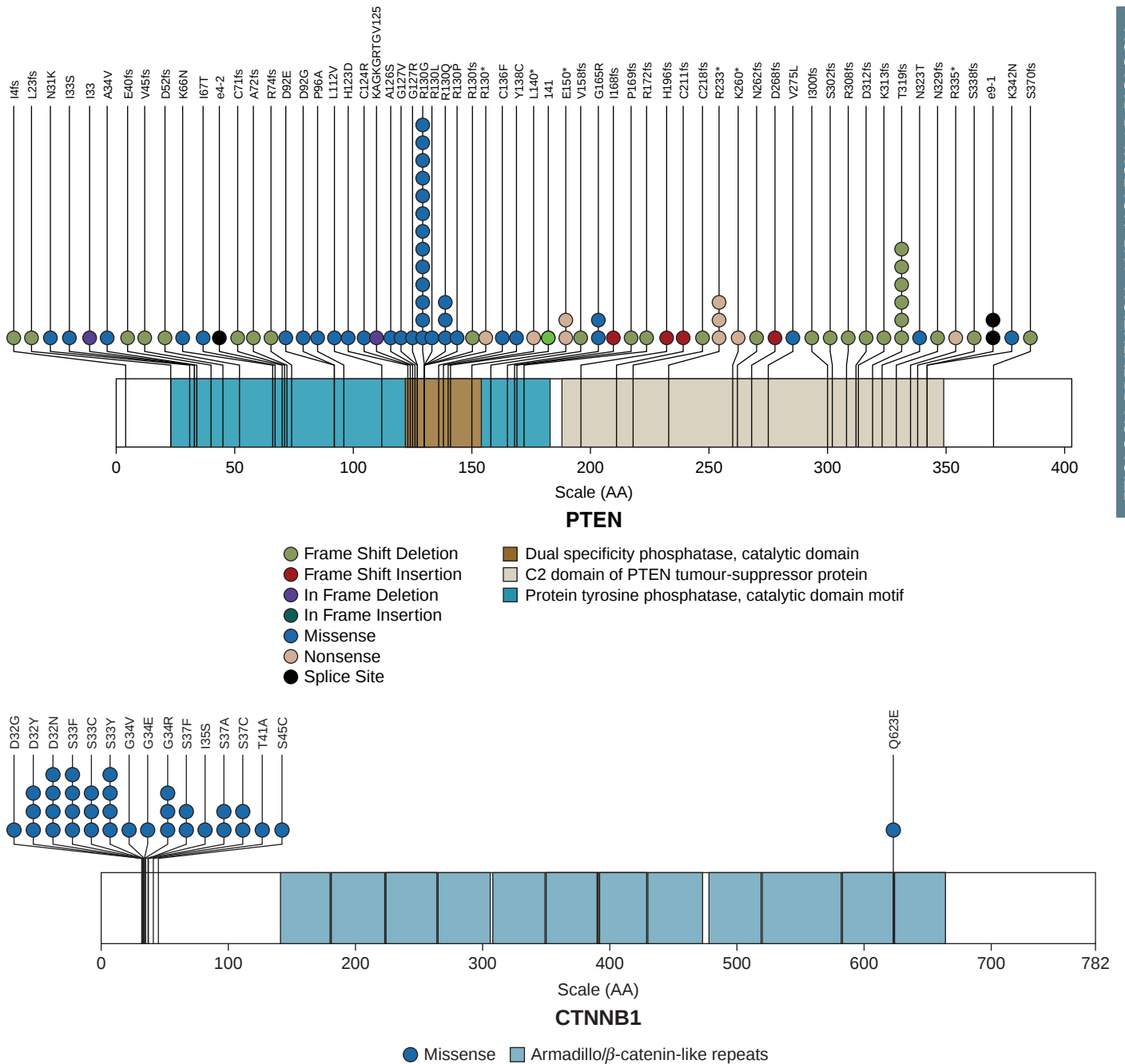


FIGURE 2.13. Mutational spectrum of the *PTEN* tumor-suppressor gene and *CTNNB1* (β -catenin) oncogene in 68 well differentiated nonhypermutated endometrial cancers from TCGA. Mutations in the *PTEN* tumor suppressor occur throughout the gene, whereas those in the *CTNNB1* oncogene are missense changes in critical amino acids that result in increased activity.

Source: Figures provided by Cyriac Kandoth and Li Ding, The Genome Institute, Washington University, St. Louis, MO.

Oncogene Alterations

ERBB2 (*HER-2/neu*)

Alterations in oncogenes have been demonstrated in endometrial cancers, but this occurs less frequently than inactivation of tumor suppressor genes (Table 2.3). Increased expression of the *HER-2/neu* receptor tyrosine kinase initially was noted in 10% of endometrial cancers (97,109,110) and was associated with advanced stage and poor outcome. Recently, it has been suggested that *HER-2/neu* overexpression may be more prevalent in patients with serous endometrial cancers (111–113). In a tissue microarray study of 483 endometrial cancers using immunohistochemical

analysis and fluorescent *in situ*-hybridization (FISH), the highest rate of *HER-2/neu* overexpression and amplification was found in serous carcinomas (43% and 29%), while this was much less frequent in grade 1 endometrioid adenocarcinomas (3% and 1%) (113).

TCGA data indicates that *HER-2/neu* is mutated in ~3% of endometrial tumors (79), but these are generally restricted to the hypermutated samples with microsatellite instability, and thus the significance of these somatic mutations is unclear. However, the gene is amplified in ~25% of uterine serous carcinomas and only ~1% of endometrioid tumors confirming a strong association with histologic subtype. These data also suggest that therapies that target *HER-2/neu* may have a role in the treatment of

uterine serous carcinomas. The levels of *HER-2/neu* overexpression in endometrial cancers are much less striking than in breast cancers. With rare exception, trastuzumab (anti *HER-2/neu* antibody) generally has not been a useful therapy in endometrial cancer. The GOG studied trastuzumab in advanced or recurrent *HER-2/neu*-amplified endometrial cancers. This study confirmed a higher rate of overexpression in serous tumors (28%) than endometrioid tumors (7%). However, there were no major responses to therapy (114).

KRAS

The *RAS* oncogenes undergo point mutations in codons 12, 13, or 61 that result in constitutively activated molecules in many types of cancers. Initially, these codons of the *KRAS*, *HRAS*, and *NRAS* genes were examined in 11 endometrial cancer cell lines (115). Mutations in codon 12 of *KRAS* were seen in four cell lines and three had mutations in codon 61 of *HRAS*. Subsequent studies of primary endometrial adenocarcinomas confirmed that codon 12 of *KRAS* were mutated in about 10% of American cases and 20% of Japanese cases (90,116–118).

TCGA data indicates that *KRAS* is mutated in ~25% of endometrioid cases and rarely in serous cases (79). There is a greater frequency of *KRAS* mutations among the hypermutator endometrioid cases (35%) than the nonhypermutator endometrioid cases (15%). *KRAS* mutations also have been identified in some endometrial hyperplasias (118)–(120), which suggests that this may be a relatively early event in the development of some Type I cancers.

PI3K

The *PTEN* tumor suppressor gene, which negatively regulates PI3K activity, is frequently mutated in Type I endometrial cancers. Conversely, the *PIK3CA* gene is oncogenically activated in some cases. The catalytic subunit of PI3K (*PIK3CA*) is located on chromosome 3q26.3 and activating mutations in this gene have been described in numerous cancer types. The p85- α regulatory subunit of PI3K (*PIK3R1*) has also been reported to be mutated in several cancer types and the p85- β regulatory subunit of PI3K (*PIK3R2*) is mutated, although much less frequently, often in the setting of microsatellite instability.

In an initial study, *PIK3CA* mutations were seen in 36% of endometrial cancers, and 24% of cases had mutations in both *PTEN* and *PIK3CA* (121). In a subsequent study, 39% of endometrial cancers and 7% of atypical endometrial hyperplasias were found to harbor mutations in *PIK3C* (122), implying that *PIK3CA* mutation occur early in tumorigenesis. As in the initial study, a high fraction of cases had co-mutation in both *PTEN* and *PIK3CA*. These and other studies (123) confirm that *PIK3CA* activating mutations occur in both serous and endometrioid endometrial cancers.

TCGA identified *PIK3CA* mutations in ~50% of both serous and endometrioid tumors (79), however *PIK3R1* mutations were generally restricted to endometrioid cases; occurring in ~40%. It has been suggested that one mechanism by which *PIK3R1* mutations are oncogenic is through the disruption of p85- α dimers that stabilize *PTEN* (124). Both inactivation of *PTEN* or activation of *PIK3CA* can lead to activation of *AKT*, which in turn leads to up-regulation of the mTOR. Recent studies have suggested that inhibitors of the *AKT*/mTOR pathway may have a role in the management of endometrial cancer (40,125). Evidence of partial responses and disease stability have been noted with the mTOR inhibitor Temsirolimus (126) and in another study response to agents targeting this pathway was enhanced by selection of patients with *PIK3CA* mutations (42).

CTNNB1 (β -catenin)

Alterations in the WNT pathway involving *E-cadherin*, *APC* and β -catenin (*CTNNB1*) have been noted in endometrial cancers. *E-cadherin* is a transmembrane glycoprotein involved in cell-cell adhesion and decreased expression in cancer cells is associated with increased invasiveness and metastatic potential. *E-cadherin* mutations do not occur in uterine serous cancers (127), but occur somewhat more commonly (~7%) in endometrioid tumors with some predisposition to those cases with microsatellite instability. *E-cadherin* expression may also be down regulated in the absence of mutations (128,129). The cytoplasmic tail of *E-cadherin* exists as a macromolecular complex with the β -catenin and *APC* gene products, which link it to the cytoskeleton. It appears that a critical function of the *APC* tumor suppressor gene is to regulate *GSK3B* phosphorylation of serine and threonine residues (codons 33, 37, 41, 45) in exon 3 of β -catenin, which results in degradation of β -catenin. Mutational inactivation of *APC* allows accumulation of β -catenin, which translocates to the nucleus and acts as a transcription factor to induce expression of cyclin D1 and perhaps other genes involved in cell cycle progression (129).

Germline *APC* mutations are responsible for the adenomatous polyposis coli syndrome and somatic mutations are common in sporadic colon cancers; but *APC* mutations had not been previously described in endometrial cancers (130,131). TCGA has identified *APC* gene mutations but these are mostly restricted to hypermutator cases and may be passengers rather than driver mutations. The *APC* gene may be inactivated in some endometrial cancers due to promoter methylation.

It has been shown that missense mutations in exon 3 of β -catenin lead to the same end result—namely abrogation of the ability of *APC* and *GSK3B* to induce β -catenin degradation—which results in nuclear localization and increased transcriptional activity (132). β -catenin mutations have been observed in several types of cancers including hepatocellular, prostate, colon and endometrial cancers (Fig. 2.13). Nuclear accumulation of β -catenin protein due to mutation of the gene has been reported in about one-third of endometrioid endometrial cancers (131,133). Mutation of β -catenin has not been observed in uterine serous carcinomas. However, TCGA data indicate that the mutational frequency is ~50% in the microsatellite stable/non-hypermutator endometrioid cancers and only 15% to 20% in the MI/hypermutator cases (Fig. 2.13, Table 2.3), suggesting that this is an important driver mutation in cases without MI (79).

FGFR2

Mutations have also been observed in the fibroblast growth factor receptor 2 (*FGFR2*) gene in about 10% of endometrial cancers (134). In TCGA, *FGFR2* mutations were found more commonly in endometrioid cancers, with a slight predilection for MI cases. A recent report indicates that *FGFR2* and *KRAS* mutations occur in a near mutually exclusive pattern. *FGFR2* mutations were found to be associated with a worse outcome among early stage endometrioid tumors (135). Further studies are needed to evaluate the significance of the identified mutations, as well as the potential clinical utility of drugs targeting the receptor (136). A number of agents that target FGF receptors are under development.

Other Oncogenes

Among nuclear transcription factors involved in stimulating proliferation, amplification of members of the *MYC* family have most often been implicated in the development of human cancers. It has been shown that *MYC* is expressed in normal endometrium (137) with higher expression in the proliferative phase. Several studies have suggested that *MYC* may be

amplified in a fraction of endometrial cancers (138,139). TCGA has identified a low frequency of somatic mutations in *MYC*, but 25% of uterine serous cancers have high-level amplification of the gene (79).

OVARIAN CANCER

Etiology

About 10% of ovarian cancers have a strong hereditary component and arise in women who carry germline mutations in cancer susceptibility genes—predominantly *BRCA1* or *BRCA2* (140). The vast majority of ovarian cancer is sporadic and arises due to accumulation of somatic genetic damage. The causes of acquired genetic alterations remain uncertain, but exogenous carcinogens have not been strongly implicated. Cellular proliferation and oxidative stress with free radical formation with associated inflammation at the time of ovulation or in association with endometriosis or infection may also contribute to accumulation of DNA damage. Regardless of the molecular mechanisms involved, reproductive events that decrease lifetime ovulatory cycles (e.g., pregnancy and birth control pills) are protective against ovarian cancer (see chapter 1) (141). The progestagenic milieu of pregnancy and the pill might also protect against ovarian cancer by increasing apoptosis of cells that have acquired genetic damage (142). The action of other reproductive hormones such as estrogens, androgens and gonadotropins also may contribute to the development of ovarian cancers.

Epithelial ovarian cancers are heterogeneous with respect to behavior (borderline vs. invasive), grade and histologic type. It has become increasingly clear that there are striking differences in the molecular pathogenesis of various disease subsets. It has been proposed that ovarian cancers can be classified as Type I or II based on histology, grade, stage, and molecular alterations (Table 2.3) (143). Type I tumors are generally confined to an ovarian mass at diagnosis, and include low-grade serous, mucinous, and most endometrioid and clear cell carcinomas. They are genetically stable and are characterized by mutations in a number of genes including *KRAS*, *BRAF*, *PTEN*, *CTNNB1*, *ARID1A*, and *PPP2R1A*. Type 2, cancers typically present at an advanced stage and are predominantly high-grade serous lesions, but also include high-grade endometrioid, carcinosarcoma, and undifferentiated cancers. This group of tumors has a high level of genetic instability with frequent chromosomal gains and losses and is characterized by *TP53* and *BRCA1/2* mutations.

There is now strong evidence to suggest that all epithelial ovarian cancers have an extraovarian origin (143). High-grade serous cancers of the ovary, fallopian tube, and peritoneum are likely derived from epithelial cells of the tubal fimbria (144). In this regard, most early serous cancers discovered in *BRCA1/2* carriers undergoing prophylactic surgery have been found to originate in the fallopian tube fimbria, and are associated with preinvasive serous tubal *in situ* carcinomas (STICs) that overexpress mutant *TP53*. In contrast, most endometrioid and clear cell cancers are thought to develop in deposits of endometriosis on the ovary or other pelvic structures. The origin of mucinous ovarian cancers is less clear and some may represent metastases from the gastrointestinal tract. It has been postulated that some mucinous and Brenner tumors arise from embryonic rests near the ovary.

As our understanding of the molecular pathogenesis of ovarian cancer continues to mature, it is likely that the various ovarian cancer subsets will increasingly be thought of as distinct entities with respect to diagnosis, treatment, and prevention. In view of this, each of the subtypes is discussed separately below.

High-Grade Serous Ovarian Cancer

High-grade serous ovarian cancer was the second cancer analyzed by TCGA project (145). This comprehensive genomic analysis confirmed prior findings, most notably these cancers are characterized by a high degree of genetic instability with many copy number alterations and inactivation of *TP53* and *BRCA1/2* and other genes in the homologous DNA repair pathway. Some previously unreported alterations also were discovered. This section will put the new TCGA data in perspective with prior studies. Additional information regarding the findings of the genomic analysis performed by the TCGA can be found in the 2011 publication and in the accompanying supplemental data (145).

DNA Copy Number Alterations

Most high-grade serous ovarian cancers are characterized by extensive genetic instability. Initially gains and losses of various segments of the genome were demonstrated using karyotyping and later at a finer level using comparative genomic hybridization (CGH) (146). Likewise, loss of heterozygosity (LOH), indicative of deletion of specific genetic loci, also was demonstrated to occur at a high frequency on many chromosomal arms (147). Most recently, it has been possible using next generation sequencing to characterize chromosomal rearrangements at the level of the actual base sequence that facilitates analysis of their functional significance (148).

TCGA examined DNA copy number alterations in 489 cases using a variety of high-resolution platforms (145). There were eight chromosomal regions with recurrent gains and 22 with losses, all of which had been described previously. There were 63 recurrent focal amplifications that encoded eight or fewer genes. The most common focal amplifications included *CCNE1* (cyclin E), *MYC* and *MECOM*, each of which was amplified in more than 20% of cancers.

It was already known prior to the TCGA study that increased activity of transcription factors such as *MYC* and various cyclins may stimulate malignant transformation. Amplification of *MYC* had been reported to occur in some ovarian cancers (149) as had amplification and overexpression of cyclin E (150,151). In studies of advanced stage ovarian cancers, high cyclin E expression was associated with poor outcome (150,152). Alterations of the PI3K pathway are frequent in ovarian cancer and it also previously had been reported that the *AKT2* (153) and *PIK3CA* gene are amplified in some cases (154).

TCGA found 50 focal deletions, and the known tumor suppressor genes *PTEN*, *RB*, and *NF1* were deleted, albeit only in a small fraction of cases (145). The latter two genes also were targeted by mutations, consistent with the two hit paradigm of tumor-suppressor gene inactivation. Although mutations in the *RB* tumor suppressor gene are not a common feature of ovarian cancers, evidence suggests that inactivation of *RB* greatly enhances tumor formation in the presence of *TP53* mutations (155). A large number of other candidate genes are in regions that are recurrently amplified or deleted in high-grade serous ovarian cancers. Considerable effort will be required to elucidate which of these represent driver events in some cancers, as opposed to alterations of no consequence for tumorigenesis or progression.

About 30% of breast cancers express increased levels of the *HER-2/neu* oncogene (156), usually due to gene amplification. Overexpression of *HER-2/neu* in breast cancer has been associated with poor survival. Expression of *HER-2/neu* is increased in a fraction of ovarian cancers (Fig. 2.14) and overexpression has been associated with poor survival in some studies (156,157). However, ovarian cancers with *HER-2/neu* overexpression rarely have high-level gene amplification. Anti-*HER-2/neu* antibody therapy (trastuzumab) has demonstrated great

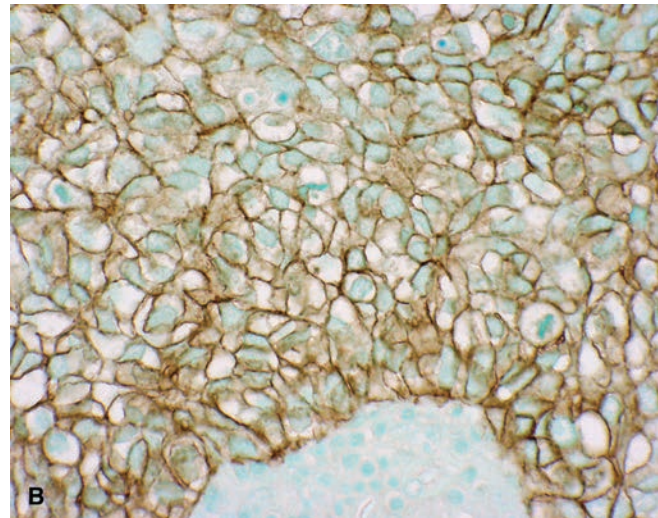
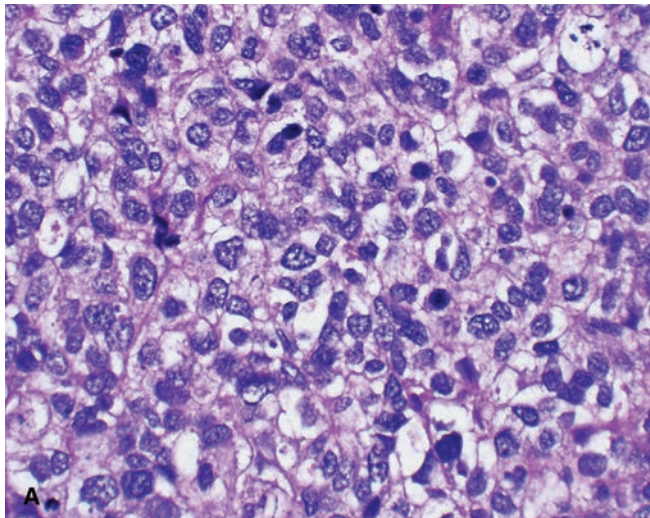


FIGURE 2.14. Overexpression of *HER-2/neu* in ovarian cancer. **A:** Serous ovarian cancer. **B:** Immunostaining for *HER-2/neu* demonstrates intense cell membrane staining indicative of overexpression.

efficacy in breast cancer and often is administered with chemotherapy in the context of both adjuvant therapy and treatment of metastatic disease (158). The use of this drug is restricted to patients whose cancers are shown to overexpress *HER-2/neu* based on immunohistochemical analysis of protein levels and/or FISH analysis of gene amplification in paraffin tumor tissue blocks. A study performed by the Gynecologic Oncology Group found that only 11% of ovarian cancers exhibited significant *HER-2/neu* overexpression (159). The response rate to single-agent trastuzumab therapy was disappointingly low (7%), but there may be some benefit using it in regimens that also include cytotoxics or other biological agents.

The cyclin dependent kinases (cdk) inhibitors act as tumor suppressors by virtue of their inhibition of cell cycle progression from G1 to S phase. Expression of several cdk inhibitors appears to be decreased in some ovarian cancers. *CDKN2A* (p16) undergoes homozygous deletions in about 15% of ovarian cancers (160). There is evidence to suggest that *CDKN2A* (161) and *CDKN2B* (p15) (162) may be inactivated via transcriptional silencing due to promoter methylation rather than mutation and/or deletion. Likewise, decreased expression of the p21/*WAF1* cdk inhibitor has been noted in a significant fraction of ovarian cancers despite the absence of inactivating mutations (163). Loss of p27 (*CDKN1B*) also may occur and correlates with poor survival in some studies (164). It has been suggested that aberrant expression of p27 in the cytoplasm may be most associated with poor outcome (165).

Mutations

TCGA performed sequencing of the coding regions and splice sites of about 18,500 genes in DNA isolated from 316 high-grade serous ovarian cancers (145). The extent of this sequencing effort in ovarian cancer was unprecedented and would not have been possible without the recent development of massively parallel sequencing technologies. Although several genes were identified that are mutated at low frequencies, *TP53*, *BRCA1* and *BRCA2* were confirmed to be the most frequently genes in high-grade ovarian cancers.

TP53

The TCGA study validated the prior finding that mutation of the *TP53* tumor suppressor gene is the most frequent genetic event in high-grade serous ovarian cancers (Table 2.4) (166–169). It is

an early event that is found in serous tubal carcinoma *in situ* (Fig. 2.15) (144). About two-thirds of high-grade serous ovarian cancers have *TP53* missense mutations in the DNA binding regions of exons 5 through 8 of the gene that result in p53 protein overexpression due to increased stability of the protein. Codons 175, 248 and 273 are mutational hot spots. These missense mutants act as dominant negative transforming genes due to their nonfunctional transcriptional activity. Loss of the other copy of the *TP53* gene is not required. Most *TP53* missense mutations are transitions rather than transversions or micro-deletions (170), which suggests that they occur spontaneously, rather than due to exogenous carcinogens.

Overexpression of mutant p53 protein may be associated with somewhat worse survival in advanced stage ovarian cancers (167,169,171). However, reports in the literature are inconsistent and are often confounded by the inclusion of ovarian cancers of various stages, grades, and histological types. Most high-grade serous ovarian cancers that do not overexpress p53 protein have *TP53* mutations that result in truncated protein products (166,171). These are usually accompanied by loss of the other copy of the gene, consistent with the classic two hit

Table 2.4 Characteristics of Common Invasive Epithelial Ovarian Carcinomas

	Mucinous	Endometrioid/ Clear Cell	High-grade Serous	Low-Grade Serous
Origin	Unclear	Endometriosis	Fallopian Tube Epithelial Cells	Fallopian Tube Epithelial Cells
Typical stage	Early	Early	Advanced	Early
Survival	Favorable	Favorable	Poor	Favorable
Commonly altered genes	<i>KRAS</i> <i>HER-2/neu</i>	<i>PTEN</i> <i>CTNNB1</i> (β -catenin) <i>ARID1A</i> <i>PPP2R1A</i> <i>PIK3CA</i>	<i>TP53</i> <i>BRCA1</i> <i>BRCA2</i>	<i>KRAS</i> <i>BRAF</i>

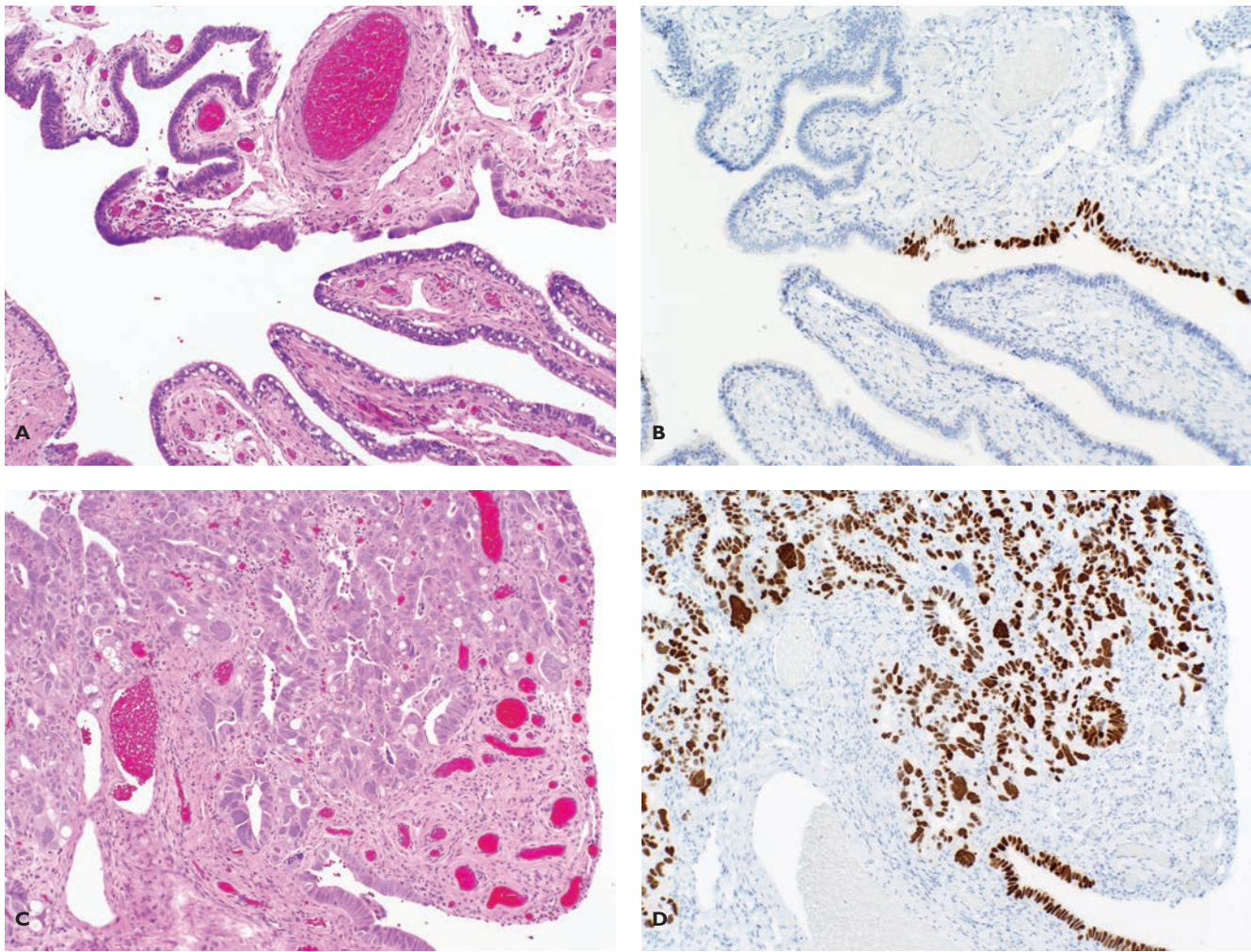


FIGURE 2.15. Overexpression of mutant *TP53* in serous tubal carcinoma in situ (**A, B**) and in high-grade serous ovarian cancer (**C, D**).

model of tumor-suppressor gene inactivation. TCGA found *TP53* mutations in 303 of 316 samples, suggesting that this is essentially a requisite event in the development of high-grade serous cancers.

BRCA1 and BRCA2

BRCA1 and *BRCA2* germline mutations were found in 9% and 8% of high-grade serous cases respectively in the TCGA study, and somatic mutations occurred in an additional 3% (145). Silencing of *BRCA1* due to promoter methylation was observed in 11% of cases as has been previously described (172,173). Defective HR repair of double stranded DNA damage due to loss of *BRCA1/2* was predicted in 31% of high-grade serous ovarian cancers. Other genes in the HR pathway are inactivated in some cancers and the HR pathway may be compromised in about half of cases (Fig. 2.16). Patients with *BRCA1* or *BRCA2* mutations have increased sensitivity to platinum chemotherapy and favorable survival relative to sporadic cases (174,175). Conversely, the emergence of platinum resistance in these cancers may occur due to “back mutations” in which the normal *BRCA1* or *BRCA2* sequence is restored (176).

Cancers with defects in the double stranded DNA HR repair pathway can be targeted effectively by inducing a second hit in the form of inhibition of the single stranded DNA repair pathway. This concept of synthetic lethality—the combination

of two genetic alterations, which on their own are nonlethal, but together result in a lethal phenotype—led to interest in inhibitors of enzymes such as poly-ADP ribose polymerase (PARP) that are involved in single stranded BER (177). Inhibition of PARP leads to the persistence of DNA lesions normally repaired by HR and makes HR-deficient cells particularly sensitive to chemotherapy-induced DNA injury (178). PARP inhibitors have been shown to be selective for cells with defects in the repair of double-strand DNA breaks by HR, particularly in the context of *BRCA1* or *BRCA2* mutation. While normal cells can repair the damage and survive, the *BRCA*-deficient cells cannot activate the HR system and therefore die (179). PARP inhibitors have demonstrated promising results in ongoing trials in ovarian cancer (180).

While only a minority of high-grade serous ovarian cancers have germline *BRCA1* or *BRCA2* mutations, sporadic ovarian cancers can harbor acquired genetic and epigenetic defects in *BRCA1/2* and in other HR genes and proteins, such as *RAD51* that may contribute to a “BRCaness profile” (181). Given the shared role that *BRCA1* and *BRCA2* have with other DNA repair genes, defects in these other DNA repair proteins could influence response to treatment, recurrence rates, and overall survival and increase sensitivity to platinum drugs and PARP inhibitors. In this regard, it was shown using the TCGA data that a DNA repair pathway score was predictive of outcome in ovarian cancer (182).

Extent of HR Defects in TCGA Ovarian Samples

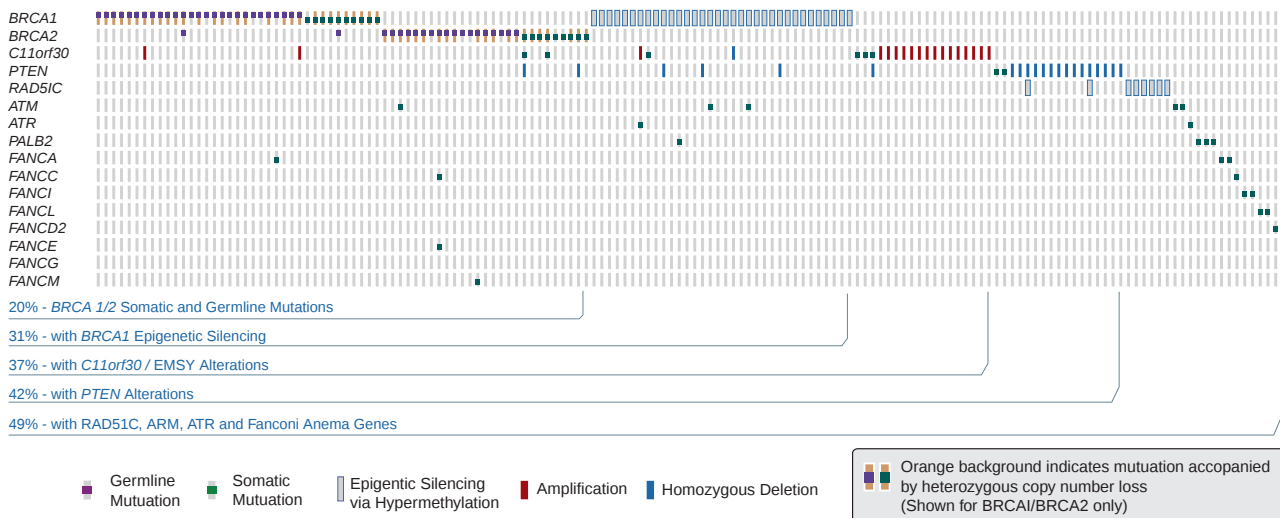


FIGURE 2.16. Genomic fingerprint of HR pathway alterations. Each column represents an individual case; each row represents a gene. Only cases with HR defects (N = 154) are shown. HR: homologous recombination.

Source: The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011;474:609–615.

Other mutations

Six other genes were found to be significantly mutated by TCGA, including *RB*, *NF1*, *FAT3*, *CSMD3*, *GABRA6*, and *CDK12*, but none was mutated in more than 6% of cancers (145). *RB* and *NF1* are known tumor suppressor genes, while *CDK12* has also been implicated in regulation of RNA splicing. *FAT3* and *GABRA6* are not expressed in serous ovarian cancers or in the fallopian tube and the significance of these mutations is unclear. A number of other known oncogenic mutations were found in *KRAS*, *NRAS*, *PIK3CA* and *BRAF*, but at low frequencies less than 1%. These mutations have been shown to have transforming activity and probably represent important drivers of some cancers.

Gene Expression

Microarray chips that contain sequences complementary to thousands of genes have been created that allow global assessment of the level of expression of each gene. Many genes have been identified that appear to be up or downregulated in the process of malignant transformation (183). In addition, microarrays have demonstrated patterns of gene expression that distinguish between histologic types (184), borderline versus invasive cases (185) and between early and advanced stage disease (186). Molecular signatures also have been identified that are predictive of response to therapy (187) and survival (187,188).

In the TCGA ovarian cancer project, a 193 gene expression signature predictive of survival was developed and validated in several other existing data sets (145). The TCGA also identified four gene expression subtypes of high-grade serous ovarian cancer (145). These were named mesenchymal, immunoreactive, differentiated, and proliferative based on the genes that characterized each subtype. Although the subtypes were independently validated in several other microarray data sets, they are not strongly predictive of response or outcome. Alterations in gene expression may be attributable to methylation of their promoters. The TCGA examined methylation using arrays that include promoters of thousands of genes. They found 168 epigenetically altered genes compared to normal fallopian tube epithelium.

Further validation of genomic signatures is needed, but genomic approaches hold the potential to guide selection of therapy in the future. Patients identified as having a “poor prognosis” molecular profile might be the best candidates for

investigational trials of new therapies. Microarray analyses have also demonstrated that dysregulation of oncogenic pathways varies considerably between ovarian cancers (189). This may provide the opportunity to incorporate biological therapies that target oncogenic pathways based on an understanding of the underlying molecular alterations in a patient’s cancer.

With the evolving characterization of the genome, networks of molecular signals that regulate cellular proliferation and death have been identified—from receptor ligand interactions at the cell membrane that transmit signals to the cytoplasm and then to the nucleus. The extensive genomic characterization of high-grade serous ovarian cancer by TCGA allowed for assessment of various signaling pathways. It was found that components of the *RB* and *PI3K/RAS* pathways were frequently altered while the homologous DNA repair pathway was frequently inactivated.

Borderline and Invasive Low-Grade Serous Ovarian Cancers

Similar to high-grade serous cancers, it is thought that borderline and low-grade serous cancers also likely arise from cells that originated in the fallopian tube epithelium. However, the underlying genetic alterations in borderline and low-grade tumors are different from those of high-grade cancers, suggesting that they are distinct entities rather than a single disease with varying degrees of differentiation.

Activating mutations in codons 12 and 13 of the *KRAS* oncogene are common in borderline serous ovarian tumors, occurring in about 25% to 50% of cases (190). In addition, activating mutations in codon 599 of *BRAF*, which is a downstream effector of *KRAS*, occur in about 20% of serous borderline tumors (191). Mutations in these two genes are mutually exclusive and result in constitutive activation of the MAP kinase pathway. Mutations in *KRAS* and *BRAF* have also been noted in cystadenoma epithelium adjacent to serous borderline tumors, suggesting that this is an early event in their development (38). Likewise, mutations in *BRAF* and *KRAS* occur in some low-grade serous ovarian cancers (143), but these mutations are rarely seen in high-grade serous ovarian cancers. Since metastatic low-grade serous and borderline cancers are generally resistant to platinum/taxane therapy, the MAP kinase pathway downstream from *KRAS/BRAF* represents an appealing target in ongoing clinical trials (192).

Overexpression of p53 protein is rare in stage I serous borderline tumors and well-differentiated serous cancers, but occurs in a minority of advanced stage borderline cases (193,194). In a study of advanced serous borderline tumors, p53 overexpression was associated with a sixfold higher risk of death (193). In some cases, invasive low-grade serous cancers may arise following an earlier diagnosis of borderline tumor. It has been shown that *TP53* mutational status was not concordant between the original borderline tumor and the subsequent invasive cancer (195). This suggests that the invasive cancer arises either independently or as a clonal outgrowth within the original tumor.

Endometrioid and Clear Cell Ovarian Cancers

About 20% of epithelial ovarian cancers have endometrioid or clear cell histology and these are thought to arise in pelvic endometriosis, usually on the ovary. Clear cell cancers and low-grade endometrioid cancers have a lower level of genetic instability than high-grade serous cases. The most common alterations in clear cell cancers are mutations of the *ARID1A* tumor suppressor gene, which is involved in chromatin remodeling, and this occurs in about 50% of cases (196,197). *ARID1A* mutations have been observed in the tumor and contiguous atypical endometriosis, but not in distant endometriotic lesions. This suggests that *ARID1A* mutations are an early event in the development of these cancers. The PI3K pathway is also frequently altered, and activating mutations of *PIK3CA* occur in about 50% of cases, and deletion of the *PTEN* tumor suppressor in about 20% (198). *PPP2R1A* encodes the α -isoform of the scaffolding subunit of the serine/threonine protein phosphatase 2A (PP2A) holoenzyme. This putative tumor suppressor complex is involved in growth and survival pathways. Missense mutations in this gene were noted in about 5% of clear cell carcinomas (196).

Mutations of these same genes also occur in endometrioid cancers: *ARID1A* (30%), *PIK3CA* (20%) and *PTEN* (20%), *PPP2R1A* (10%) (199,200). In addition, about 30% of endometrioid cancers have mutations the *CTNNB1* gene that encodes β -catenin, a nuclear transcription factor involved in the WNT pathway. These mutations occur in exon 3 at or adjacent to the serine/threonine phosphorylation sites and stabilize the protein product leading to nuclear overexpression and increased transcriptional activity. In some endometrioid ovarian cancers with abnormal nuclear accumulation of β -catenin that lack mutations in this gene, the *APC*, *AXIN1*, or *AXIN2* genes that regulate β -catenin activity are mutated (201). This suggests that in addition to the mutations that are also present in clear cell cancers, endometrioid cancers frequently have alterations in the WNT signaling pathway (Table 2.4). Mouse models in which the WNT and the PIK3/PTEN pathways are inactivated leads to the development of endometriosis and endometrioid cancers (202,203). Targeting of the latter pathway has some efficacy in recurrent ovarian cancers (204).

High-grade endometrioid ovarian cancers typically have molecular features similar to high-grade serous ovarian cancers, including genetic instability and *TP53* mutations. This suggests that these tumors may sometimes be misclassified by pathologists based on light microscopy.

Synchronous Endometrioid Ovarian and Endometrial Cancers

As noted above, about 20% of endometrioid ovarian cancers have *PTEN* mutations (200). Synchronous endometrioid cancers are sometimes encountered in the endometrium and ovary that are indistinguishable microscopically. In some of these cases, identical *PTEN* mutations have been identified suggesting

that the ovarian tumor represents a metastasis from the endometrium (205). In other cases, the *PTEN* mutation seen in the endometrial cancer was not found in the ovarian tumor suggesting that these represent two distinct primary cancers. Mutational analysis of *PTEN*, *CTNNB1* and other genes frequently mutated in endometrioid cancers is helpful when a mutation is present in both cancers or in one cancer and absent in the other, but this approach often may often be uninformative. It has been reported that mitochondrial DNA mutations are fairly common in endometrial cancers (206), and mitochondrial DNA sequencing has been proposed as an alternative method of determining whether synchronous endometrioid cancers of the ovary and endometrium represent separate primary cancers.

Mucinous Ovarian Cancer

Similar to mucinous colorectal cancers, mucinous ovarian cancers frequently have *KRAS* mutations (143). These mutations occur in 50% to 75% of mucinous ovarian cancers and are missense changes in the hotspot codons. *BRAF* mutations have not been found in mucinous ovarian cancers (207). Identical *KRAS* mutations have been found in mucinous carcinomas and adjacent mucinous cystadenomas and borderline tumors, suggesting that the latter lesions represent premalignant precursors (143). Amplification of *HER-2/neu* has also been described in a subset of mucinous ovarian cancers (143). *TP53* and other genes that are mutated in other histological types of ovarian cancer have not been found to be altered in mucinous cancers. These findings are supportive of the theory that many mucinous ovarian cancers may be metastatic from the gastrointestinal tract.

Stromal Ovarian Tumors

The genetic alterations driving stromal tumors of the ovary were unknown until recently when it became possible to screen the entire genome using next generation sequencing. Essentially all adult granulosa tumors were found to have a missense mutation in codon 134 of *FOXL2*, a gene encoding a transcription factor known to be critical for granulosa cell development (208). This mutation was also found in about 20% of thecomas and in 10% of juvenile granulosa cell tumors, but not in other types of sex cord stromal tumors. In addition, *DICER1* mutations in the RNase IIIb domain were found in about 30% of nonepithelial ovarian tumors, predominantly in Sertoli-Leydig cell tumors (60%) (209). These mutations were restricted to codons encoding metal-binding sites within the RNase IIIb catalytic centers, which are critical for microRNA interaction and cleavage.

CERVICAL CANCER

Etiology

Although the incidence of cervical cancer has fallen by over 80% in developed countries due to widespread implementation of cervical screening, in developing areas of the world it is still the most common cancer in women. Almost all cervical cancers are caused by sexually transmitted human papilloma virus (HPV) infection, as are many vaginal and vulvar cancers. The epidemiology and biology of HPV infection and its role in screening and prevention are discussed in Chapters 1 (Epidemiology) and 7 (Preinvasive lower genital tract disease).

Unlike most other types of human cancers that occur due to mutations in oncogenes and/or tumor suppressor genes that disrupt their normal genetic sequence, cervical cancers arise as a consequence of viral inactivation of the *TP53* and *RB* tumor

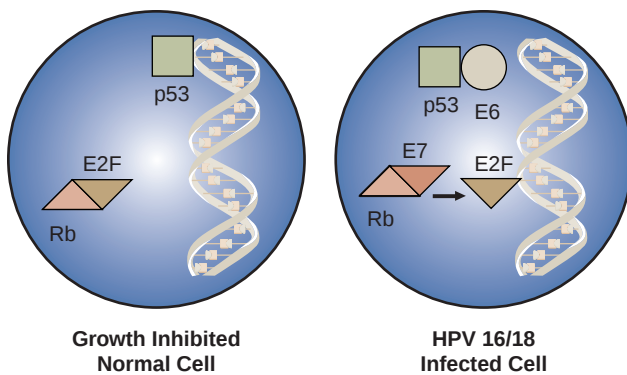


FIGURE 2.17. Role of *TP53* and *RB* genes in cervical carcinogenesis. The HPV 16/18 E6 and E7 proteins inactivate the *TP53* and *RB* genes respectively.

suppressors by the HPV E6 and E7 oncoproteins respectively (Fig. 2.17) (210). Variations in oncogenic potential between HPV subtypes may be related in part to differences in the efficiency with which E6 and E7 bind to and inactivate these tumor suppressors (211,212). In some studies, the levels of E6 and E7 in invasive cervical cancers have been found to predict outcome, whereas HPV viral load does not (213). There is also evidence that HPV E6/E7 may interact directly with other genes such as telomerase that enhance growth and inhibit apoptosis. In addition, the cyclin dependent kinase inhibitor p16 is strikingly upregulated in most cervical dysplasias and cancers (214). P16 detection may represent a useful adjunct to improve the positive predictive value of high-risk HPV testing for detection of cervical dysplasia.

HPV negative cervical cancers are uncommon, but have been reported to exhibit overexpression of mutant p53 protein (215). This suggests that inactivation of *T53* is a requisite event in cervical carcinogenesis. The biology of HPV related transformation, including the role of E6/E7, is discussed in greater detail in Chapter 7. This chapter will focus on the secondary genetic alterations that have been observed in invasive cervical cancers.

Secondary Genomic Changes

HPV associated cervical carcinogenesis with inactivation of the *TP53* tumor suppressor gene leads to genomic instability that results in secondary genetic alterations that play a role in the development and phenotype of these cancers. Over time this ongoing instability leads to significant intratumoral heterogeneity as genetic damage continues to accumulate. Most cervical cancers are aneuploid and comparative genomic hybridization studies have shown that areas of DNA copy number gain or loss are common. A strikingly consistent finding of various studies is the high frequency of gains on chromosome 3q in both squamous cancers (216,217) and adenocarcinomas (218). Other chromosomes that exhibit frequent gains include 1q and 11q. The most common areas of chromosomal loss include chromosomes 3p and 2q and 13q (219). The frequency of gains and losses at various genomic locations may be random to a certain extent, but there are areas of the genome that are more susceptible to breakage leading to translocations or loss/gain. Abnormalities seen in invasive cancers using comparative genomic hybridization also have been identified in high-grade dysplasias, suggesting that these are early and perhaps requisite events in cervical carcinogenesis (217,220,221).

Alterations in gene dosage due to chromosomal gains or losses have the potential to lead to changes in expression of genes involved in regulation of processes central to malignant transformation such as growth, differentiation, and apoptosis. Cervical carcinogenesis is also accompanied by changes in DNA

methylation that affect gene expression. Regardless of the cause, some changes in gene dosage likely represent collateral damage and have no effect on development and evolution of the malignant phenotype. However, it is likely that over time there is selection for clones that exhibit enhanced growth and invasive potential. It is possible that genetic instability may also enhance the emergence of resistance to radiation and chemotherapy.

A recent study examined gene dosage in locally advanced cervical cancers using microarrays. Alterations were frequent and there were 14 regions with recurrent gains and 14 with recurrent loss. The most common alterations were gain on 1q, 3q, 5p, 20q, and Xq and loss on 2q, 3p, 4p, 11q, and 13q, each involving 44% to 76% of the patients. Four genes on 3p (*RYBP*, *GBE1*) and 13q (*FAM48A*, *MED4*) correlated with outcome at both the gene dosage and expression level and were validated in the independent cohort. Despite circumstantial evidence provided by studies such as this, with the exception of the fragile histidine triad (*FHIT*) gene on chromosome 3p14, it has been difficult to prove that genomic gains and losses result in alterations in specific oncogenes or tumor suppressor genes that are directly involved in tumor development. The *FHIT* gene is frequently deleted in many different cancers, including cervical cancer (222-224). Decreased expression of this putative tumor suppressor gene is an early event in some cervical cancers (224,225). In one study, *FHIT* protein expression was markedly reduced or absent in 71% of invasive cancers, 52% of HSILs associated with invasive cancer, and 21% of HSILs without associated invasive cancer (224). In addition, reduced expression is associated with poor prognosis in advanced cervical cancers (226).

The role of several oncogenes has been examined in cervical carcinomas including most prominently the *RAS* and *MYC* genes. Mutant *RAS* genes are capable of cooperating with HPV in transforming cells *in vitro*. There is some evidence that mutations in either *KRAS* or *HRAS* may play a role in a subset of cervical cancers (215,227-230). *MYC* amplification and overexpression may be an early event in the development of some cervix cancers (231). Overexpression of *MYC* has been demonstrated in one-third of early invasive carcinomas and some CIN 3 lesions. In some studies, amplification correlated with poor prognosis in early stage cases (232).

Gene silencing due to promoter hypermethylation also may play a role in cervical carcinogenesis (233,234). In this regard, expression of the *RASSF1A* gene on chromosome 3p21 is frequently lost in cervical cancers, particularly adenocarcinomas (235,236). The function of this gene is not completely understood, but is thought to be involved in ras mediated signal transduction pathways. Hypermethylation of genes associated with programmed cell death (apoptosis) and tumor suppressor genes have also been described in cervical cancers.

GESTATIONAL TROPHOBLASTIC DISEASE

The genetic alterations that underlie gestational trophoblastic disease have been elucidated to a great extent. The most prominent feature of these tumors is an imbalance of parental chromosomes. In partial moles, this involves an extra haploid copy of one set of paternal chromosomes (XXY, XXX, or YYY). Complete moles generally are characterized by two pairs of one paternal haploid set of chromosomes (XX) and an absence of maternal chromosomes, while a minority are (XY) due to dispermy. Although the risk of repeat molar pregnancy is only about 1%, women who have had two molar pregnancies have about a 25% risk of developing another mole. Although this suggests a hereditary defect that affects gametogenesis, this remains speculative. Thus far, there is no convincing evidence that damage to specific tumor-suppressor genes or oncogenes contributes

to the development of gestational trophoblastic disease. However, the presence of two identical copies of each chromosome in most complete moles could facilitate transformation due to increased or decreased expression of imprinted genes involved in growth regulatory pathways. In addition, inactivation of a tumor-suppressor gene on a paternal chromosome that might not normally be manifest because of the presence of a wild-type allele on the maternal chromosome could become significant in cells with two copies of the same haploid paternal genome.

Microarray studies have identified several genes that are differentially expressed compared to normal villi, particularly genes associated with cellular apoptosis, immune suppression,

and cell invasion (237,238). In one study in which genomic techniques were used to compare gene expression between moles that spontaneously regressed and those that subsequently developed metastatic GTN identified 16 differentially expressed transcripts (238). Down-regulation of ferritin light polypeptide (*FTL*) and insulin-like growth factor binding protein 1 (*IGFBP1*) was confirmed in cases that subsequently developed GTN compared with those that regressed. Studies have also suggested that changes in expression of genes involved in apoptosis, such as greater expression of the antiapoptotic gene *Mcl-1*, may be involved in progression of a molar pregnancy requiring chemotherapy (239).

REFERENCES

- DeVita VT, Lawrence TS, Rosenberg SA. *DeVita Hellman and Rosenberg's Cancer: Principles and Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2011.
- Samuels Y, Bardelli A, Lopez-Otin C. The cancer genome. In: DeVita VT, Lawrence DK, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins; 2011:141–148.
- Camacho DF, Pienta KJ. Disrupting the networks of cancer. *Clin Cancer Res*. 2012;18:2801–2808.
- Kucherlapati R. Biology of personalized cancer medicine. 9 ed. In: DeVita VT, Lawrence DK, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011:141–148.
- Arteaga CL, Baselga J. Impact of genomics on personalized cancer medicine. *Clin Cancer Res*. 2012;18:612–618.
- Reed SI. Cell Cycle. 9 ed. In: DeVita VT, Lawrence D K, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011:68–81.
- Thompson SL, Bakhoum SE, Compton DA. Mechanisms of chromosomal instability. *Curr Biol*. 2010;20:R285–R295.
- Karantza V, White E. Mechanisms of Cell Death. 9 ed. In: DeVita VT, Lawrence D K, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011: 82–90.
- Chao DT, Korsmeyer SJ. BCL-2 family: regulators of cell death. *Annu Rev Immunology*. 1998;16:395–419.
- Verdine GL, Walensky LD. The challenge of drugging undruggable targets in cancer: lessons learned from targeting BCL-2 family members. *Clin Cancer Res*. 2007;13:7264–7270.
- Brandon M, Baldi P, Wallace DC. Mitochondrial mutations in cancer. *Oncogene*. 2006;25:4647–4662.
- Amaravadi RK, Thompson CB. The roles of therapy-induced autophagy and necrosis in cancer treatment. *Clin Cancer Res*. 2007;13:7271–7279.
- Lebovitz CB, Bortnik SB, Gorski SM. Here, there be dragons: charting autophagy-related alterations in human tumors. *Clin Cancer Res*. 2012;18:1214–1226.
- Wong KK, Sharpless NE, DePinho RA. Telomeres, Telomerase, and Cancer. 9 ed. In: DeVita VT, Lawrence D K, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011:41–47.
- O'Sullivan RJ, Karlseder J. Telomeres: protecting chromosomes against genome instability. *Nature Rev*. 2010;11:171.
- Shay JW, Keith WN. Targeting telomerase for cancer therapeutics. *Br J Cancer*. 2008;98:677–683.
- Murnane JP. Telomere loss as a mechanism for chromosome instability in human cancer. *Cancer Res*. 2010;70:4255–4259.
- Wan M, Li WZ, Duggan BD, et al. Telomerase activity in benign and malignant epithelial ovarian tumors. *J Natl Cancer Inst*. 1997;19:89:437–441.
- Takakura M, Kyo S, Kanaya T, et al. Expression of human telomerase subunits and correlation with telomerase activity in cervical cancer. *Cancer Res*. 1998;58:1558–1561.
- Brien TP, Kallakury BV, Lowry CV, et al. Telomerase activity in benign endometrium and endometrial carcinoma. *Cancer Res*. 1997;57:2760–2764.
- Kyo S, Takakura M, Kohama T, et al. Telomerase activity in human endometrium. *Cancer Res*. 1997;57:610–614.
- Buseman CM, Wright WE, Shay JW. Is telomerase a viable target in cancer? *Mutat Res*. 2012;730:90–97.
- Wang JCY, Dick JE. Cancer Stem Cells. 9 ed. In: DeVita VT, Lawrence D K, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011: 128–140.
- D'Angelo RC, Wicha MS. Stem cells in normal development and cancer. *Prog Mol Biol Transl Sci*. 2010;95:113–158.
- Burgos-Ojeda D, Rueda BR, Buckanovich RJ. Ovarian cancer stem cell markers: Prognostic and therapeutic implications. *Cancer Lett*. 2012;322:1–7.
- Li Y, Laterra J. Cancer stem cells: distinct entities or dynamically regulated phenotypes? *Cancer Res*. 2012;72:576–580.
- Bolton KL, Ganda C, Berchuck A, et al. Role of common genetic variants in ovarian cancer susceptibility and outcome: progress to date from the Ovarian Cancer Association Consortium (OCAC). *J Intern Med*. 2012;271:366–378.
- Esteller M. Epigenetics in cancer. *N Engl J Med*. 2008;358:1148–1159.
- Jones PA., Michels KB. Epigenetics of Cancer. 9 ed. In: DeVita VT, Lawrence D K, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011: 41–47.
- Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010;363:1693–1703.
- Cantley LC, Carpenter CL, Hahn WC, et al. Cell Signaling. 9th ed. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins 2011:57–67.
- Bubril EM, Yarden Y. The EGF receptor family: spearheading a merger of signaling and therapeutics. *Curr Opin Cell Biol*. 2007;19:124–134.
- Shepard HM, Jin P, Slamon DJ, et al. Herceptin. *Handb Exp Pharmacol*. 2008;183–219.
- Kumar A, Petri ET, Halmos B, et al. Structure and clinical relevance of the epidermal growth factor receptor in human cancer. *J Clin Oncol*. 2008;26:1742–1751.
- Summy JM, Gallick GE. Treatment for advanced tumors: SRC reclaims center stage. *Clin Cancer Res*. 2006;12:1398–1401.
- Tokunaga E, Oki E, Egashira A, et al. Deregulation of the Akt pathway in human cancer. *Curr Cancer Drug Targets*. 2008;8:27–36.
- Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. *Cancer Res*. 2012;72:2457–2467.
- Ho CL, Kurman RJ, Dehari R, et al. Mutations of BRAF and KRAS precede the development of ovarian serous borderline tumors. *Cancer Res*. 2004;64:6915–6918.
- Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507–2516.
- Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. *J Clin Oncol*. 2010;28:1075–1083.
- Salmena L, Carracedo A, Pandolfi PP. Tenets of PTEN tumor suppression. *Cell*. 2008;133:403–414.
- Janku F, Wheler JJ, Westin SN, et al. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. *J Clin Oncol*. 2012;30:777–782.
- Leiderman YI, Kiss S, Mukai S. Molecular genetics of RB1—the retinoblastoma gene. *Semin Ophthalmol*. 2007;22:247–254.
- Knudsen ES, Wang JY. Targeting the RB-pathway in cancer therapy. *Clin Cancer Res*. 2010;16:1094–1099.
- Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. *J Clin Oncol*. 2006;24:1770–1783.
- Berchuck A, Kohler MF, Marks JR, et al. The p53 tumor suppressor gene frequently is altered in gynecologic cancers. *Am J Obstet Gynecol*. 1994;170:246–252.

47. Soussi T. p53 alterations in human cancer: more questions than answers. *Oncogene*. 2007;26:2145–2156.
48. Elliott RL, Blobe GC. Role of transforming growth factor Beta in human cancer. *J Clin Oncol*. 2005;23:2078–2093.
49. Ikushima H, Miyazono K. TGFbeta signalling: a complex web in cancer progression. *Nat Rev Cancer*. 2010;10:415–424.
50. Iorio MV, Croce CM. MicroRNAs in cancer: small molecules with a huge impact. *J Clin Oncol*. 2009;27:5848–5856.
51. Merritt WM, Lin YG, Han LY, et al. Dicer, Drosha, and outcomes in patients with ovarian cancer. *N Engl J Med*. 2008;359:2641–2650.
52. Vander Heiden MG. Cancer Metabolism. 9 ed. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011:91–100.
53. Hirschhauser F, Sattler UG, Mueller-Klieser W. Lactate: a metabolic key player in cancer. *Cancer Res*. 2011;71:6921–6925.
54. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009;461:1071–1078.
55. Gordon DJ, Barbie DA, D'Andrea AD, et al. Mechanisms of Genomic Instability. 9th ed. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins 2011:23–40.
56. Jalal S, Earley JN, Turchi JJ. DNA repair: from genome maintenance to biomarker and therapeutic target. *Clin Cancer Res*. 2011;17:6973–6984.
57. Berger AH, Pandolfi PP. Cancer Susceptibility Syndromes. 9 ed. In: DeVita VT, Lawrence D K, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 9e. Philadelphia: Lippincott Williams & Wilkins 2011:161–170.
58. Wijnen J, de Leeuw W, Vasen H, et al. Familial endometrial cancer in female carriers of MSH6 germline mutations. *Nat Genet*. 1999;23:142–144.
59. Friedberg EC. How NER protects against cancer. *Nat Rev Cancer*. 2001;1:22–33.
60. Park JS, Jeon EK, Chun SH, et al. ERCC1 (excision repair cross-complementation group 1) expression as a predictor for response of neoadjuvant chemotherapy for FIGO stage 2B uterine cervix cancer. *Gynecol Oncol*. 2011;120:275–279.
61. Starcevic D, Dalal S, Sweasy JB. Is there a link between DNA polymerase beta and cancer? *Cell Cycle*. 2004;3:998–1001.
62. Nielsen M, van Steenbergen LN, Jones N, et al. Survival of MUTYH-associated polyposis patients with colorectal cancer and matched control colorectal cancer patients. *J Natl Cancer Inst*. 2010;102:1724–1730.
63. Derheimer FA, Kastan MB. Multiple roles of ATM in monitoring and maintaining DNA integrity. *FEBS Lett*. 2010;584:3675–3681.
64. Li X, Heyer WD. Homologous recombination in DNA repair and DNA damage tolerance. *Cell Res*. 2008;18:99–113.
65. Moynahan ME. The cancer connection: BRCA1 and BRCA2 tumor suppression in mice and humans. *Oncogene*. 2002;21:8994–9007.
66. Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. *Nat Genet*. 2010;42:410–414.
67. Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet*. 2011;43:879–882.
68. Dansonka-Mieszkowska A, Kluska A, Moes J, et al. A novel germline PALB2 deletion in Polish breast and ovarian cancer patients. *BMC Med Genet*. 2010;11:20.
69. Rafnar T, Gudbjartsson DF, Sulem P, et al. Mutations in BRIP1 confer high risk of ovarian cancer. *Nat Genet*. 2011;43:1104–1107.
70. Wood LD, Parsons DW, Jones S, et al. The genomic landscapes of human breast and colorectal cancers. *Science*. 2007;318:1108–1113.
71. Deligdisch L, Holinka CF. Endometrial carcinoma: two diseases? *Cancer Detect Prev*. 1987;10:237–246.
72. McConechy MK, Ding J, Cheang MC, et al. Use of mutation profiles to refine the classification of endometrial carcinomas. *J Pathol*. 2012;228(1):20–30.
73. Simpkins SB, Bocker T, Swisher EM, et al. MLH1 promoter methylation and gene silencing is the primary cause of microsatellite instability in sporadic endometrial cancers. *Hum Mol Genet*. 1999;8:661–666.
74. Salvesen HB, MacDonald N, Ryan A, et al. Methylation of hMLH1 in a population-based series of endometrial carcinomas. *Clin Cancer Res*. 2000;6:3607–3613.
75. Risinger JI, Berchuck A, Kohler MF, et al. Genetic instability of microsatellites in endometrial carcinoma. *Cancer Res*. 1993;53:5100–5103.
76. Faquin WC, Fitzgerald JT, Lin MC, et al. Sporadic microsatellite instability is specific to neoplastic and preneoplastic endometrial tissues. *Am J Clin Pathol*. 2000;113:576–582.
77. Esteller M, Catusas L, Matias-Guiu X, et al. hMLH1 promoter hypermethylation is an early event in human endometrial tumorigenesis. *Am J Pathol*. 1999;155:1767–1772.
78. Kanaya T, Kyo S, Maida Y, et al. Frequent hypermethylation of MLH1 promoter in normal endometrium of patients with endometrial cancers. *Oncogene*. 2003;22:2352–2360.
79. The Cancer Genome Atlas Research Network. Integrated genomic analysis of endometrial cancer. *Nature*. 2013. (in press).
80. Shah NK, Currie JL, Rosenshein N, et al. Cytogenetic and FISH analysis of endometrial carcinoma. *Cancer Genet Cytogenet*. 1994;73:142–146.
81. Baloglu H, Cannizzaro LA, Jones, et al. Atypical endometrial hyperplasia shares genomic abnormalities with endometrioid carcinoma by comparative genomic hybridization. *Hum Pathol*. 2001;32:615–622.
82. Kiechle M, Hinrichs M, Jacobsen A, et al. Genetic imbalances in precursor lesions of endometrial cancer detected by comparative genomic hybridization. *Am J Pathol*. 2000;156:1827–1833.
83. Moreno-Bueno G, Sanchez-Estevéz C, Cassia R, et al. Differential gene expression profile in endometrioid and nonendometrioid endometrial carcinoma: STK15 is frequently overexpressed and amplified in nonendometrioid carcinomas. *Cancer Res*. 2003;63:5697–5702.
84. Risinger JI, Maxwell GL, Chandramouli GV, et al. Microarray analysis reveals distinct gene expression profiles among different histologic types of endometrial cancer. *Cancer Res*. 2003;63:6–11.
85. Mutter GL, Baak JP, Fitzgerald JT, et al. Global expression changes of constitutive and hormonally regulated genes during endometrial neoplastic transformation. *Gynecol Oncol*. 2001;83:177–185.
86. Bidus MA, Risinger JI, Chandramouli GV, et al. Prediction of lymph node metastasis in patients with endometrioid endometrial cancer using expression microarray. *Clin Cancer Res*. 2006;12:83–88.
87. Ferguson SE, Olshen AB, Viale A, et al. Stratification of intermediate-risk endometrial cancer patients into groups at high risk or low risk for recurrence based on tumor gene expression profiles. *Clin Cancer Res*. 2005;11:2252–2257.
88. Kohler MF, Berchuck A, Davidoff AM, et al. Overexpression and mutation of p53 in endometrial carcinoma. *Cancer Res*. 1992;52:1622–1627.
89. Lukes AS, Kohler MF, Pieper CF, et al. Multivariable analysis of DNA ploidy, p53, and HER-2/*neu* as prognostic factors in endometrial cancer. *Cancer*. 1994;73:2380–2385.
90. Enomoto T, Fujita M, Inoue M, et al. Alterations of the p53 tumor suppressor gene and its association with activation of the c-K_{ras}-2 proto-oncogene in premalignant and malignant lesions of the human uterine endometrium. *Cancer Res*. 1993;53:1883–1888.
91. Okamoto A, Sameshima Y, Yamada Y, et al. Allelic loss on chromosome 17p and p53 mutations in human endometrial carcinoma of the uterus. *Cancer Res*. 1991;51:5632–5636.
92. Risinger JI, Dent GA, Ignar-Trowbridge D, et al. Mutations of the p53 gene in human endometrial carcinoma. *Molec Carcinog*. 1992;5:250–253.
93. Yaginuma Y, Westphal H. Analysis of the p53 gene in human uterine carcinoma cell lines. *Cancer Res*. 1991;51:6506–6509.
94. Hachisuga T, Fukuda K, Uchiyama M, et al. Immunohistochemical study of p53 expression in endometrial carcinomas: correlation with markers of proliferating cells and clinicopathologic features. *Int J Gynecol Cancer*. 1993;3:363–368.
95. Hamel NW, Sebo TJ, Wilson TO, et al. Prognostic value of p53 and proliferating cell nuclear antigen expression in endometrial carcinoma. *Cancer Res*. 1996;56:192–198.
96. Ito K, Watanabe K, Nasim S, et al. Prognostic significance of p53 overexpression in endometrial cancer. *Cancer Res*. 1994;54:4667–4670.
97. Khalifa MA, Mannel RS, Haraway SD, et al. Expression of EGFR, HER-2/*neu*, p53, and PCNA in endometrioid, serous papillary, and clear cell endometrial adenocarcinomas. *Cancer Res*. 1994;53:84–92.
98. Service RF. Research news: Stalking the start of colon cancer. *Science*. 1994;263:1559–1560.
99. Liu FS, Kohler MF, Marks JR, et al. Mutation and overexpression of the p53 tumor suppressor gene frequently occurs in uterine and ovarian sarcomas. *Obstet Gynecol*. 1994;83:118–124.
100. Hall KL, Teneriello MG, Taylor RR, et al. Analysis of Ki-ras, p53, and MDM2 genes in uterine leiomyomas and leiomyosarcomas. *Cancer Res*. 1997;57:330–335.
101. Kong D, Suzuki A, Zou TT, et al. PTEN1 is frequently mutated in primary endometrial carcinomas. *Nat Genet*. 1997;17:143–144.
102. Risinger JI, Hayes AK, Berchuck A, et al. PTEN/MMAC1 mutations in endometrial cancers. *Cancer Res*. 1997;57:4736–4738.
103. Tashiro H, Blazes MS, Wu R, et al. Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecologic malignancies. *Cancer Res*. 1997;57:3935–3940.
104. Kanamori Y, Kigawa J, Itamochi H, et al. Correlation between loss of PTEN expression and Akt phosphorylation in endometrial carcinoma. *Clin Cancer Res*. 2001;7:892–895.
105. Risinger JI, Hayes K, Maxwell GL, et al. PTEN mutation in endometrial cancers is associated with favorable clinical and pathologic characteristics. *Clin Cancer Res*. 1998;4:3005–3010.
106. Milner J, Ponder B, Hughes-Davies L, et al. Transcriptional activation functions in BRCA2. *Nature*. 1997;386:772–773.

107. Mutter GL, Ince TA, Baak JP, et al. Molecular identification of latent precancers in histologically normal endometrium. *Cancer Res.* 2001;61:4311–4314.
108. Mutter GL, Lin MC, Fitzgerald JT, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. *J Natl Cancer Inst.* 2000;92:924–930.
109. Berchuck A, Rodriguez G, Kinney RB, et al. Overexpression of *HER-2/neu* in endometrial cancer is associated with advanced stage disease. *Am J Obstet Gynecol.* 1991;164(1 Pt 1):15–21.
110. Lu KH, Bell DA, Welch WR, et al. Evidence for the multifocal origin of bilateral and advanced human serous borderline ovarian tumors. *Cancer Res.* 1998;58:2328–2330.
111. Slomovitz BM, Broaddus RW, Burke TW, et al. *Her-2/neu* overexpression and amplification in uterine papillary serous carcinoma. *J Clin Oncol.* 2004;22:3126–3132.
112. Santin AD, Bellone S, Van SS, et al. Determination of *HER2/neu* status in uterine serous papillary carcinoma: comparative analysis of immunohistochemistry and fluorescence in situ hybridization. *Gynecol Oncol.* 2005;98:24–30.
113. Morrison C, Zanagnolo V, Ramirez N, et al. *HER-2* is an independent prognostic factor in endometrial cancer: association with outcome in a large cohort of surgically staged patients. *J Clin Oncol.* 2006;24:2376–2385.
114. Fleming GF, Sill MW, Darcy KM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, *HER2*-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010;116:15–20.
115. Boyd J, Risinger JI. Analysis of oncogene alterations in human endometrial carcinoma: prevalence of *ras* mutations. *Mol Carcinog.* 1991;4:189–195.
116. Ignar-Trowbridge D, Risinger JI, Dent GA, et al. Mutations of the *Ki-ras* oncogene in endometrial carcinoma. *Am J Obstet Gynecol.* 1992;167:227–232.
117. Enomoto T, Inoue M, Perantoni AO, et al. *K-ras* activation in premalignant and malignant epithelial lesions of the human uterus. *Cancer Res.* 1991;51:5308–5314.
118. Sasaki H, Nishii H, Tada A, et al. Mutation of the *Ki-ras* protooncogene in human endometrial hyperplasia and carcinoma. *Cancer Res.* 1993;53:1906–1910.
119. Duggan BD, Felix JC, Munderspach LI, et al. Early mutational activation of the *c-Ki-ras* oncogene in endometrial carcinoma. *Cancer Res.* 1994;54:1604–1607.
120. Mutter GL, Wada H, Faquin WC, et al. *K-ras* mutations appear in the premalignant phase of both microsatellite stable and unstable endometrial carcinogenesis. *Mol Pathol.* 1999;52:257–262.
121. Oda K, Stokoe D, Taketani Y, et al. High frequency of coexistent mutations of *PIK3CA* and *PTEN* genes in endometrial carcinoma. *Cancer Res.* 2005;65:10669–10673.
122. Hayes MP, Wang H, Espinal-Witter R, et al. *PIK3CA* and *PTEN* mutations in uterine endometrioid carcinoma and complex atypical hyperplasia. *Clin Cancer Res.* 2006;12:5932–5935.
123. Rudd ML, Price JC, Fogoros S, et al. A unique spectrum of somatic *PIK3CA* (p110alpha) mutations within primary endometrial carcinomas. *Clin Cancer Res.* 2011;17:1331–1340.
124. Cheung LW, Hennessy BT, Li J, et al. High frequency of *PIK3R1* and *PIK3R2* mutations in endometrial cancer elucidates a novel mechanism for regulation of *PTEN* protein stability. *Cancer Discov.* 2011;1:170–185.
125. Abraham RT, Gibbons JJ. The mammalian target of rapamycin signaling pathway: twists and turns in the road to cancer therapy. *Clin Cancer Res.* 2007;13:3109–3114.
126. Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol.* 2011;29:3278–3285.
127. Risinger JI, Berchuck A, Kohler MF, et al. Mutations of the *E-cadherin* gene in human gynecologic cancers. *Nat Genet.* 1994;7:98–102.
128. Fujimoto J, Ichigo S, Hori M, et al. Expressions of *E-cadherin* and α - and β -catenin mRNAs in uterine endometrial cancers. *Eur J Gynaecol Oncol.* 1998;19:78–81.
129. Hirohashi S. Inactivation of the *E-cadherin*-mediated cell adhesion system in human cancers. *Am J Pathol.* 1998;153:333–339.
130. O'Sullivan MJ, McCarthy TV, Doyle CT. Familial adenomatous polyposis: from bedside to benchside. *Am J Clin Pathol.* 1998;109:521–526.
131. Moreno-Bueno G, Hardisson D, Sanchez C, et al. Abnormalities of the *APC*/ β -catenin pathway in endometrial cancer. *Oncogene.* 2002;21:7981–7990.
132. Mitra AB, Murty VV, Pratap M, et al. *ERBB2* (*HER2/neu*) oncogene is frequently amplified in squamous cell carcinoma of the uterine cervix. *Cancer Res.* 1994;54:637–639.
133. Fukuchi T, Sakamoto M, Tsuda H, et al. β -catenin mutation in carcinoma of the uterine endometrium. *Cancer Res.* 1998;58:3526–3528.
134. Pollock PM, Gartside MG, Dejeza LC, et al. Frequent activating *FGFR2* mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. *Oncogene.* 2007.
135. Byron SA, Gartside M, Powell MA, et al. *FGFR2* point mutations in 466 endometrioid endometrial tumors: relationship with *MSI*, *KRAS*, *PIK3CA*, *CTNNB1* mutations and clinicopathological features. *PLoS ONE.* 2012;7:e38081.
136. Brooks AN, Kilgour E, Smith PD. Molecular pathways: fibroblast growth factor signaling: a new therapeutic opportunity in cancer. *Clin Cancer Res.* 2012;18:1855–1862.
137. Odom LD, Barrett JM, Pantazis CG, et al. Immunocytochemical study of *ras* and *myc* proto-oncogene polypeptide expression in the human menstrual cycle. *Am J Obstet Gynecol.* 1989;161:1663–1668.
138. Monk BJ, Chapman JA, Johnson GA, et al. Correlation of *c-myc* and *HER-2/neu* amplification and expression with histopathologic variables in uterine corpus cancer. *Am J Obstet Gynecol.* 1994;171:1193–1198.
139. Williams JA, Jr., Wang ZR, Parrish RS, et al. Fluorescence in situ hybridization analysis of *HER-2/neu*, *c-myc*, and *p53* in endometrial cancer. *Exp Mol Pathol.* 1999;67:135–143.
140. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci USA.* 2011;108:18032–8037.
141. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk. Collaborative analysis of twelve US case-control studies: IV. The pathogenesis of epithelial ovarian cancer. *Am J Epidemiol.* 1992;136:1212–1220.
142. Rodriguez GC, Walmer DK, Cline M, et al. Effect of progestin on the ovarian epithelium of macaques: cancer prevention through apoptosis? *J Soc Gynecol Invest.* 1998;5:271–276.
143. Kurman RJ, Shih I. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm. *Hum Pathol.* 2011;42:918–931.
144. Mehra K, Mehrad M, Ning G, et al. STICS, SCOUTs and *p53* signatures; a new language for pelvic serous carcinogenesis. *Front Biosci (Elite Ed).* 2011;3:625–634.
145. The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474:609–615.
146. Kallioniemi A, Kallioniemi OP, Sudar D, et al. Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. *Science.* 1992;258:818–821.
147. Cliby W, Ritland S, Hartmann L, et al. Human epithelial ovarian cancer allelotyping. *Cancer Res.* 1993;53(suppl 8):2393–2398.
148. McBride DJ, Etemadmoghadam D, Cooke SL, et al. Tandem duplication of chromosomal segments is common in ovarian and breast cancer genomes. *J Pathol.* 2012;227(4):446–455.
149. Tashiro H, Niyazaki K, Okamura H, et al. *c-myc* overexpression in human primary ovarian tumors: its relevance to tumor progression. *Int J Cancer.* 1992;50:828–833.
150. Farley J, Smith LM, Darcy KM, et al. Cyclin E expression is a significant predictor of survival in advanced, suboptimally debulked ovarian epithelial cancers: a Gynecologic Oncology Group study. *Cancer Res.* 2003;63:1235–1241.
151. Etemadmoghadam D, George J, Cowin PA, et al. Amplicon-dependent *CCNE1* expression is critical for clonogenic survival after cisplatin treatment and is correlated with 20q11 gain in ovarian cancer. *PLoS ONE.* 2010;5:e15498.
152. Rosen DG, Yang G, Deavers MT, et al. Cyclin E expression is correlated with tumor progression and predicts a poor prognosis in patients with ovarian carcinoma. *Cancer.* 2006;106:1925–1932.
153. Bellacosa A, de Feo D, Godwin AK, et al. Molecular alterations of the *AKT2* oncogene in ovarian and breast carcinomas. *Int J Cancer.* 1995;64:280–285.
154. Shayesteh L, Lu Y, Kuo WL, et al. *PIK3CA* is implicated as an oncogene in ovarian cancer. *Nat Genet.* 1999;21:99–102.
155. Flesken-Nikitin A, Choi KC, Eng JP, et al. Induction of carcinogenesis by concurrent inactivation of *p53* and *Rb1* in the mouse ovarian surface epithelium. *Cancer Res.* 2003;63:3459–3463.
156. Slamon DJ, Godolphin W, Jones LA, et al. Studies of *HER-2/neu* proto-oncogene in human breast and ovarian cancer. *Science.* 1989;244:707–712.
157. Berchuck A, Kamel A, Whitaker R, et al. Overexpression of *HER-2/neu* is associated with poor survival in advanced epithelial ovarian cancer. *Cancer Res.* 1990;50:4087–4091.
158. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in *HER2*-positive breast cancer. *N Engl J Med.* 2011;365:1273–1283.
159. Bookman MA, Darcy KM, Clarke-Pearson D, et al. Evaluation of monoclonal humanized anti-*HER2* antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of *HER2*: a phase II trial of the Gynecologic Oncology Group. *J Clin Oncol.* 2003;21:283–290.
160. Schultz DC, Vanderveer L, Buetow KH, et al. Characterization of chromosome 9 in human ovarian neoplasia identifies frequent genetic imbalance on 9q and rare alterations involving 9p, including *CDKN2*. *Cancer Res.* 1995;55:2150–2157.

161. McCluskey LL, Chen C, Delgadillo E, et al. Differences in p16 gene methylation and expression in benign and malignant ovarian tumors. *Cancer Res.* 1999;72:87–92.
162. Liu Z, Wang LE, Wang L, et al. Methylation and messenger RNA expression of p15INK4b but not p16INK4a are independent risk factors for ovarian cancer. *Clin Cancer Res.* 2005;11:4968–4976.
163. Levesque MA, Katsaros D, Massobrio M, et al. Evidence for a dose-response effect between p53 (but not p21WAF1/Cip1) protein concentrations, survival, and responsiveness in patients with epithelial ovarian cancer treated with platinum-based chemotherapy. *Clin Cancer Res.* 2000;6:3260–3270.
164. Korkolopoulou P, Vassilopoulos I, Konstantinidou AE, et al. The combined evaluation of p27Kip1 and Ki-67 expression provides independent information on overall survival of ovarian carcinoma patients. *Cancer Res.* 2002;62:404–414.
165. Rosen DG, Yang G, Cai KQ, et al. Subcellular localization of p27kip1 expression predicts poor prognosis in human ovarian cancer. *Clin Cancer Res.* 2005;11:632–637.
166. Casey G, Lopez ME, Ramos JC, et al. DNA sequence analysis of exons 2 through 11 and immunohistochemical staining are required to detect all known p53 alterations in human malignancies. *Oncogene.* 1996;13:1971–1981.
167. Hartmann L, Podratz K, Keeney G, et al. Prognostic significance of p53 immunostaining in epithelial ovarian cancer. *J Clin Oncol.* 1994;12:64–69.
168. Kohler MF, Kerns BJ, Humphrey PA, et al. Mutation and overexpression of p53 in early-stage epithelial ovarian cancer. *Obstet Gynecol.* 1993;81:643–650.
169. Marks JR, Davidoff AM, Kerns B, et al. Overexpression and mutation of p53 in epithelial ovarian cancer. *Cancer Res.* 1991;51:2979–2984.
170. Kohler MF, Marks JR, Wiseman RW, et al. Spectrum of mutation and frequency of allelic deletion of the p53 gene in ovarian cancer. *J Natl Cancer Inst.* 1993;85:1513–1519.
171. Havrilesky L, Hamdan H, Darcy K, et al. Prognostic significance of p53 mutation and p53 overexpression in advanced epithelial ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003;21:3814–3825.
172. Esteller M, Silva JM, Dominguez G, et al. Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. *J Natl Cancer Inst.* 2000;92:564–569.
173. Baldwin RL, Nemeth E, Tran H, et al. BRCA1 promoter region hypermethylation in ovarian carcinoma: a population-based study. *Cancer Res.* 2000;60:5329–5333.
174. Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. *N Engl J Med.* 1996;335:1413–1416.
175. Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA.* 2012;307:382–390.
176. Norquist B, Wurz KA, Pennil CC, et al. Secondary somatic mutations restoring BRCA1/2 predict chemotherapy resistance in hereditary ovarian carcinomas. *J Clin Oncol.* 2011;29:3008–3015.
177. Annunziata CM, O'Shaughnessy J. Poly (ADP-ribose) polymerase as a novel therapeutic target in cancer. *Clin Cancer Res.* 2010;16:4517–4526.
178. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature.* 2005;434:917–921.
179. Banerjee S, Kaye SB, Ashworth A. Making the best of PARP inhibitors in ovarian cancer. *Nat Rev Clin Oncol.* 2010;7:508–519.
180. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366:1382–1392.
181. Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. *J Clin Oncol.* 2010;28:3555–3561.
182. Kang J, D'Andrea AD, Kozono D. A DNA repair pathway-focused score for prediction of outcomes in ovarian cancer treated with platinum-based chemotherapy. *J Natl Cancer Inst.* 2012;104:670–681.
183. Welsh JB, Zarrinkar PP, Sapinoso LM, et al. Analysis of gene expression profiles in normal and neoplastic ovarian tissue samples identifies candidate molecular markers of epithelial ovarian cancer. *Proc Natl Acad Sci USA.* 2001;98:1176–1181.
184. Schwartz DR, Kardia SL, Shedden KA, et al. Gene expression in ovarian cancer reflects both morphology and biological behavior, distinguishing clear cell from other poor-prognosis ovarian carcinomas. *Cancer Res.* 2002;62:4722–4729.
185. Bonome T, Lee JY, Park DC, et al. Expression profiling of serous low malignant potential, low-grade, and high-grade tumors of the ovary. *Cancer Res.* 2005;65:10602–10612.
186. Shridhar V, Lee J, Pandita A, et al. Genetic analysis of early- versus late-stage ovarian tumors. *Cancer Res.* 2001;61:5895–5904.
187. Spentzos D, Levine DA, Kolia S, et al. Unique gene expression profile based on pathologic response in epithelial ovarian cancer. *J Clin Oncol.* 2005;23:7911–7918.
188. Berchuck A, Iversen ES, Luo J, et al. Microarray analysis of early stage serous ovarian cancers shows profiles predictive of favorable outcome. *Clin Cancer Res.* 2009;15:2448–2455.
189. Bild AH, Yao G, Chang JT, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. *Nature.* 2006;439:353–357.
190. Mok SCH, Bell DA, Knapp RC, et al. Mutation of K-ras protooncogene in human ovarian epithelial tumors of borderline malignancy. *Cancer Res.* 1993;53:1489–1492.
191. Singer G, Oldt R, III, Cohen Y, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. *J Natl Cancer Inst.* 2003;95:484–486.
192. Diaz-Padilla I, Malpica AL, Minig L, et al. Ovarian low-grade serous carcinoma: a comprehensive update. *Gynecol Oncol.* 2012;126:279–285.
193. Gershenson DM, Deavers M, Diaz S, et al. Prognostic significance of p53 expression in advanced-stage ovarian serous borderline tumors. *Clin Cancer Res.* 1999;5:4053–4058.
194. Berchuck A, Kohler MF, Hopkins MP, et al. Overexpression of p53 is not a feature of benign and early-stage borderline epithelial ovarian tumors. *Cancer Res.* 1994;52:232–236.
195. Ortiz BH, Ailawadi M, Colitti C, et al. Second primary or recurrence? Comparative patterns of p53 and K-ras mutations suggest that serous borderline ovarian tumors and subsequent serous carcinomas are unrelated tumors. *Cancer Res.* 2001;61:7264–7267.
196. Jones S, Wang TL, Shih I, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. *Science.* 2010;330:228–231.
197. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med.* 2010;363:1532–1543.
198. Anglesio MS, Carey MS, Kobel M, et al. Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Symposium, June 24th, 2010. *Gynecol Oncol.* 2011;121:407–415.
199. McConechy MK, Anglesio MS, Kallinger SE, et al. Subtype-specific mutation of PPP2R1A in endometrial and ovarian carcinomas. *J Pathol.* 2011;223:567–573.
200. Obata K, Morland SJ, Watson RH, et al. Frequent PTEN/MMAC mutations in endometrioid but not serous or mucinous epithelial ovarian tumors. *Cancer Res.* 1998;58:2095–2097.
201. Wu R, Zhai Y, Fearon ER, et al. Diverse mechanisms of beta-catenin deregulation in ovarian endometrioid adenocarcinomas. *Cancer Res.* 2001;61:8247–8255.
202. Wu R, Hendrix-Lucas N, Kuick R, et al. Mouse model of human ovarian endometrioid adenocarcinoma based on somatic defects in the Wnt/beta-catenin and PI3K/Pten signaling pathways. *Cancer Cell.* 2007;11:321–333.
203. Dinulescu DM, Ince TA, Quade BJ, et al. Role of K-ras and Pten in the development of mouse models of endometriosis and endometrioid ovarian cancer. *Nat Med.* 2005;11:63–70.
204. Behbakht K, Sill MW, Darcy KM, et al. Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011;123:19–26.
205. Lin WM, Forgacs E, Warshal DP, et al. Loss of heterozygosity and mutational analysis of the PTEN/MMAC1 gene in synchronous endometrial and ovarian carcinomas. *Clin Cancer Res.* 1998;4:2577–2583.
206. Guerra F, Kurelac I, Magini P, et al. Mitochondrial DNA genotyping reveals synchronous nature of simultaneously detected endometrial and ovarian cancers. *Gynecol Oncol.* 2011;122:457–458.
207. Gemignani ML, Schlaerth AC, Bogomolnii F, et al. Role of KRAS and BRAF gene mutations in mucinous ovarian carcinoma. *Cancer Res.* 2003;63:378–381.
208. Shah SP, Kobel M, Senz J, et al. Mutation of FOXL2 in granulosa-cell tumors of the ovary. *N Engl J Med.* 2009;360:2719–2729.
209. Heravi-Moussavi A, Anglesio MS, Cheng SW, et al. Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers. *N Engl J Med.* 2012;366:234–242.
210. Scheffner M, Werness BA, Huibregtse JM, et al. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell.* 1990;63:1129–1136.
211. Scheffner M, Munger K, Byrne JC, et al. The state of the p53 and retinoblastoma gene in human cervical carcinoma cell lines. *Proc Natl Acad Sci USA.* 1991;88:5523–5527.
212. Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science.* 1990;248:76–79.
213. de Boer MA, Jordanova ES, Kenter GG, et al. High human papillomavirus oncogene mRNA expression and not viral DNA load is associated

- with poor prognosis in cervical cancer patients. *Clin Cancer Res.* 2007;13:132–138.
214. Wang SS, Trunk M, Schiffman M, et al. Validation of p1INK4a as a marker of oncogenic human papillomavirus infection in cervical biopsies from a population-based cohort in Costa Rica. *Cancer Epidemiol Biomarkers Prev.* 2004;13:1355–1360.
 215. Parker MF, Arroyo GF, Geradts J, et al. Molecular characterization of adenocarcinoma of the cervix. *Cancer Res.* 1997;64:242–251.
 216. Narayan G, Pulido HA, Koul S, et al. Genetic analysis identifies putative tumor-suppressor sites at 2q35-q36.1 and 2q36.3-q37.1 involved in cervical cancer progression. *Oncogene.* 2003;22:3489–3499.
 217. Umayahara K, Numa F, Suehiro Y, et al. Comparative genomic hybridization detects genetic alterations during early stages of cervical cancer progression. *Genes Chromosomes Cancer.* 2002;33:98–102.
 218. Yang YC, Shyong WY, Chang MS, et al. Frequent gain of copy number on the long arm of chromosome 3 in human cervical adenocarcinoma. *Cancer Genet Cytogenet.* 2001;131:48–53.
 219. Lando M, Holden M, Bergersen LC, et al. Gene dosage, expression, and ontology analysis identifies driver genes in the carcinogenesis and chemoradioresistance of cervical cancer. *PLoS Genet.* 2009;5:e1000719.
 220. Lin WM, Michalopoulos EA, Dhurander N, et al. Allelic loss and microsatellite alterations of chromosome 3p14.2 are more frequent in recurrent cervical dysplasias. *Clin Cancer Res.* 2000;6:1410–1414.
 221. Kirchhoff M, Rose H, Petersen BL, et al. Comparative genomic hybridization reveals a recurrent pattern of chromosomal aberrations in severe dysplasia/carcinoma in situ of the cervix and in advanced-stage cervical carcinoma. *Genes Chromosomes Cancer.* 1999;24:144–150.
 222. Birrer MJ, Hendricks D, Farley J, et al. Abnormal Fhit expression in malignant and premalignant lesions of the cervix. *Cancer Res.* 1999;59:5270–5274.
 223. Huang LW, Chao SL, Chen TJ. Reduced Fhit expression in cervical carcinoma: correlation with tumor progression and poor prognosis. *Cancer Res.* 2003;90:331–337.
 224. Connolly DC, Greenspan DL, Wu R, et al. Loss of fhit expression in invasive cervical carcinomas and intraepithelial lesions associated with invasive disease. *Clin Cancer Res.* 2000;6:3505–3510.
 225. Liu FS, Hsieh YT, Chen JT, et al. (fragile histidine triad) gene analysis in cervical intraepithelial neoplasia. *Cancer Res.* 2001;82:283–290.
 226. Krivak TC, McBroom JW, Seidman J, et al. Abnormal fragile histidine triad (FHIT) expression in advanced cervical carcinoma: a poor prognostic factor. *Cancer Res.* 2001;61:4382–4385.
 227. Grendys ECJ, Barnes WA, Weitzel J, et al. Identification of H, K, and N-ras point mutations in stage IB cervical carcinoma. *Cancer Res.* 1997;65:343–347.
 228. Koulos JP, Wright TC, Mitchell MF, et al. Relationships between c-Ki-ras mutations, HPV types, and prognostic indicators in invasive endocervical adenocarcinomas. *Cancer Res.* 1993;48:364–369.
 229. Riou G, Barrois M, Sheng ZM, et al. Somatic deletions and mutations of c-Ha-ras gene in human cervical cancers. *Oncogene.* 1988;3:329–333.
 230. Van Le L, Stoerker J, Rinehart CA, et al. H-ras codon 12 mutation in cervical dysplasia. *Cancer Res.* 1993;49:181–184.
 231. Riou G, Le MG, Favre M, et al. Human papillomavirus-negative status and c-myc gene overexpression: independent prognostic indicators of distant metastasis for early-stage invasive cervical cancers. *J Natl Cancer Inst.* 1992;84:1525–1526.
 232. Bourhis J, Le MG, Barrois M, et al. Prognostic value of c-myc proto-oncogene overexpression in early invasive carcinoma of the cervix. *J Clin Oncol.* 1990;8:1789–1796.
 233. Dong SM, Kim HS, Rha SH, et al. Promoter hypermethylation of multiple genes in carcinoma of the uterine cervix. *Clin Cancer Res.* 2001;7:1982–1986.
 234. Virmani AK, Muller C, Rath A, et al. Aberrant methylation during cervical carcinogenesis. *Clin Cancer Res.* 2001;7:584–589.
 235. Wong YF, Selvanayagam ZE, Wei N, et al. Expression genomics of cervical cancer: molecular classification and prediction of radiotherapy response by DNA microarray. *Clin Cancer Res.* 2003;9:5486–5492.
 236. Kuzmin I, Liu L, Dammann R, et al. Inactivation of RAS association domain family 1A gene in cervical carcinomas and the role of human papillomavirus infection. *Cancer Res.* 2003;63:1888–1893.
 237. Kim SJ, Lee SY, Lee C, et al. Differential expression profiling of genes in a complete hydatidiform mole using cDNA microarray analysis. *Gynecol Oncol.* 2006;103:654–660.
 238. Feng HC, Tsao SW, Ngan HY, et al. Differential expression of insulin-like growth factor binding protein 1 and ferritin light polypeptide in gestational trophoblastic neoplasia: combined cDNA suppression subtractive hybridization and microarray study. *Cancer.* 2005;104:2409–2416.
 239. Fong PY, Xue WC, Ngan HY, et al. Mcl-1 expression in gestational trophoblastic disease correlates with clinical outcome: a differential expression study. *Cancer.* 2005;103:268–276.

3

Hereditary Gynecologic Cancers

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INTRODUCTION

Identifying a woman with gynecologic cancer as having a hereditary cancer syndrome has tremendous implications for both the patient herself and for her family members. Hereditary Breast and Ovarian Cancer syndrome, caused by germline mutations in *BRCA1* or *BRCA2*, as well as Lynch syndrome, caused by germline mutations in *MLH1*, *MSH2*, *MSH6*, or *PMS2*, are the most common hereditary syndromes that include gynecologic cancers as part of their cancer spectrum. Other syndromes that include gynecologic cancers include Cowden's syndrome (*PTEN* germline mutation), Peutz-Jeghers syndrome (*STK11* germline mutation), and Li-Fraumeni syndrome (*TP53* germline mutation) (Table 3.1). All of these syndromes are caused by mutations in tumor-suppressor genes. In order for an individual to develop a cancer associated with one of these syndromes, both the maternally and paternally inherited copy of the relevant gene must be inactivated as described by Knudsen's two hit hypothesis (1). Women with hereditary cancer syndromes have inherited, from either their mother or their father, a nonworking copy of one of the relevant genes and this defect is present in all of their cells.

Table 3.1 Selected Hereditary Cancer Syndromes with Gynecologic Manifestations

Syndrome	Gene	Chromosome	Predominant Cancers
Hereditary breast/ovarian cancer	<i>BRCA1</i>	17q21	Breast, ovary
	<i>BRCA2</i>	13q12	
Lynch syndrome	<i>MSH2</i>	2p16	Colon, endometrium, ovary and urinary tract
	<i>MLH1</i>	3p21	
	<i>MSH6</i>	2p16	
	<i>PMS2</i>	7p22	
Cowden syndrome	<i>PTEN</i>	10q23	Breast, thyroid and endometrial
Li-Fraumeni syndrome	<i>TP53</i>	17p13	Breast, sarcomas, leukemias, and brain
Peutz-Jeghers syndrome	<i>STK11</i>	19p13	Colon, breast, gastric, and ovarian sex cord-stromal tumors with annular tubules (SCTAT)

Therefore, in order for cancer to develop in a susceptible tissue through defects in a specific pathway, only the second working copy of the relevant gene needs to be lost. This is why the cancers occur earlier and more frequently than in the general population. This also explains why not all individuals with an inherited predisposition develop cancer, as it is possible that the second working copy of the relevant tumor suppressor gene is never lost in a susceptible tissue. Further, as these syndromes are all caused by mutations in a single allele of the relevant tumor suppressor gene, they are all autosomal dominant disorders in which each offspring is at 50% risk of inheriting the cancer predisposition.

In recent years, there has been increasing emphasis placed on developing guidelines to assist physicians in recognizing those patients in whom genetic counseling and testing may be helpful. In addition, new prognostic and therapeutic implications that distinguish a cancer patient with a hereditary cancer syndrome have been discovered. Finally, recommendations for prevention of cancer have been refined over the last decade and will be discussed in this chapter.

HEREDITARY BREAST OVARIAN CANCER SYNDROME

Epidemiology

Of all common solid tumors, ovarian, fallopian tube, and primary peritoneal cancers have the highest proportion that is caused by heritable germline mutations, with mutations in *BRCA1* and *BRCA2* accounting for the vast majority. In one series from University of Washington, of 360 patients undergoing primary surgery for epithelial ovarian, fallopian tube, or primary peritoneal cancer, 63 (17.5%) patients had a deleterious mutation in either *BRCA1* or *BRCA2*. Three (0.8%) patients had deleterious mutations in *TP53* and 2 (0.5%) patients had deleterious mutations in *MSH6* (2). Additionally, 17 (4.7%) patients harbored germline loss of function mutations in 1 of 8 other genes known to be important in inherited breast cancer (*CHEK2*, *PALB2*, *BARD1*, *BRIP1*, *RAD50*, *RAD51C*, *NBN*, and *MRE11*), though it is not yet known if risks associated with mutations in these other genes are great enough to be considered causative or if loss of function mutations in these genes act more as modifiers of cancer risk.

When just pelvic serous cancer is examined, 16% to 18% of unselected patients with high-grade pelvic serous cancer have been reported to have a deleterious *BRCA1* or *BRCA2* mutation (3–5). In 2005, Pal and colleagues reported on a population-based series of 121 incident pelvic serous cancers diagnosed in the Tampa, Florida region from 2000 to 2003. In this series, 20 (16.5%) patients had a deleterious *BRCA* mutation identified on sequencing of *BRCA1* and *BRCA2* (3). When the cohort was stratified by family history, mutations

were found in 10 (9.9%) of 101 patients without any family history of breast or ovarian cancer in first- or second-degree relatives. In 2011, Zhang and colleagues reported an updated population-based series of 1342 invasive ovarian cancers ascertained in Ontario, Canada, from 1995 to 1999 and from 2002 to 2004. In this series, 135 (18.0%) of 751 patients with serous ovarian cancer had a deleterious *BRCA1* or *BRCA2* mutation identified (4). Of note, 6.1% of the nonfounder mutations identified in this study were large genomic rearrangements not detected on sequencing and only identified on multiplex ligation-dependent probe amplification (MLPA) testing. In 2012, Alsop and colleagues found 118 (16.6%) *BRCA1* and *BRCA2* mutations in 709 patients with incident pelvic serous cancers ascertained as part of the Australia Ovarian Cancer Study from 2002 to 2006. Additionally, similar to the Pal study, 62 (8.3%) of 749 patients without a significant family had a germline *BRCA* mutation identified, and 44% of all the mutations identified in the study occurred in the absence of a family history (5).

Given this substantial frequency of mutations in women with pelvic serous cancer irrespective of family history, both the American College of Obstetricians and Gynecologists and the National Comprehensive Cancer Network state that it is reasonable to offer testing for *BRCA* mutations to any woman with high-grade serous ovarian cancer if it will impact the care of either the woman or her close family members (6, 7).

Pathology

BRCA1- and *BRCA2*-associated cancers appear to be associated only with specific histological subtypes of ovarian and fallopian tube cancer. In one of the first studies to examine this issue, Boyd and colleagues genotyped 189 consecutive Jewish patients with invasive epithelial ovarian cancer, seen at Memorial Sloan-Kettering Cancer Center for the 3 common Ashkenazi founder mutations. Of the 88 patients with a founder mutation in *BRCA1* or *BRCA2*, 60 (68%) had serous ovarian cancer and 12 (14%) had adenocarcinoma, not otherwise specified. Twelve (14%) and 2 (2%) patients had endometrioid and clear cell ovarian cancer, respectively. No patient with mucinous ovarian cancer had a *BRCA* mutation (8). More recently, in the 2011 Zhang report, 82% of *BRCA*-associated cancers were serous, 16% were endometrioid, 1.2% were clear cell, and 0% were mucinous (4).

It should be noted that, in most of the studies to date, the proportion of endometrioid and clear cell carcinomas associated with *BRCA* mutations may be overrepresented. *BRCA*-associated serous ovarian cancers have been reported to appear “pseudo-endometrioid,” resulting in misclassification unless serous specific immunohistochemical markers are used (9). In the 2012 Alsop report, *BRCA1* or *BRCA2* mutations were identified in 10 (8.9%) of 119 cancers initially diagnosed as endometrioid. However, 8 of these cancers were subsequently reclassified as serous or unspecified carcinoma after immunohistopathology review. Similarly, of the 4 (6.3%) of 63 cancers initially classified as clear cell identified as having a *BRCA* mutation, 3 were reclassified to be high-grade serous with focal clear cell differentiation (5).

Natural History of *BRCA*-associated Ovarian Cancer

Over a dozen studies have reported on differences in outcome between *BRCA*-associated and sporadic ovarian and fallopian tube cancers (8, 10–19). In the first study to address this issue, Rubin and colleagues, utilizing a case-control design, reported on 53 patients with a deleterious *BRCA1* mutation. They found

that patients with advanced stage *BRCA1*-associated disease had a median survival of 77 months compared to a median survival of 29 months in age, stage, and histologic subtype matched controls (10). In 2008, Chetrit and colleagues reported on an Israeli population-based series including data from 779 Jewish women with invasive epithelial ovarian cancer genotyped for the three Ashkenazi founder mutations. In this series, *BRCA* mutation status was associated with an increase in survival from 37.9 months to 53.7 months (15). Most recently, investigators from the Cancer Genome Atlas (TCGA) project reported that patients with stage II to IV high-grade serous ovarian or fallopian tube cancer and germline or sporadic mutations in *BRCA1* or *BRCA2* had improved outcome compared to patients without evidence of *BRCA* deficiency (median overall survival 66.5 vs. 41.9 months, $p = 0.0003$) (17). Interestingly, in this series, tumors associated with mutations in *BRCA1* or *BRCA2* also had improved outcome compared to patients with silencing of *BRCA1* due to methylation of the *BRCA1* promoter, suggesting that the mechanism of loss of *BRCA* function may be relevant to the biology and clinical behavior of these tumors.

Until recently, most studies examining the impact of *BRCA* mutations on outcome have analyzed carriers of *BRCA1* mutations and carriers of *BRCA2* mutations together. However, mutations in *BRCA1* and *BRCA2* cause related, but distinct, cancer susceptibility syndromes. Given this, it is possible that response to therapy and clinical outcome may differ between carriers of *BRCA1* mutations and carriers of *BRCA2* mutations. In the first study to examine this issue, Yang et al. reexamined data from the TCGA ovarian project. In this report, patients with *BRCA2*-associated ovarian cancer had markedly better outcome than those with *BRCA* wildtype tumors (HR = 0.33; 95% CI, 0.16–0.69). *BRCA1*-associated tumors also appeared to have a somewhat better outcome than *BRCA* wildtype tumors (HR = 0.76; 95% CI, 0.43–1.35), but this result did not reach statistical significance (20). In a single institution retrospective cohort from Memorial Sloan-Kettering Cancer Center, Hyman and colleagues reported on the outcome of 190 stage III to IV high-grade serous ovarian and fallopian tube cancer patients genotyped for *BRCA* mutations. Similar to the TCGA series, *BRCA2*-associated tumors were associated with significantly improved outcome compared to *BRCA* wildtype tumors (HR = 0.20; 95% CI, 0.06–0.65). In this study, a trend suggesting that *BRCA1*-associated tumors may have improved outcome compared to *BRCA* wildtype tumors (HR = 0.70; 95% CI, 0.36–1.38) was also noted (18). Most recently, Bolton et al. reported on a pooled series of 3,879 invasive epithelial ovarian cancers genotyped for *BRCA* mutations and found that in a model adjusted for age at diagnosis, stage, grade, and histology, both *BRCA2* (HR = 0.49; 95% CI, 0.39–0.61) and *BRCA1* (HR = 0.73; 95% CI, 0.64–0.84) had improved outcome compared to *BRCA* wildtype tumors. Tests of heterogeneity also demonstrated that hazard ratio for *BRCA2* mutation carriers was significantly different from the HR for *BRCA1* mutation carriers (19). Given the clear differences in the outcome between *BRCA* mutated and *BRCA* wildtype tumors, several authors have recommended that, at least for participants on clinical trials, we should obtain germline *BRCA* mutation status and stratify outcomes for the presence or absence of mutations (21, 22).

Therapeutic Implications

BRCA1 and *BRCA2* are known to be necessary for repair of double strand DNA breaks through homologous recombination (23, 24). Therefore, tumor cells from *BRCA*-associated ovarian cancers that have no working copy of either *BRCA1* or *BRCA2* are believed to be exquisitely sensitive to agents that induce double strand DNA breaks, such as platinum-based chemotherapy. While this mechanism likely explains at least some of the survival

advantage seen in *BRCA*-associated ovarian cancer, until recently knowledge of this information did not provide a new therapeutic opportunity as almost all patients with serous ovarian cancer receive platinum-based chemotherapeutics as part of first-line therapy. In 2005, however, 2 independent groups hypothesized that the *BRCA*-dependent homologous recombination pathway could be stressed by inhibiting poly (ADP-ribose) polymerase (PARP), an enzyme necessary for the repair of single strand DNA breaks (25, 26). If this enzyme (and repair of single strand DNA breaks) is inhibited during DNA replication, the advancing replication fork converts single strand DNA breaks into double strand breaks to be repaired by homologous recombination. In patients with a germline mutation in *BRCA1* or *BRCA2*, the single nonmutant allele is sufficient for allowing repair in non-tumor-associated cells. However, tumor associated cells have lost both working alleles of either *BRCA1* or *BRCA2* and therefore cannot utilize homologous recombination, forcing the cell to use error-prone nonhomologous end joining, which frequently leads to complex rearrangements and eventual apoptosis (27).

The first clinical data supporting the potential utility of PARP inhibitors in *BRCA*-associated tumors were published in 2009 (28). In this phase 1 trial, 60 patients, including 22 with either a documented *BRCA1* or *BRCA2* mutation, received increasing doses of a novel PARP inhibitor, olaparib. Radiologic response or stable disease was observed in 11 (9 ovarian and 2 breast cancer) of 19 patients with heavily pretreated *BRCA*-associated ovarian, breast or prostate cancer. This was followed shortly thereafter by a phase 2 study evaluating activity of olaparib at two dose levels in 57 patients with *BRCA*-associated pelvic serous cancer (29). In this series, 11 of 33 patients treated at the higher dose level had complete or partial response and an additional 12 patients had stable disease. Given the promising results of these first two trials, there are over a dozen ongoing or planned trials of PARP inhibitors in *BRCA*-associated pelvic serous cancer (30). Further, given that 9% to 15% of sporadic ovarian cancer has silencing of the homologous recombination pathway through methylation of the *BRCA1* promoter (17, 31, 32), PARP inhibitors are also being actively investigated for treatment of sporadic disease.

Genetic Counseling for Hereditary Breast and Ovarian Cancer Syndrome

Approximately 1 in 345 to 1 in 800 women have a *BRCA1* or *BRCA2* mutation associated with hereditary breast and ovarian cancer (33, 34). Hereditary breast and ovarian cancer syndrome is seen in all racial and ethnic groups. However, due to the phenomenon of genetic drift, several racial and ethnic groups have seen a marked increase in the population frequency of specific mutations, known as founder mutations. Best known of the founder mutations are the 185delAG and 5382insC mutations in *BRCA1* and the 6174delT mutation in *BRCA2* that are collectively found in 1 of 40 individuals of eastern European Jewish (Ashkenazi) heritage. Increased incidence of *BRCA* mutations has also been seen in individuals of Icelandic, Swedish, Dutch, Polish, French Canadian, and Hungarian descent.

The vast majority of deleterious mutations in *BRCA1* and *BRCA2* are nonsense mutations that lead to a premature stop codon and a truncated protein. While most protein-truncating mutations are detected by direct sequencing of *BRCA1* and *BRCA2*, approximately 6% to 18% of clearly deleterious mutations are caused by large genomic deletions or rearrangements that will not be picked up on direct sequencing and need to instead be screened for by methods such as MLPA (35–37). Additionally 6% to 17% of individuals undergoing direct sequencing of *BRCA1* or *BRCA2* will have a missense mutation identified that causes a single amino acid substitution in the protein (38). These missense mutations are termed variants of

uncertain significance, as it is frequently not possible to characterize whether the protein can tolerate the resulting amino acid substitution or if the substitution will cause abrogation of protein function.

Genetic counselors and other appropriately trained genetic professionals can assist in determining what are the most appropriate genetic tests for an individual patient. In addition, they can assist in interpreting the results in context with the family history. Further, the genetic counselor can assist in identifying who is the most appropriate individual to initiate genetic testing with, as in many families, it may be more informative to initiate testing in a relative other than the present individual. Lastly, genetic counselors can help identify other relatives who should be informed of a potential inherited risk (39) and can assist patients with plans for such communication.

CANCER RISKS ASSOCIATED WITH A *BRCA1* OR *BRCA2* MUTATION

For women with mutations in *BRCA1*, lifetime risks, through age 70, of pelvic (ovarian, fallopian tube, or primary peritoneal) cancer are on the order of 39% to 46%. For women with mutations in *BRCA2*, the lifetime risk of pelvic cancer is 12% to 20% (40, 41). The average age of diagnosis of *BRCA1*-associated pelvic cancers is 53, which is approximately 10 years earlier than the average age of diagnosis of sporadic ovarian or fallopian tube cancer. Interestingly, the average age of *BRCA2*-associated pelvic cancer is 60 to 62 years, which is no earlier than seen with sporadic disease (5, 8). When considering the timing of risk-reduction approaches, it is also important to know risks of cancer by the age of menopause. For women with *BRCA1* mutations, 10% to 21% will develop pelvic cancer by age 50, but only 2% to 3% of women with *BRCA2* mutations will develop pelvic cancer by the same age (41, 42).

Breast cancer risks are also markedly elevated for women with mutations in these genes, with risks of breast cancer approaching 65% to 74% by age 70 for both carriers of *BRCA1* and *BRCA2* mutations (40, 41). Breast cancer also occurs substantially earlier than seen in the general population, with 26% to 34% of carriers of either *BRCA1* or *BRCA2* mutations developing breast cancer by age 50 (40, 41, 43).

A number of genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that modify breast and/or gynecologic cancer risk in the setting of a *BRCA1* or *BRCA2* mutation (44). Unfortunately, none of these markers, alone or in combination, has been shown to alter *BRCA*-associated cancer risk at a magnitude necessary to appreciably guide recommendations for risk-reduction strategies (45).

GUIDELINES FOR OFFERING GENETIC RISK ASSESSMENT FOR HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Several organizations have proposed guidelines for offering genetic risk assessment for hereditary breast and ovarian cancer syndrome. Likely, most relevant to the gynecologic oncologist are the guidelines jointly published by the American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO) (6) and those published by the National Comprehensive Cancer Network (NCCN) (7). Briefly, both of these guidelines state that hereditary cancer risk assessment is a process that: (a) should include assessment of risk, education, and counseling; (b) should be conducted by a physician,

genetic counselor, or other provider with experience in cancer genetics; and (c) may include genetic testing after appropriate counseling and consent is obtained.

Specifically, ACOG and SGO recommend that women with greater than approximately a 20% to 25% chance of having a *BRCA1* or *BRCA2* mutation be offered a genetic risk assessment. Further, they state that it is reasonable to offer genetic risk assessment to any woman who has greater than a 5% to 10% chance of having a *BRCA1* or *BRCA2* mutation. Specific constellations of personal and family history that meet this threshold are outlined in Table 3.2.

There are also several risk prediction models, such as BRCAPRO, BOADICEA, and IBIS, that can assist in predicting the likelihood of a patient having a mutation in *BRCA1* or *BRCA2*. Each of these models, however, has unique advantages and limitations, and selecting the appropriate model is generally best done with the assistance of a genetics professional.

Of particular note to physicians taking care of women with ovarian, fallopian tube, or primary peritoneal cancer, given 16% to 18% of all patients with serous ovarian cancer (including 8% to 10% of patients with no significant family history) will have a

Table 3.2 American College of Obstetricians and Gynecologists and Society of Gynecologic Oncologists Criteria for Offering Genetic Risk Assessment for Hereditary Breast and Ovarian Cancer Syndrome

Patients with greater than an approximate 20%–25% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment is recommended:

- Women with a personal history of both breast cancer and ovarian cancer^a
- Women with ovarian cancer^a and a close relative^b with ovarian cancer or premenopausal breast cancer
- Women with ovarian cancer^a who are of Ashkenazi Jewish ancestry
- Women with breast cancer at age 50 years or younger and a close relative^b with ovarian cancer^a or male breast cancer at any age
- Women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger
- Women with a close relative^b with a known *BRCA1* or *BRCA2* mutation

Patients with greater than an approximate 5%–10% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment may be helpful:

- Women with breast cancer at age 40 years or younger
- Women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high-grade, serous histology at any age
- Women with bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger)
- Women with breast cancer at age 50 years or younger and a close relative^b with breast cancer at age 50 years or younger
- Women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger
- Women with breast cancer at any age and two or more close relatives^b with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age 50 years or younger)
- Unaffected women with a close relative^b who meets one of the previous criteria

^aCancer of the peritoneum and fallopian tubes should be considered a part of the spectrum of the hereditary breast and ovarian cancer syndrome.

^bClose relative is defined as a first-degree relative (mother, sister, daughter) or second-degree relative (grandmother, granddaughter, aunt, niece).

Source: From ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 2009;113:957–966, with permission

Table 3.3 Risk-Reduction Recommendations for Carriers of *BRCA1* and *BRCA2* Mutations

Breast

- Annual mammography and annual breast MRI starting by age 30
- RRSO to reduce breast cancer risk between age 35 and 40 and when childbearing is complete
- Consider chemoprevention with tamoxifen, raloxifene, or an aromatase inhibitor
- Consider RRM

Ovary/Fallopian Tube

- RRSO to reduce ovarian and fallopian tube cancer risk between age 35 and 40 and when childbearing is complete
- Consider chemoprevention with oral contraceptives
- Consider ovarian cancer screening with q6 month transvaginal ultrasound and CA-125 from age 30–35 years until definitive risk-reduction with RRSO

RRSO, risk-reducing salpingo-oophorectomy; RRM, risk-reducing mastectomy.

Source: Adapted from National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology – Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2012. <http://www.nccn.org>. 2012.

deleterious *BRCA1* or *BRCA2* mutation (3–5), both the AGOG/SGO and NCCN practice guidelines state that it is reasonable to offer genetic risk assessment to any women with high-grade pelvic serous cancer if it will impact either her care or the care of her close family members (6, 7).

Screening and Prevention

For unaffected patients with a deleterious mutation in *BRCA1* or *BRCA2*, there are several options to reduce the risk of both gynecologic and breast cancer (Table 3.3).

Screening

Ovarian/Fallopian Tube Cancer

Screening for ovarian and fallopian tube cancer in the general population is not recommended. Reasons for this include the limited sensitivity and specificity of transvaginal ultrasound and CA-125 serum screening. Perhaps equally important is the low annual incidence of disease. In 2008, the annual incidence of ovarian cancer in women over 50 years was 1 in 2785 per year (46). Given this incidence, in order to achieve a positive predictive value of 10% (i.e., 1 ovarian cancer detected for every 10 surgeries) a screening approach must have a specificity of 99.7% in the setting of 100% sensitivity, which has not been achievable with current technologies. However, the annual incidence of ovarian cancer in women over 50 is 1.0% to 2.5% in *BRCA1* mutation carriers and 0.4% to 0.8% in *BRCA2* mutation carriers (40). In this setting, assuming an annual incidence of disease of 1%, a screening regimen with 100% sensitivity only needs a specificity of 91% to achieve a positive predictive value of 10%, which is potentially achievable with current imaging and serum screening approaches. In 2002, Scheuer and colleagues reported the experience of 62 women with a documented mutation in *BRCA1* or *BRCA2* who participated in ovarian cancer screening with twice-yearly transvaginal ultrasound and CA-125 (47). In this cohort, 5 of 7 ovarian and peritoneal cancers were screen detected, with 4 of these cancers being stage I or stage II. During the course of this study, however, another 5 of 55 women without cancer underwent exploratory surgery due to abnormal screening results. Together these results suggest that

twice-yearly transvaginal ultrasound and CA-125 screening in women with *BRCA1* or *BRCA2* mutations was associated with possibly acceptable 71% sensitivity, 91% specificity, and 50% positive predictive values. Importantly, a similar screening program at Cedars-Sinai Medical Center could not replicate these results. In this series of 213 women at increased risk of ovarian cancer, including 33 with mutations in *BRCA1* or *BRCA2*, only 4 of 8 invasive ovarian cancers were screen detected, and 3 of the 4 screen detected cancers were stage IIIc (48). In 2007, Hermesen and colleagues reported on the experience of 888 women with *BRCA1* or *BRCA2* mutations who participated in ovarian cancer screening with annual transvaginal ultrasound and CA-125 for a mean of 1.7 years between 1993 and 2005. In this study, 5 of the 10 incident invasive cancers presented as interval cancers with a normal screening result 3 to 10 months prior to diagnosis. Further, of the 5 screen detected cancers, 4 were stage III or IV, leading the authors to conclude that annual screening is not efficacious (49).

Of note, all of the studies to date commenting on ovarian cancer screening in *BRCA* mutation carriers have been retrospective case series and not rigorously conducted prospective screening trials. Two such prospective trials specifically targeting women at familial/inherited risk are either ongoing or recently completed, but not reported. In the recently completed Gynecologic Oncology Group study 0199, a prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer, participants elected either surveillance with annual transvaginal ultrasound and every 3 month CA-125 interrogated with the risk of ovarian cancer (ROCA) algorithm or risk-reducing salpingo-oophorectomy (RRSO) (50). All participants in the study were genotyped, and just under 400 of the approximately 1600 women who elected surveillance had a *BRCA* mutation. The study has completed data collection and is currently in analysis. The UK familial ovarian cancer screening study (UK FOCSS) is the other ongoing large-scale trial of women at familial or inherited risk (51). In this study, approximately 2350 women with greater than a 10% lifetime risk of ovarian cancer are being followed with annual transvaginal ultrasound and every 4 month CA-125 also interrogated with the ROCA algorithm. Study results are expected in 2013–2014.

Until results from GOG 199 and UK FOCSS are available, despite the absence of clear evidence for benefit, women with mutations in *BRCA1* or *BRCA2* likely should be recommended to consider ovarian cancer screening with transvaginal ultrasound and CA-125 determinations every 6 months from age 30 to 35 until they undergo definitive risk-reduction with risk-reducing salpingo-oophorectomy (7).

Breast Cancer

For patients with a deleterious mutation in *BRCA1* or *BRCA2*, annual mammography starting by age 30 is recommended (7, 52). However, several studies have suggested that mammography alone in women with *BRCA* mutations is inadequate. In 2001, Brekelmans and colleagues reported that 4 of 9 invasive breast cancers in 128 *BRCA* mutation carriers presented as palpable masses in the interval between screens (53). Similarly, in 2002, Scheuer et al. reported that 7 of 12 invasive breast cancers diagnosed in 251 *BRCA* mutation carriers undergoing mammographic screening presented as interval cancers (47). Due to the relatively low sensitivity of mammography, breast MRI has been investigated as a complimentary imaging modality. Three of the largest studies to date have shown a 71% to 78% sensitivity of breast MRI for *BRCA*-associated cancers compared to a 36% to 40% sensitivity for mammography (54). Further, in 2011, Warner and colleagues demonstrated that the addition of annual MRI to annual mammography led to a down staging of *BRCA*-associated breast cancers (adjusted hazard ratio for the

development of stage II to IV breast cancer associated with MRI screening = 0.30; 95% CI, 0.12–0.72) (55). Currently both the National Comprehensive Cancer Network and the American Cancer Society recommend the combination of annual mammography and annual breast MRI, beginning by age 30, for breast screening in women with *BRCA* mutations (7, 52).

Chemoprevention

Ovarian/Fallopian Tube Cancer

Multiple studies have suggested that use of oral contraceptives in the general population is associated with a substantial and long-lasting reduction in the risk of ovarian cancer (56). Given this, several authors have examined the impact of oral contraceptives on ovarian cancer risk in the setting of *BRCA1* or *BRCA2* mutations. In a recent meta-analysis of 5 case-control and retrospective cohort studies, Iodice and colleague found that ever use of oral contraceptives was associated with a significant reduction in ovarian cancer risk in both *BRCA1* (summary relative risk = 0.51; 95% CI, 0.40–0.65) and *BRCA2* (summary relative risk = 0.52; 95% CI, 0.31–0.87) mutation carriers (57). Further, longer use was associated with a greater risk-reduction, with a 36% risk reduction seen for each 10 years of use (summary relative risk = 0.64; 95% CI, 0.53–0.78).

When caring for women with *BRCA1* or *BRCA2* mutations, it is important, however, to evaluate for both breast and ovarian cancer risk, and the data regarding breast cancer risk has been somewhat more conflicting. Of 5 published studies addressing the impact of oral contraceptives on breast cancer risk in *BRCA1* mutation carriers, 3 suggested an increased risk of breast cancer with oral contraceptive use and 2 showed no increase in risk (58–62). Similarly in the 3 studies reporting on breast cancer risk with oral contraceptive use in *BRCA2* mutation carriers, 2 studies suggested an increased risk, and one study showed no increase in risk (58, 60, 62). In the Iodice meta-analysis, neither *BRCA1* (summary relative risk = 1.09; 95% CI, 0.77–1.54) nor *BRCA2* (summary relative risk = 1.15; 95% CI, 0.61–2.18) mutation carriers demonstrated a statistically significant increased risk of breast cancer with oral contraceptive use. However, oral contraceptive formulations used before 1975 were associated with an increased risk of breast cancer (summary relative risk = 1.47; 95% CI, 1.06–2.04). Given the data currently available, it likely still makes sense to counsel patients that oral contraceptives may be associated with some adverse impact on breast cancer risk. This potential risk, however, needs to be balanced against the risk of unintended pregnancy and the benefit of oral contraceptives on ovarian cancer risk.

Breast Cancer

The selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, in addition to the aromatase inhibitor exemestane have been studied in the general population as chemoprevention for breast cancer. Tamoxifen is the only one of these agents that has been studied in women with *BRCA* mutations. King and colleagues, in a reanalysis of the NSABP P-1 trial, found a suggestion that tamoxifen was associated with protection against *BRCA2* associated breast cancer (risk ratio, 0.38; 95% CI, 0.06–1.56) but not *BRCA1* associated breast cancer (risk ratio, 1.67; 95% CI, 0.32–10.70), though neither of these results reached statistical significance (63). It was speculated that the reason for this possible differential effect was the different estrogen receptor phenotypes of breast cancer seen between *BRCA1* and *BRCA2* mutations carriers. *BRCA2*-associated breast cancers are ER positive 65% to 80% of the time, as opposed to only 10% to 25% of *BRCA1*-associated breast cancers (64, 65). In 2000, Narod and colleagues looked at the impact of therapeutic tamoxifen on contralateral breast cancer risk. In

this study, tamoxifen appeared to be associated with a reduction of contralateral breast cancer risk in both *BRCA1* (odds ratio 0.38; 95% CI, 0.19–0.74) and *BRCA2* (odds ratio 0.63; 95% CI, 0.20–1.50) mutation carriers (66). Of potential significance, *BRCA1* mutation carriers who received tamoxifen in this study likely had ER positive disease. Weitzel et al. have subsequently demonstrated that, in women with *BRCA* mutations who develop contralateral breast cancer, the ER status of the second breast cancer is highly concordant with the ER status of the first breast cancer, suggesting that women with ER positive *BRCA1*-associated breast cancer are more likely to develop a second ER positive cancer and therefore more likely to benefit from hormonal chemoprevention (67).

Risk-Reducing Surgery

Salpingo-Oophorectomy

Impact on ovarian cancer risk. Two of the earliest studies to examine the impact of risk-reducing salpingo-oophorectomy (RRSO) on ovarian cancer risk were published in 2002. The first of these was a prospective cohort study from Memorial Sloan-Kettering Cancer Center. In this study, 170 women with a documented deleterious mutation in *BRCA1* or *BRCA2* elected either surveillance or RRSO. In this series, RRSO was associated with a 75% reduction in the subsequent risk of breast or *BRCA*-associated gynecologic cancer (HR = 0.25; 95% CI, 0.08–0.74) (68). When the impact of RRSO on gynecologic risk alone was examined, there was a suggestion of an approximately 85% reduction in gynecologic cancer risk (HR = 0.15; 95% CI, 0.02–1.31). Simultaneous with this report, a retrospective study from University of Pennsylvania found that RRSO was associated with an approximately 96% reduction in gynecologic cancer risk (HR = 0.04; 95% CI, 0.01–0.16) (69). However, a commentary from Klaren et al. pointed out that the retrospective study may have over-estimated the risk-reduction conferred (70). Since that time, several other studies have suggested that oophorectomy is associated with an 71% to 89% reduction in gynecologic cancer risk and a 2009 meta-analysis concluded that RRSO was associated with approximately an 79% reduction in risk of *BRCA*-associated gynecologic cancer (HR = 0.21; 95% CI, 0.12–0.39) (71).

The origin of peritoneal cancers after RRSO is not entirely clear. Some of these may represent recurrence of occult ovarian or tubal malignancies that were not recognized at time of initial pathologic evaluation, emphasizing the need for careful pathologic evaluation of the entire ovary and fallopian tube at time of RRSO. It has also been speculated that the peritoneal cancer can arise from exfoliated tubal cells (endosalpingiosis) that implant on the peritoneum and undergo malignant transformation in that location. Lastly, some authors have suggested that peritoneal malignancies can start exclusively in the peritoneum through müllerian metaplasia (72). Irrespective of the origin, it is important that patients undergoing RRSO be informed of the small possibility of primary peritoneal cancer occurring after the procedure.

Impact on breast cancer risk. In the first study examining the impact of RRSO on breast cancer risk, Rebbeck and colleagues found that RRSO in women with a *BRCA1* mutation was associated with a 47% reduction in *BRCA1*-associated breast cancer risk (HR = 0.53; 95% CI, 0.33–0.84) (73). In the prospective study by Kauff et al. reported in 2002, which examined both *BRCA1* and *BRCA2* mutation carriers, RRSO appeared to be associated with approximately a 68% reduction in breast cancer risk (HR = 0.32; 95% CI, 0.08–1.20) (68). In 2008, Kauff and Rebbeck pooled their updated prospective data and were able to report on 597 women with breast tissue at risk who had RRSO or surveillance and were prospectively followed for 2.8 years (74). When women with *BRCA1* and *BRCA2* mutations were examined together, RRSO was associated with a 47%

reduction in breast cancer risk (HR = 0.53; 95% CI, 0.29–0.96). However when *BRCA1* and *BRCA2* mutation carriers were examined separately, women with *BRCA2* mutations had a 72% reduction in breast cancer risk compared to women who left their ovaries *in situ* (HR = 0.28; 95% CI, 0.08–0.92). Women with *BRCA1* mutations appeared to have a 39% reduction in breast cancer risk (HR = 0.61; 95% CI, 0.30–1.22), but despite this being the largest prospective study to date, these results did not reach statistical significance. An exploratory analysis examining the impact of RRSO on breast cancer stratified for ER status was also performed. In this analysis, RRSO appeared to be profoundly protective against ER positive breast cancer (HR = 0.22; 95% CI, 0.05–1.05). Not unexpectedly, no impact against ER-negative breast cancer was noted (HR = 1.10; 95% CI, 0.48–2.51).

Impact on life expectancy. Domchek and colleagues reported on results of a prospective cohort study concluding that RRSO was associated with reduction in breast cancer-specific (HR = 0.44; 95% CI, 0.26–0.76), ovarian cancer-specific (HR = 0.21; 95% CI, 0.06–0.80), and all-cause mortality (HR = 0.40; 95% CI, 0.26–0.61) (75). While the effect of RRSO on mortality demonstrated by Domchek and colleagues is almost certainly present, there is a fair amount of instability in the estimates of the actual magnitude of this effect, as participants could be ascertained to this study as many as 20 years prior to the identification of *BRCA1* and *BRCA2*, but in many cases likely only underwent genotyping (and inclusion in the final analysis) if: (a) they lived long enough for clinical testing to become available and (b) they developed a cancer of interest.

Even given the limitations of this and other studies evaluating the efficacy of RRSO on subsequent cancer risk and mortality, for carriers of *BRCA1* and *BRCA2* mutations, RRSO remains the best available protection against pelvic serous cancer and should be strongly considered between 35 and 40 years of age and after childbearing is complete.

Technical considerations. Given that the ovaries and fallopian tubes are both at risk for malignant transformation, it is imperative that all of the ovaries and distal fallopian tube are removed at time of RRSO. In order to do this, it is necessary that the surgeon be able to enter the retroperitoneal space and ligate the infundibulopelvic ligament at least 2 cm from its insertion into the ovary.

Malignant cells leading to upstaging of disease have also been found in peritoneal cytology specimens from a number of women undergoing RRSO (76). Given these findings, washing likely should be performed at time of peritoneal entry in all women undergoing RRSO.

Additionally as 2% to 10% of RRSO specimens obtained from *BRCA* mutation carriers have an occult malignancy detected at time of pathologic review (77), it is essential that the entire ovary and fallopian tube be serially sectioned to minimize the possibility of a small invasive cancer going undetected (6). The fimbrial ends of the fallopian tubes are the most frequent site of occult invasive serous carcinomas (78–80), and these lesions are best visualized using the SEE-FIM (sectioning and extensively examining the fimbriated end) method (81). Briefly, in this method, the fimbriated portion of the fallopian tube is sectioned lengthwise (sagittally) in multiple planes to maximize exposure of the tubal plicae. When this method is utilized, serous tubal intraepithelial carcinoma (STIC), a putative precursor to invasive serous carcinoma, is also identified in as many as 5% to 8% of specimens obtained at time of RRSO in women with mutations in *BRCA1* or *BRCA2* (82, 83). Both the occult fallopian tube malignancies and STIC lesions typically overexpress mutant *TP53* protein (84). Patients in whom small high-grade invasive serous cancers are found incidentally at RRSO generally receive adjuvant chemotherapy. The role of chemotherapy in the management of serous tubal intraepithelial carcinoma (STIC) is less clear (76).

Timing of procedure. For most women with mutations in either *BRCA1* or *BRCA2*, RRSO should generally be considered between age 35 and 40 and when childbearing is complete (6). For women with *BRCA1* mutations, this age is recommended because only 2% to 3% of women with mutations in this gene will develop pelvic serous cancer by age 40, but 10% to 21% of *BRCA1* mutation carriers will develop pelvic serous cancer by age 50 years (40–42). For women with *BRCA2* mutations, the risk of pelvic serous cancer by age 50 is only 2% to 3%. However, women with *BRCA2* mutations who defer RRSO until the age of natural menopause, likely lose the profound reduction against *BRCA2*-associated breast cancer conferred by RRSO (74). For women with *BRCA2* mutations who have already had bilateral mastectomy and ovarian ablation is not being utilized as part of adjuvant therapy for a prior breast cancer, RRSO likely can be reasonably deferred until the mid-40s.

Mastectomy

Several studies have demonstrated that risk-reducing mastectomy (RRM) in women with *BRCA1* or *BRCA2* mutation is associated with an approximately 90% reduction in the risk of new breast cancer (85, 86). Importantly, the impact on life expectancy may be markedly less, as the majority of these cancers in women undergoing both mammography and breast MRI will be diagnosed at a curable stage. In a decision analysis by Kurian et al. RRM at age 40 (in addition to RRSO at age 40 and breast screening starting at age 25) only increased the probability of survival to age 70 from 74% to 77% in carriers of *BRCA1* mutations and from 80% to 82% in carriers of *BRCA2* mutations (87). Given these relatively small absolute changes in survival, either intensive breast screening or risk-reducing mastectomy is likely a reasonable option for a woman with a *BRCA1* or *BRCA2* mutation.

LYNCH SYNDROME

Epidemiology

Approximately 5% of endometrial cancer cases may be attributed to an inherited predisposition (88). Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, accounts for the majority of these cases. Individuals with Lynch syndrome have a germline mutation in one of four genes in the DNA mismatch repair family; *MLH1*, *MSH2*, *MSH6*, or *PMS2*. While Lynch syndrome has historically been characterized by an increased risk for colorectal cancer, women with Lynch syndrome also have a substantial risk for endometrial cancer. The estimated risk for colon cancer in women is 40% to 60% and in men as high as 80% (89, 90). In women, the lifetime endometrial cancer risk is approximately 40% to 60%. In a study specifically looking at individuals with *MSH6* mutations, risk for endometrial cancer was 26% by age 70 and as high as 44% by 80 years of age, and lifetime risk of colon cancer was 10% by age 70 and 20% by age 80 (91). Women with Lynch syndrome also have an approximate 5% to 10% lifetime risk for developing ovarian cancer. Other cancers associated with Lynch syndrome include cancers of the stomach, small bowel, renal pelvis and ureter, and brain.

In the general population, Lynch syndrome occurs in about 1 in 600 to 1 in 3000 individuals (92, 93). In a population-based study on endometrial cancer patients, the incidence of Lynch syndrome was 2.3%, which is similar to the 2.2% incidence of Lynch syndrome among colon cancer patients (94). For women with endometrial cancer under the age of 50, the proportion with Lynch syndrome increases to 5% to 9% (95–97). The mean age of diagnosis for endometrial cancer in women with Lynch syndrome is 47 years, which is substantially lower than the mean age of diagnosis of endometrial cancer in the general population, 60 years. Women with Lynch syndrome are at increased risk of

developing synchronous or metachronous cancers. In a study that examined 101 women with Lynch syndrome who had developed both GI cancer and gynecologic cancer, 51% presented, at a median age of 44, with their gynecologic cancer first, and 49% presented with their GI cancer first (98).

Prior to the discovery of the genes responsible for Lynch syndrome, criteria were formulated to identify families with Lynch syndrome for research studies. The initial Amsterdam I criteria focused on colon cancer and were subsequently revised (Amsterdam II), to include all Lynch syndrome-associated cancers. The criteria include: (a) three or more relatives with Lynch syndrome-associated cancers, (b) two affected relatives in successive generations, (c) one affected relative is a first-degree relative of the other two, and (d) one or more relatives with Lynch syndrome-associated cancer diagnosed before the age of 50 years.

Pathology

Unlike the ovarian cancers associated with *BRCA1* and *BRCA2* mutations, the endometrial cancers associated with Lynch syndrome span a broader spectrum. In a study by Broaddus et al., 43 of 50 (86%) endometrial cancers were endometrioid histology, with the remainder being papillary serous carcinoma, clear cell carcinoma, and malignant mixed müllerian tumors (99). Interestingly, all of the nonendometrioid tumors in this study occurred in patients with *MSH2* mutations. Among all of the patients with Lynch syndrome, 78% were diagnosed at stage I, 10% at stage II, and 12% at stage III or IV. Lymphovascular space involvement was noted in 24% of the cases, and 26% had deep myometrial involvement that was defined as invasion greater than 50%. Endometrial cancers that arise in the lower uterine segment are rare in the general population, but are seen more frequently in women with Lynch syndrome. In a study by Westin et al., almost one third of patients with endometrial cancers arising in the lower uterine segment were suspected to have Lynch syndrome, based on tumor studies or germline testing (100). This characteristic phenotype is similar to the increased proportion of right-sided colon cancers seen in individuals with Lynch syndrome. Other pathologic features that have been seen more frequently in Lynch syndrome-associated colon cancers, including poor tumor differentiation and tumor infiltrating lymphocytes, have not been seen consistently in Lynch syndrome associated endometrial cancers.

The ovarian cancers seen in Lynch syndrome also have a different stage and histology spectrum from that seen in women with sporadic disease. In a recent series, 22 (47%) of 47 Lynch-associated epithelial ovarian cancers presented at stage I. Further, serous cancers were underrepresented in this series, accounting for only 28% of tumors. Endometrioid, clear cell, and mucinous histologies were seen in 35%, 17%, and 5%, respectively (101).

Genetic Risk Assessment for Lynch Syndrome

For gynecologic oncologists, identifying Lynch syndrome in a patient with endometrial cancer has important implications for both the woman with cancer and for her family members. Individuals with Lynch syndrome are at significant lifetime risk of developing a second primary malignancy. Therefore, when an endometrial cancer patient is identified as having Lynch syndrome, appropriate colon cancer screening can be initiated. In addition, if a specific mutation in one of the DNA mismatch repair genes is identified in the endometrial cancer patient, her family members can undergo targeted predictive genetic testing for the same mutation.

Historically, guidelines to assist physicians in identifying patients with Lynch syndrome have focused on colon cancer patients. The Bethesda criteria, which were established in 1997

and revised in 2004, assist physicians in identifying colon cancer patients who may have Lynch syndrome (102). However, it has become increasingly clear that Lynch syndrome patients often present with endometrial or ovarian cancer as their first cancer. In 2007, the Society of Gynecologic Oncologists provided guidelines to assist in identifying patients for whom genetic risk assessment may be helpful (Table 3.4). They specifically recommended that women who have a greater than approximately 20% to 25% chance of having Lynch syndrome be offered risk assessment (103). Individuals meeting this criteria include women with endometrial cancer who fulfill the Amsterdam criteria; patients with synchronous or metachronous endometrial and colorectal cancer whose first cancer was diagnosed at less than age 50, patients with synchronous or metachronous ovarian and colorectal cancer whose first cancer diagnosed at

Table 3.4 Society of Gynecologic Oncologists Criteria for Offering Genetic Risk Assessment for Lynch Syndrome

Patients with greater than approximately 20%–25% chance of having Lynch syndrome and for whom genetic risk assessment is recommended:

- Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria as listed below:
 - At least three relatives with a sentinel Lynch-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis) in one lineage;
 - One affected individual should be a first-degree relative of the other two;
 - At least 2 successive generations should be affected;
 - At least 1 Lynch-associated cancer should be diagnosed before age 50.
- Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e., microsatellite instability (MSI) or immunohistochemical loss of expression of MLH1, MSH2, MSH6, or PMS2)
- Patients with a first- or second-degree relative with a known mismatch repair gene mutation

Patients with greater than approximately 5%–10% chance of having Lynch syndrome and for whom genetic risk assessment may be helpful:

- Patients with endometrial or colorectal cancer diagnosed prior to age 50
- Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch syndrome–associated tumor^a at any age
- Patients with endometrial or colorectal cancer and a first-degree relative with a Lynch syndrome–associated tumor^a diagnosed prior to age 50
- Patients with colorectal or endometrial cancer diagnosed at any age with two or more first- or second-degree-relatives^b with Lynch syndrome–associated tumors^a, regardless of age
- Patients with a first or second-degree relative^b that meets the above criteria

^aLynch-associated tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.
^bFirst and second-degree relatives are parents, siblings, children, aunts, uncles, nieces, nephews, grandparents and grandchildren.

Source: Adapted from Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2007;107: 159–162, with permission¹⁰³

less than 50, patients with endometrial cancer with molecular or immunohistochemical evidence of a mismatch repair defect, and patients with a first or second degree relative with a known mismatch repair gene mutation. In addition, the Society of Gynecologic Oncologists guidelines also identified a category of patients who have a 5% to 10% risk for Lynch syndrome and for whom genetic risk assessment may be helpful. These include patients with endometrial cancer diagnosed at less than age 50, patients with an endometrial or ovarian cancer and a synchronous or metachronous colon cancer at any age, and patients with endometrial cancer diagnosed at any age with 2 or more first- or second-degree relatives with Lynch syndrome–associated cancers, regardless of age.

While family history remains an important component in identifying individuals who may benefit from genetic risk assessment for Lynch syndrome, tumor testing for evidence of mismatch repair defects is an intermediate step that can be useful for triaging which patients may be at risk for having one of the germline DNA mismatch repair mutations (104, 105). These tumor tests include immunohistochemistry for 1 of the 4 mismatch repair proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and microsatellite instability (MSI) analysis. Both of these studies can be performed on formalin-fixed, paraffin-embedded tissues and can be a first step in the evaluation of Lynch syndrome in a patient with endometrial cancer. Although it has been suggested that it may be cost-effective to do these tests on all endometrial cancers (106), this approach has not yet been widely adopted. For immunohistochemistry tests, the absence of a specific mismatch repair protein in the tumor is considered abnormal. For example, a tumor may demonstrate loss of staining of *MSH2* with normal staining of *MLH1*, *MSH6*, and *PMS2*. The loss of staining of *MSH2* in the tumor reflects that both copies of the gene are nonfunctional and suggests that the woman has a likely *MSH2* germline mutation.

For MSI testing, both tumor and normal tissues are required. MSI testing reflects the tumor phenotype of deficient DNA repair. When a tumor has deficient DNA repair capability, multiple mistakes occur in the DNA in both coding and noncoding regions. These mistakes are especially common in regions of mononucleotide and dinucleotide repeats, such as CCCCCC or CGCGCG. The National Cancer Institute has identified 7 of these sites on the genome that can be examined for microsatellite instability testing (BAT25, BAT26, BAT40, D2S123, D5S346, D173250, and TGF-BR2). Tumors with allelic shift in 2 or more microsatellites in the panel are considered MSI-high. Tumors with allelic shift in only one microsatellite are considered MSI-low. Tumors with no allelic shift in all 7 microsatellites are considered microsatellite-stable. For MSI-high tumors with loss of *MLH1* by IHC, methylation-specific PCR for *MLH1* proximal promoter region –248 to –178 is performed to detect possible methylation of the *MLH1* promoter. When methylation is present, the patient most likely has a sporadic carcinoma rather than a Lynch syndrome–associated cancer (*MLH1* promoter methylation is discussed in more detail in Chapter 2).

Immunohistochemistry can also direct genetic testing specifically for which one of the four DNA mismatch repair genes should be tested. For example, in individuals who have lost *MSH2* by immunohistochemistry, genetic testing can be initiated specifically for the *MSH2* gene. Once a specific germline mutation has been identified, at-risk family members can be tested for the same germline mutation, but at a substantially reduced cost.

Screening and Prevention

Screening and Chemoprevention

Guidelines for screening and prevention of Lynch syndrome–associated cancers have been published and should be reviewed with patients when the diagnosis of Lynch syndrome is made

(107, 108) (Table 3.5). Colon cancer screening is recommended in individuals with Lynch syndrome every 1 to 2 years starting at the age of 20 to 25 years (or 30 years in patients with known *MSH6* mutations). Jarvinen et al. reported a reduction in the incidence of invasive colorectal cancer from 16% to 6% ($p = 0.014$), with a relative risk of death of 0.34 (95% CI, 0.17–0.68) in individuals with Lynch syndrome who received colonoscopy or sigmoidoscopy and barium enema every 3 years compared to those who received no routine screening (109).

In contrast to colon cancer screening, there are no proven screening strategies for the early detection of endometrial or ovarian cancer in women with Lynch syndrome. Two European studies reported a high false-positive rate and poor efficacy using measurement of endometrial stripe by transvaginal ultrasound as an endometrial cancer screening tool (110, 111). More promising, two studies have reported identification of premalignant lesions and endometrial cancers in asymptomatic women with Lynch syndrome using office endometrial biopsy as a screening strategy (112, 113). One of these studies included 175 women with known *MLH1*, *MSH2*, or *MSH6* gene mutations and reported a stage migration with 7% of women in the surveillance group presenting with Stage III/IV disease versus 17% of women who presented symptomatically (112). The second study on 100 women from Lynch kindreds reported that routine endometrial sampling resulted in a significantly higher rate of malignancies and premalignancies compared with prior historical controls in which routine annual endometrial sampling was not performed (6.3% vs. 1.4%, $p = 0.026$) (113). No studies have examined the mortality impact of annual endometrial sampling in women with Lynch syndrome. Consensus guidelines currently recommend consideration of annual surveillance with endometrial biopsy for evaluation of the uterus and transvaginal ultrasound for evaluation of the ovaries (108). It is important to emphasize to the patient that data to support these recommendations are limited. A study by Huang et al. demonstrated the feasibility and acceptability of performing the annual endometrial biopsy, while the patient is sedated for the screening colonoscopy in women with Lynch syndrome (114). There was a substantial

reduction in reported pain when the procedures were done concurrently under sedation.

In the general population, progestin-based oral contraceptives have been shown to decrease endometrial and ovarian cancer risk by 50% (56, 115, 116). Progestin therapy is also effective at reversing complex atypical hyperplasia and early endometrial cancer (117, 118). While there are no epidemiologic data to support the role of progestins or progestin-based oral contraceptives as chemoprevention in women known to have Lynch syndrome, a short-term biomarker study demonstrated a significant decrease in endometrial proliferation using both 150 mg depo medroxyprogesterone acetate and 30 μ g ethinyl estradiol/0.3 mg norgestrel oral contraceptive pill (119). An ongoing trial is examining the use of the levo-norgestrel IUD as a chemopreventive in women with Lynch syndrome.

Risk-Reducing Surgery

Risk-reducing hysterectomy and salpingo-oophorectomy are reasonable options for prevention of endometrial and ovarian cancer in women with Lynch syndrome. A multi-institutional retrospective study of women with Lynch syndrome demonstrated that the incidence of endometrial cancer fell from 33% to 0% in women who underwent hysterectomy, and the incidence of ovarian cancer fell from 5.4% to 0% in women who underwent salpingo-oophorectomy (120). The risk of primary peritoneal cancer after oophorectomy in women with Lynch syndrome is unclear, although one case report has been published (121). It is also important to note that occult endometrial cancers have been found in asymptomatic women at the time of risk-reducing hysterectomy and salpingo-oophorectomy (122–124).

Women with Lynch syndrome should be counseled that the estimated risk for endometrial cancer by age 40 does not exceed 2% and the estimated risk of ovarian cancer by age 40 does not exceed 1% (90). Therefore, women with Lynch syndrome can complete childbearing prior to consideration of risk-reducing surgery. In addition, there does not appear to be a contraindication to estrogen replacement therapy after risk-reducing surgery. Two studies have performed cost-effectiveness analyses of options for gynecologic risk reduction in women with Lynch syndrome (125, 126). Both studies found that risk-reducing hysterectomy and salpingo-oophorectomy led to both the lowest cost and the greatest increase in quality-adjusted life years.

For patients undergoing colonic resection for a Lynch-associated colorectal cancer, it may be reasonable to discuss concomitant hysterectomy with BSO. However, for premenopausal patients who are diagnosed with Lynch syndrome at the same time as their colorectal cancer, there can be substantial fertility and psychosocial issues associated with this approach.

Table 3.5 Risk-Reduction Recommendations for Women with Lynch Syndrome

Gastrointestinal

- Colonoscopy every 1–2 years beginning at age 20–25 (or age 30 for women with *MSH6* mutations)
- Consider esophagogastroduodenoscopy (EGD) every 2–3 years beginning at age 30–35
- Consider capsule endoscopy every 2–3 years beginning at age 30–35
- Consider chemoprevention with aspirin or NSAIDs

Gynecologic

- Patients should be aware that abnormal vaginal bleeding warrants evaluation
- Consider screening with annual endometrial biopsy and transvaginal ultrasound beginning at age 30
- Consider chemoprevention with oral contraceptives or progestins
- Consider risk-reducing hysterectomy with bilateral salpingo-oophorectomy between age 35 and 40 and when childbearing is complete

Urologic

- Consider annual urinalysis starting at age 25–30

OTHER INHERITED SYNDROMES WITH A GYNECOLOGIC CANCER COMPONENT

Cowden Syndrome, Li-Fraumeni syndrome, and Peutz-Jeghers syndrome are rare autosomal dominant inherited cancer susceptibility syndromes that include gynecologic cancers as part of their cancer spectrum.

Cowden Syndrome

Cowden syndrome is caused by germline mutations in the *PTEN* gene. Individuals with Cowden Syndrome are at increased risk for both benign and malignant processes. These include gastrointestinal polyps, thyroid disease, benign breast

Adapted from Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA* 2006;296(12): 1507–1517 and National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology—Colorectal Cancer Screening. Version 2.2012. <http://www.nccn.org>. 2012.

disease, mucocutaneous lesions, as well as breast, thyroid, and endometrial cancer (127). The lifetime risk of endometrial cancer in a woman with Cowden's syndrome has been estimated to be 5% to 28% (128, 129). Current NCCN guidelines recommend observation for and prompt evaluation of abnormal uterine bleeding (7). Screening with endometrial biopsies and/or ultrasound measurement of the endometrial stripe is being evaluated in the context of ongoing research studies.

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is caused by germline mutations in *TP53* and is characterized by early-onset breast cancer, soft-tissue and bone sarcomas, adrenal cortical tumors, and brain tumors (130). Although not a major cancer risk in individuals with Li-Fraumeni syndrome, cases of ovarian cancer have been reported. While screening breast MRI is recommended beginning at age 20 to 25, there are no current screening recommendations for gynecologic cancers in women with Li-Fraumeni syndrome (7, 131).

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is caused by germline mutations in *STK11*. Peutz-Jeghers is generally characterized by multiple gastro-intestinal polyps and pigmented lesions on the lips and buccal mucosa. Women with this syndrome also have a markedly increased risk for gastrointestinal and breast malignancies (132). Gynecologic cancers associated with this syndrome include sex cord-stromal tumors with annular tubules (SCTAT) of the ovary and adenoma malignum of the cervix (133). SCTAT are typically benign and bilateral. Adenoma malignum of the cervix is a rare and aggressive neoplasm that can also be seen in Peutz-Jeghers syndrome. It is often difficult to diagnose both clinically and histologically. On imaging, the tumor appears as a multicystic endocervical mass. Histologically, the tumor appears well differentiated, but the natural history can be aggressive. Due to the rarity of the syndrome and the gynecologic cancers, it is unclear whether women with Peutz-Jeghers should be screened. Yearly pelvic exam and pap smear beginning at age 25 have been recommended. However, the role of pelvic imaging is unclear (134).

REFERENCES

- Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA*. 1971;68(4):820–823.
- Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci USA*. 2011;108(44):18032–18037.
- Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer*. 2005;104(12):2807–2816.
- Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol Oncol*. 2011;121(2):353–357.
- Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol*. 2012;30(21):2654–2663.
- ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol*. 2009;113(4):957–966.
- National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology—Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2012. <http://www.nccn.org>. 2012.
- Boyd J, Sonoda Y, Federici MG, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. *JAMA*. 2000;283(17):2260–2265.
- Soslow RA, Han G, Park KJ, et al. Morphologic patterns associated with BRCA1 and BRCA2 genotype in ovarian carcinoma. *Mod Pathol*. 2012;25(4):625–636.
- Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. *N Engl J Med*. 1996;335(19):1413–1416.
- Ramus SJ, Fishman A, Pharoah PD, et al. Ovarian cancer survival in Ashkenazi Jewish patients with BRCA1 and BRCA2 mutations. *Eur J Surg Oncol*. 2001;27(3):278–281.
- Ben David Y, Chetrit A, Hirsh-Yecheskel G, et al. Effect of BRCA mutations on the length of survival in epithelial ovarian tumors. *J Clin Oncol*. 2002;20(2):463–466.
- Cass I, Baldwin RL, Varkey T, et al. Improved survival in women with BRCA-associated ovarian carcinoma. *Cancer*. 2003;97(9):2187–2195.
- Pal T, Permuth-Wey J, Kapoor R, et al. Improved survival in BRCA2 carriers with ovarian cancer. *Fam Cancer*. 2007;6(1):113–119.
- Chetrit A, Hirsh-Yecheskel G, Ben-David Y, et al. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. *J Clin Oncol*. 2008;26(1):20–25.
- Gallagher DJ, Konner JA, Bell-McGuinn KM, et al. Survival in epithelial ovarian cancer: a multivariate analysis incorporating BRCA mutation status and platinum sensitivity. *Ann Oncol*. 2011;22(5):1127–1132.
- Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011;474(7353):609–615.
- Hyman DM, Zhou Q, Iasonos A, et al. Improved survival for BRCA2-associated serous ovarian cancer compared with both BRCA-negative and BRCA1-associated serous ovarian cancer. *Cancer*. 2012;118(15):3703–3709.
- Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA*. 2012;307(4):382–390.
- Yang D, Khan S, Sun Y, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. *JAMA*. 2011;306(14):1557–1565.
- Kauff ND. Is It time to stratify for BRCA mutation status in therapeutic trials in ovarian cancer? *J Clin Oncol*. 2008;26(1):9–10.
- Hyman DM, Spriggs DR. Unwrapping the implications of BRCA1 and BRCA2 mutations in ovarian cancer. *JAMA*. 2012;307(4):408–410.
- Husain A, He G, Venkatraman ES, et al. BRCA1 up-regulation is associated with repair-mediated resistance to cis-diamminedichloroplatinum(II). *Cancer Res*. 1998;58(6):1120–1123.
- Yuan SS, Lee SY, Chen G, et al. BRCA2 is required for ionizing radiation-induced assembly of Rad51 complex in vivo. *Cancer Res*. 1999;59(15):3547–3551.
- Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005;434(7035):913–917.
- Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005;434(7035):917–921.
- Heitz F, Harter P, Ewald-Riegler N, et al. Poly(ADP-ribosylation) polymerases: mechanism and new target of anticancer therapy. *Expert Rev Anticancer Ther*. 2010;10(7):1125–1136.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361(2):123–134.
- Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245–251.
- Banerjee S, Kaye S. PARP inhibitors in BRCA gene-mutated ovarian cancer and beyond. *Curr Oncol Rep*. 2011;13(6):442–449.
- Baldwin RL, Nemeth E, Tran H, et al. BRCA1 promoter region hypermethylation in ovarian carcinoma: a population-based study. *Cancer Res*. 2000;60(19):5329–5333.
- Geisler JP, Hatterman-Zogg MA, Rathe JA, et al. Frequency of BRCA1 dysfunction in ovarian cancer. *J Natl Cancer Inst*. 2002;94(1):61–67.
- Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. *Am J Hum Genet*. 1997;60(3):496–504.
- Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br J Cancer*. 2000;83(10):1301–1308.
- Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53

- in families at high risk of breast cancer. *JAMA*. 2006;295(12):1379–1388.
36. Palma MD, Domchek SM, Stopfer J, et al. The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high-risk breast cancer families. *Cancer Res*. 2008;68(17):7006–7014.
 37. Judkins T, Rosenthal E, Arnell C, et al. Clinical significance of large rearrangements in BRCA1 and BRCA2. *Cancer*. 2012;118(21):5210–5216.
 38. Hall MJ, Reid JE, Burbidge LA, et al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. *Cancer*. 2009;115(10):2222–2233.
 39. Offit K, Groeger E, Turner S, et al. The “duty to warn” a patient’s family members about hereditary disease risks. *JAMA*. 2004;292(12):1469–1473.
 40. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*. 2003;72(5):1117–1130.
 41. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003;302(5645):643–646.
 42. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clin Cancer Res*. 2002;8(12):3776–3781.
 43. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1998;62(3):676–689.
 44. Barnes DR, Antoniou AC. Unravelling modifiers of breast and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: update on genetic modifiers. *J Internal Med*. 2012;271(4):331–343.
 45. Stadler ZK, Thom P, Robson ME, et al. Genome-wide association studies of cancer. *J Clin Oncol*. 2010;28(27):4255–4267.
 46. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 18 Regs Research Data, Nov 2011 Sub (2000)–(2009). 2011.
 47. Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. *J Clin Oncol*. 2002;20(5):1260–1268.
 48. Liede A, Karlan BY, Baldwin RL, et al. Cancer incidence in a population of Jewish women at risk of ovarian cancer. *J Clin Oncol*. 2002;20(6):1570–1577.
 49. Hermesen BB, Olivier RI, Verheijen RH, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. *Br J Cancer*. 2007;96(9):1335–1342.
 50. Greene MH, Piedmonte M, Alberts D, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev*. 2008;17(3):594–604.
 51. Rosenthal AN. Ovarian cancer screening in the high-risk population—the UK Familial Ovarian Cancer Screening Study (UKFOCSS). *Int J Gynecol Cancer*. 2012;22 (suppl. 1):S27–S28.
 52. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57(2):75–89.
 53. Brekelmans CT, Seynaeve C, Bartels CC, et al. Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. *J Clin Oncol*. 2001;19(4):924–930.
 54. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet*. 2005;365(9473):1769–1778.
 55. Warner E, Hill K, Causer P, et al. Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. *J Clin Oncol*. 2011;29(13):1664–1669.
 56. Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet*. 2008;371(9609):303–314.
 57. Iodice S, Barile M, Rotmensz N, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. *Eur J Cancer*. 2010;46(12):2275–2284.
 58. Narod SA, Dube MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst*. 2002;94(23):1773–1779.
 59. Heimdal K, Skovlund E, Moller P. Oral contraceptives and risk of familial breast cancer. *Cancer Detect Prev*. 2002;26(1):23–27.
 60. Haile RW, Thomas DC, McGuire V, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1863–1870.
 61. Gronwald J, Byrski T, Huzarski T, et al. Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. *Breast Cancer Res Treat*. 2006;95(2):105–109.
 62. Brohet RM, Goldgar DE, Easton DF, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. *J Clin Oncol*. 2007;25(25):3831–3836.
 63. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA*. 2001;286(18):2251–2256.
 64. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *J Clin Oncol*. 2002;20(9):2310–2318.
 65. Foulkes WD, Metcalfe K, Sun P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. *Clin Cancer Res*. 2004;10(6):2029–2034.
 66. Narod SA, Brunet JS, Ghadirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. *Lancet*. 2000;356(9245):1876–1881.
 67. Weitzel JN, Robson M, Pasini B, et al. A comparison of bilateral breast cancers in BRCA carriers. *Cancer Epidemiol Biomarkers Prev*. 2005;14(6):1534–1538.
 68. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2002;346(21):1609–1615.
 69. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002;346(21):1616–1622.
 70. Klaren HM, van’t Veer LJ, van Leeuwen FE, et al. Potential for bias in studies on efficacy of prophylactic surgery for BRCA1 and BRCA2 mutation. *J Natl Cancer Inst*. 2003;95(13):941–947.
 71. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst*. 2009;101(2):80–87.
 72. Dubeau L. The cell of origin of ovarian epithelial tumours. *Lancet Oncol*. 2008;9(12):1191–1197.
 73. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. *J Natl Cancer Inst*. 1999;91(17):1475–1479.
 74. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol*. 2008;26(8):1331–1337.
 75. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. 2010;304(9):967–975.
 76. Manchanda R, Drapkin R, Jacobs I, et al. The role of peritoneal cytology at risk-reducing salpingo-oophorectomy (RRSO) in women at increased risk of familial ovarian/tubal cancer. *Gynecol Oncol*. 2012;124(2):185–191.
 77. Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in BRCA1 or BRCA2. *J Clin Oncol*. 2007;25(20):2921–2927.
 78. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. *J Clin Oncol*. 2005;23(1):127–132.
 79. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. *Gynecol Oncol*. 2006;100(1):58–64.
 80. Yates MS, Meyer LA, Deavers MT, et al. Microscopic and early-stage ovarian cancers in BRCA1/2 mutation carriers: building a model for early BRCA-associated tumorigenesis. *Cancer Prev Res*. 2011;4(3):463–470.
 81. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *The Am J Surg Pathol*. 2006;30(2):230–236.
 82. Shaw PA, Rouzbahman M, Pizer ES, et al. Candidate serous cancer precursors in fallopian tube epithelium of BRCA1/2 mutation carriers. *Mod Pathol*. 2009;22(9):1133–1138.
 83. Powell CB, Chen LM, McLennan J, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. *Int J Gynecol Cancer*. 2011;21(5):846–851.
 84. Kuhn E, Kurman RJ, Vang R, et al. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma—evidence supporting the clonal relationship of the two lesions. *J Pathol*. 2012;226(3):421–426.
 85. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2001;345(3):159–164.
 86. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol*. 2004;22(6):1055–1062.

87. Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. *J Clin Oncol*. 2010;28(2):222–231.
88. Gruber SB, Thompson WD. A population-based study of endometrial cancer and familial risk in younger women. Cancer and Steroid Hormone Study Group. *Cancer Epidemiol Biomarkers Prev*. 1996;5(6):411–417.
89. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer*. 1999;81(2):214–218.
90. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. 2011;305(22):2304–2310.
91. Baglietto L, Lindor NM, Dowdy JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. *J Natl Cancer Inst*. 2010;102(3):193–201.
92. Dunlop MG, Farrington SM, Nicholl I, et al. Population carrier frequency of hMSH2 and hMLH1 mutations. *Br J Cancer*. 2000;83(12):1643–1645.
93. de la Chapelle A. The incidence of Lynch syndrome. *Fam Cancer*. 2005;4(3):233–237.
94. Hampel H, Panescu J, Lockman J, et al. Comment on: screening for Lynch syndrome (hereditary non-polyposis colorectal cancer) among endometrial cancer patients. *Cancer Res*. 2007;67(19):9603.
95. Lu KH, Schorge JO, Rodabaugh KJ, et al. Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer. *J Clin Oncol*. 2007;25(33):5158–5164.
96. Berends MJ, Wu Y, Sijmons RH, et al. Toward new strategies to select young endometrial cancer patients for mismatch repair gene mutation analysis. *J Clin Oncol*. 2003;21(23):4364–4370.
97. Matthews KS, Estes JM, Conner MG, et al. Lynch syndrome in women less than 50 years of age with endometrial cancer. *Obstet Gynecol*. 2008;111(5):1161–1166.
98. Lu KH, Dinh M, Kohlmann W, et al. Gynecologic cancer as a “sentinel cancer” for women with hereditary nonpolyposis colorectal cancer syndrome. *Obstet Gynecol*. 2005;105(3):569–574.
99. Broadus RR, Lynch HT, Chen LM, et al. Pathologic features of endometrial carcinoma associated with HNPCC: a comparison with sporadic endometrial carcinoma. *Cancer*. 2006;106(1):87–94.
100. Westin SN, Lacour RA, Urbauer DL, et al. Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome. *J Clin Oncol*. 2008;26(36):5965–5971.
101. Ketabi Z, Bartuma K, Bernstein I, et al. Ovarian cancer linked to Lynch syndrome typically presents as early-onset, non-serous epithelial tumors. *Gynecol Oncol*. 2011;121(3):462–465.
102. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst*. 2004;96(4):261–268.
103. Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. 2007;107(2):159–162.
104. Backes FJ, Leon ME, Ivanov I, et al. Prospective evaluation of DNA mismatch repair protein expression in primary endometrial cancer. *Gynecol Oncol*. 2009;114(3):486–490.
105. Leenen CH, van Lier MG, van Doorn HC, et al. Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer ≤ 70 years. *Gynecol Oncol*. 2012;125(2):414–420.
106. Resnick K, Straughn JM Jr, Backes F, et al. Lynch syndrome screening strategies among newly diagnosed endometrial cancer patients. *Obstet Gynecol*. 2009;114(3):530–536.
107. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA*. 2006;296(12):1507–1517.
108. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology—Colorectal Cancer Screening. Version 2.2012. <http://www.nccn.org>. 2012.
109. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000;118(5):829–834.
110. Rijcken FE, Mourits MJ, Kleibeuker JH, et al. Gynecologic screening in hereditary nonpolyposis colorectal cancer. *Gynecol Oncol*. 2003;91(1):74–80.
111. Dove-Edwin I, Boks D, Goff S, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer*. 2002;94(6):1708–1712.
112. Renkonen-Sinisalo L, Butzow R, Leminen A, et al. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *Int J Cancer*. 2007;120(4):821–824.
113. Gerritzen LH, Hoogerbrugge N, Oei AL, et al. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. *Fam Cancer*. 2009;8(4):391–397.
114. Huang M, Sun C, Boyd-Rogers S, et al. Prospective study of combined colon and endometrial cancer screening in women with lynch syndrome: a patient-centered approach. *J Oncol Pract*. 2011;7(1):43–47.
115. Weiss NS, Sayvetz TA. Incidence of endometrial cancer in relation to the use of oral contraceptives. *N Engl J Med*. 1980;302(10):551–554.
116. Combination oral contraceptive use and the risk of endometrial cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *JAMA*. 1987;257(6):796–800.
117. Vereide AB, Arnes M, Straume B, et al. Nuclear morphometric changes and therapy monitoring in patients with endometrial hyperplasia: a study comparing effects of intrauterine levonorgestrel and systemic medroxyprogesterone. *Gynecol Oncol*. 2003;91(3):526–533.
118. Kim YB, Holschneider CH, Ghosh K, et al. Progesterone alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. *Cancer*. 1997;79(2):320–327.
119. Lu K, Chen L, Lynch H, et al. A prospective, multi-center randomized study of oral contraceptive vs. depo-provera for the prevention of endometrial cancer in women with Lynch syndrome. *Soc Gynecol Oncol*. 2010.
120. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med*. 2006;354(3):261–269.
121. Schmeler KM, Daniels MS, Soliman PT, et al. Primary peritoneal cancer after bilateral salpingo-oophorectomy in two patients with Lynch syndrome. *Obstet Gynecol*. 2010;115(2 Pt 2):432–434.
122. Chung L, Broadus R, Crozier M, et al. Unexpected endometrial cancer at prophylactic hysterectomy in a woman with hereditary nonpolyposis colon cancer. *Obstet Gynecol*. 2003;102(5 Pt 2):1152–1155.
123. Pistorius S, Kruger S, Hohl R, et al. Occult endometrial cancer and decision making for prophylactic hysterectomy in hereditary nonpolyposis colorectal cancer patients. *Gynecol Oncol*. 2006;102(2):189–194.
124. Palma L, Marcus V, Gilbert L, et al. Synchronous occult cancers of the endometrium and fallopian tube in an MSH2 mutation carrier at time of prophylactic surgery. *Gynecol Oncol*. 2008;111(3):575–578.
125. Kwon JS, Sun CC, Peterson SK, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. *Cancer*. 2008;113(2):326–335.
126. Yang KY, Caughey AB, Little SE, et al. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) families. *Fam Cancer*. 2011;10(3):535–543.
127. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet*. 2000;37(11):828–830.
128. Gustafson S, Zbuk KM, Scacheri C, et al. Cowden syndrome. *Semin Oncol*. 2007;34(5):428–434.
129. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res*. 2012;18(2):400–407.
130. Chompret A, Brugieres L, Ronsin M, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. *Br J Cancer*. 2000;82(12):1932–1937.
131. Mai PL, Malkin D, Garber JE, et al. Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium. *Cancer Genet*. 2012;205(10):479–487.
132. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res*. 2006;12(10):3209–3215.
133. Young RH, Welch WR, Dickersin GR, et al. Ovarian sex cord tumor with annular tubules: review of 74 cases including 27 with Peutz-Jeghers syndrome and four with adenoma malignum of the cervix. *Cancer*. 1982;50(7):1384–1402.
134. Beggs AD, Latchford AR, Vasen HF, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. *Gut*. 2010;59(7):975–986.

4

Invasion, Metastasis, and Angiogenesis

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INTRODUCTION

Gynecologic cancers are potentially curable if diagnosed at an early stage, when the tumor remains confined to the primary organ; survival is compromised by the dissemination or metastasis of the disease to vital organs at more advanced stages. In ovarian cancer, the leading cause of death for gynecologic malignancies in the United States, survival rates decrease dramatically with advanced disease presentation. The 5-year relative survival rate in advanced ovarian cancer with spread outside the pelvis is 26.9%, in contrast to a rate of 91.5% in stage I disease. A similar pattern is seen in cancers of the cervix and uterine corpus, with 5-year relative survival rates for localized disease of 90.7% and 95.4%, respectively; for distant disease, the rates are 16.2% and 16.4%, respectively (Howlader, et al: http://seer.cancer.gov/csr/1975_2009_pops09). The progression from hyperplasia to carcinoma *in situ* to invasive and then metastatic cancer determines staging and prognosis (Fig. 4.1).

Metastasis, the spread of malignant cells from the primary tumor to other sites, requires tumor cells detach from their primary mass, invade the stroma, travel to a secondary site via the lymphatic and/or the vascular system, extravasate and migrate within the secondary stroma, and grow (1). Tumor cells must also interact closely with elements in their microenvironment and

communicate with them to successfully achieve metastasis (2,3). The peritoneum, omentum, and mesenteric serosa are permissive environments to which the tumor cells attach and grow, co-opting support cells and vasculature to sustain their survival and growth. Through overcoming anoikis, a form of apoptosis triggered by loss of attachment to the solid extracellular matrix (ECM) substratum, cancer cells survive in the intra-abdominal milieu and in the peritoneal fluid or ascites (4,5).

The endothelium is the cellular lining on the luminal side of blood vessels, which serve as the first docking interface for circulating tumor cells. The endothelium creates a semi-permeable barrier sitting over its basement membrane; together they control blood–tissue exchanges of fluids, nutrients, and metabolic wastes, while preventing access to and from the tissues for pathogens and tumor cells (6). Altering endothelial cell–cell adhesion alters this critical endothelial barrier function. Loss of cell–cell adhesion allows endothelial cells to constrict in response to noxious stimuli. Constriction permits retraction, leaving acellular regions of sub-endothelial basement membrane exposed. Tumor cells attach to and degrade these denuded matrix regions (7).

The primary tumor and metastatic sites also have a high metabolic demand requiring adequate blood supply, absent which, tumor cells survive by autophagy, internal protein degradation, and recycling (8,9). Angiogenesis, the formation of new vessels, is necessary both as a route for metastasis and to provide the metastatic sites with exogenous nutrients to support tumor

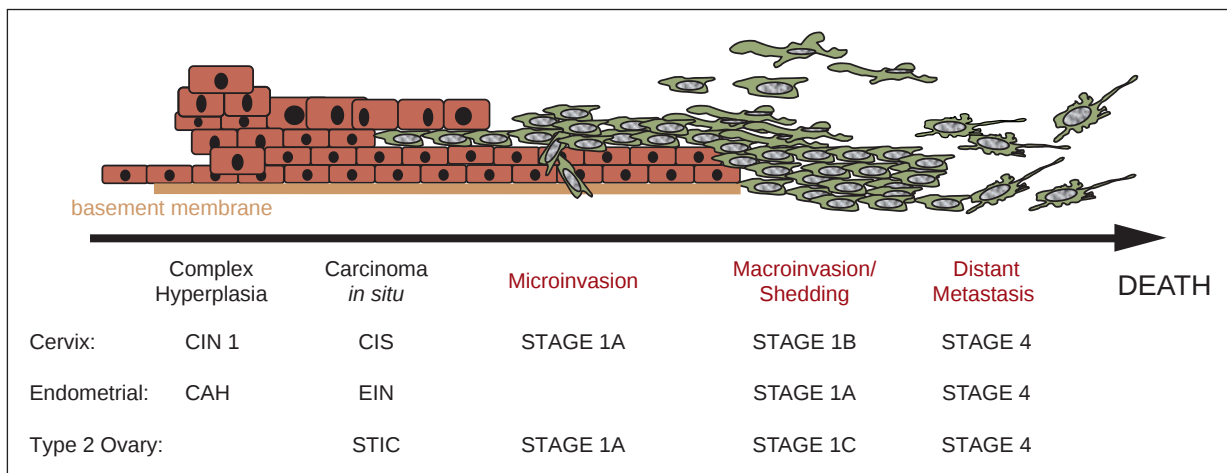


FIGURE 4.1. Paradigm of cancer progression. Progression from the earliest detectable event of complex hyperplasia to overt invasive and metastatic malignancy is over a decade for endometrial and cervical cancers. The new recognition of the tubal epithelium as the source for type 2 high-grade serous ovarian cancer leaves this time frame still undetermined. Where identified early, each of these cancers has a high cure rate and long overall survival. However, when identified at or beyond the stage of microinvasion, progressive disease and death from disease is common.

growth (1). Many proangiogenic and antiangiogenic factors are secreted into and by elements of the tumor microenvironment leading to new vasculature that supports tumor survival and progression (10). Invasion, angiogenesis, and metastasis are thus orchestrated within the tumor microenvironment through a dynamic interaction between the tumor cells, the ECM, stromal and immunologic cells, and secreted chemokines and growth factors (1,2). Cancer cells use normal cellular processes to survive and progress, albeit without the tight regulation seen in normal cells. Tumor cells adapt in response to environmental and cellular stress and upregulate different mechanisms as cell migration, angiogenesis, autophagy, and apoptosis for their survival (11).

PATTERNS OF SPREAD

Gynecological cancers are able to disseminate in a multitude of ways (Fig. 4.2), and morbidity and mortality are associated with extent of tumor spread, invasion, and metastasis. The classical mechanism of dissemination of solid tumors is invasion of surrounding tissues followed by subsequent hematogenous and/or lymphatic spread. Endometrial and cervical cancers tend to be found as solid disease that extends locally and/or spreads in a defined pattern through the lymphatics, and later through

the vasculature. Their staging is dependent on the extent of local structural invasion and/or lymph node status. In most solid tumors, such as these gynecologic cancers and breast cancer, death is usually the consequence of distant metastasis.

In ovarian and fallopian tube carcinomas, primary and early dissemination occurs through the shedding of tumor cells (2,12) directly into the abdominal cavity; these cells then spread via the passive movement of peritoneal fluid. Cancer cells in the peritoneal fluid or ascites survive in this hypoxic, structure-free milieu by resisting anoikis (13). Attachment to serosa or peritoneum precedes local invasion and secondary metastasis; the presence of lymph node disease in ovarian cancer indicates invasion, involvement of the next step after shedding. Vascular dissemination for these and peritoneal serous cancers is a late event leading to parenchymal organ metastasis. Therefore, the ability of a tumor to spread or shed is not an isolated process; it requires upregulation of survival mechanisms as well as close interaction with other cells and the local environmental milieu (2,14).

MICROENVIRONMENT

The genetic and phenotypic make-up of a tumor is a major determinant of its metastatic efficiency, and a receptive microenvironment is a prerequisite for successful tumor growth (15,16).

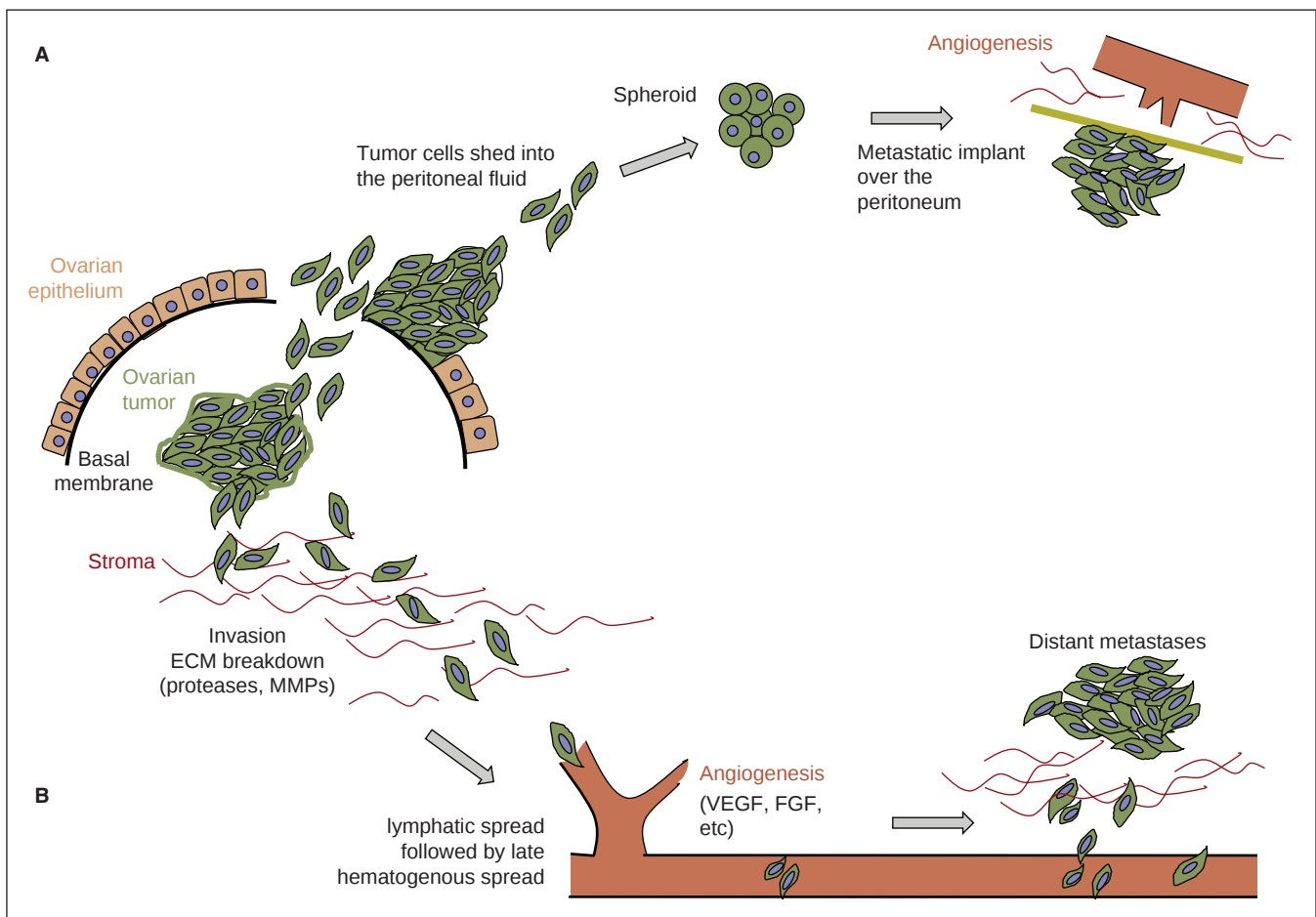


FIGURE 4.2. Ovarian cancer: shedding and spreading. The primary ovarian tumor located in the ovarian stroma metastasizes in two different ways. The first mechanism **(A)**, occurring early is by shedding cancer cells into the peritoneal cavity after reaching the ovarian surface; the second mechanism **(B)**, later occurring, is invasion into surrounding tissues. Cells shed in the peritoneal fluid, form spheroids that have acquired mechanisms to resist anoikis. These spheroids will then implant on the peritoneal mesothelial surface and cause stromal activation with desmoplasia, inflammation, and angiogenesis. ECM: extra-cellular matrix; FGF: fibroblast growth factor; MMPs: matrix metalloproteinases; VEGF: vascular endothelial growth factor.

Sir James Paget stated in 1889 that the microenvironment of each organ, *the soil*, influences the survival and growth of tumor cells, *the seed* (16,17). Multiple overlapping signal and adhesion networks cooperate to enable molecular and structural remodeling of tissues that overall support tumor invasion, growth, and metastatic dissemination. Cellular behavior and the activation or inactivation of genes are influenced heavily by the microenvironment (1,14). Gene expression profiling and proteomics have identified a variety of factors that are upregulated in the microenvironment of gynecological tumors. This reinforces the idea that complex interplay of molecules and signals are needed for tumor sustainability. Additionally, the microenvironment has a plasticity that allows participating elements to vary throughout the events of cancer progression. The flexibility of the microenvironment supports survival of the tumor cells and their ability to withstand an otherwise harsh environment with elements of hypoxia, metabolic stress, and inflammation (3).

Inflammation/Priming

Inflammation may promote carcinogenesis and dissemination through several mechanisms affecting growth, invasion, angiogenesis, and neoplastic changes (18). These inflammatory mechanisms include but are not limited to the production of reactive oxygen species and free radicals that directly damage DNA and proteins, and production of proinflammatory/proangiogenic molecules, such as cytokines, tumor necrosis factor- α (TNF α), and interleukins (18). Various immune cells have been found as part of the tumor inflammatory infiltrate. Among them, macrophages play a central role in most solid malignancies (19). Some T cells facilitate invasion of tumor cells by altering macrophages into a more invasive phenotype in an IL-4 dependent manner supporting the idea that inflammation mediators play a role in cancer progression (20). Inflammatory factors can also increase inflammatory enzymes such as cyclooxygenase-2, which lead to the production of other proinflammatory products (21). Studies have shown an inverse relationship between nonsteroidal anti-inflammatory drugs and reduced risk of ovarian and cervical cancers (18,22,23).

Multiple causes of local inflammation including exposure to talc, asbestos, and presence of endometriosis and recurrent pelvic inflammatory disease have been identified as putative risk factors for ovarian cancer (24,25). Cervical cancer studies have shown that, in addition to HPV, other sexually transmitted infections such as herpes simplex virus and Chlamydia are associated with increased risk of carcinoma *in situ* and/or invasive cervical cancer (26). It is believed that the subsequent inflammatory response and micro-ulceration that follows these non-HPV infections increase the epithelial cell repair and proliferation, permitting or promoting transformation (27). One study reported that cervical inflammation, independent of infections, was associated with squamous metaplasia of the cervix, a precursor to malignancy (28).

The menstrual cycle is a physiologic inflammatory process. The endometrium is a dynamic cyclic organ with cycles of growth, remodeling, differentiation, and angiogenesis. Estrogen drives these changes by facilitating the release of inflammatory mediators from the epithelial, stromal, and vascular cells of the endometrium (18,29). Increased exposure of the endometrium to inflammation occurs by the same mechanisms that are considered risk factors for endometrial cancer. These endometrial risk factors include unopposed estrogen use, polycystic ovarian syndrome, excessive menstruation, obesity, and diabetes. Therefore, it is believed that inflammation alone or in conjunction with estrogen plays a role in the development of endometrial cancer (18).

Tumor cells coopt normal host cells and rely on communication with other cell types including macrophages, T cells and

other immune cells, endothelial cells, and stromal cells (20). Cancer cells may also cause transdifferentiation of host cells. Tumor-released inflammatory cytokines act on local cells to convert host fibroblasts into cancer-associated fibroblasts (CAFs). Activated CAFs help promote ovarian and endometrial tumor cell invasion through activation and production of growth factors, such as tumor growth factor- β (TGF β) and chemokines (14,30,31). CAFs are part of a paracrine loop that increases cancer cell invasion (30). Furthermore, there are multiple cell interactions and stimulatory and inhibitory factors leading to feedback loops that help amplify and sustain the tumor cells in this environment (32).

Communication between tumor cells and host cells at distant tissue sites via circulating factors, immune cells, chemokines, and growth factors can prime and direct the location of future metastatic tumor growth (33). Tumor-associated macrophages, recruited by the presence of the tumor, alter the local chemokine balance resulting in directed migration, proliferation, and differentiation of the vascular cell network and inflammatory infiltrate of the tumor microenvironment. This functions to support tumor growth, both at the primary tumor and upon metastasis (20). Shibuya and colleagues demonstrated enhanced matrix metalloproteinase (MMP)-9, a protease that breaks down the ECM, was measured in the lung preceding demonstrable tumor cell metastasis, suggesting that this was induced by signals from the distant primary tumor in a paracrine fashion (34). Therefore, the role of the immune system in cancer is complex and supports the idea that a permissive microenvironment is critical for the initiation of tumor growth and establishment of metastatic lesions at secondary sites (15).

Chemokines/Growth Factors

Chemotactic cytokines, known as chemokines, are small, secreted proteins or peptides that help regulate cell motility. Their primary function is chemoattraction and activation of leukocytes that then recruit other immune and/or inflammatory cells from the blood to the affected site. These proteins are implicated in initiation and progression of cancer (35). Cancer cells and many cells in the malignant microenvironment produce and/or respond to chemokines in an autocrine or paracrine manner via chemotaxis, migration up a concentration gradient, or chemokinesis, migration within a chemoattractant milieu (32). Chemokines and their receptors act at many stages of tumor progression, ranging from cell transformation, angiogenesis promotion, to tumor and supporting cell growth. Tumor cell passage through the ECM, the vasculature, and/or lymphatics is mediated by chemokines (35). Growth factors, differentiated from chemokines by their definition initially as growth promoters for epithelial not inflammatory cells, also play a role in tumor ascites formation, motility, invasion, and migration (24).

One of many important chemokine pairs is the receptor CXCR4 and its ligand CXCL12. Together, they activate signaling pathways that enhance proliferation, migration, angiogenesis, and invasion of gynecologic cancers (36,38). Normal ovaries express very little CXCR4; whereas, it is expressed in approximately 60% of ovarian cancers. CXCL12 is expressed in more than 90% of ovarian cancers (37). CXCR4 was found to be the only receptor of 14 chemokine receptors studied to be expressed in ovarian cancer cells (38). Its expression is an independent negative prognostic factor for progression-free and overall survival in ovarian cancer (39). AMD3100, a CXCR4 inhibitor, blocked CXCL12-stimulated migration of ovarian cancer cells *in vitro* (40,41). Blockade of CXCR4/CXCL12 activation led to reduced tumor growth and prolonged survival in ovarian cancer xenografts (37).

Interleukins-8 (IL-8) and -6 (IL-6) are multifunctional chemokines that are secreted by multiple cell types, including monocytes,

neutrophils, endothelial and mesothelial cells, and tumor cells. They are usually activated during an inflammatory response and function to recruit other immune cells to the affected site (42). Recent studies have shown that tumor progression and metastasis are associated with overexpression of these chemokines (43,44). Ovarian cyst fluid, effusions, blood, and tumor tissue have elevated IL-8 and IL-6 expression, correlated with poor overall survival (42,43). Bellone et al. demonstrated elevated serum levels of IL-6 in endometrial cancer patients and showed this was associated with a more aggressive and chemotherapy-resistant endometrial cancer (45). Preclinical data suggest that IL-8 and IL-6 increase resistance to chemotherapeutic treatments in ovarian cancer cells (46,47). Collectively, these observations provide rationale for targeting these chemokines therapeutically in gynecological cancers. Preliminary findings using an anti-IL-6 receptor antibody against ovarian cancer are encouraging (43).

Autotaxin (ATX) is a glycoprotein shown to have a critical role in invasive and angiogenic tumor and endothelial cell behavior (48,49). *ENPP2*, encoding ATX, has been identified as a drug resistance candidate gene (50,52). ATX is multifunctional inducing cell motility, angiogenesis, invasion, and metastasis in multiple models through its cleavage of lysophosphatidylcholine to yield lysophosphatidic acid (LPA), a major gynecologic cancer growth factor. Elevated expression of ATX or aberrant expression of LPA and its receptors has been found in most gynecologic cancers (48). High circulating plasma ATX concentrations

are found in patients with recurrent ovarian cancer (51). Lack of specificity and sensitivity of circulating ATX concentration has precluded its application as a cancer biomarker. However, because of its important role in the development and progression of cancer, numerous studies are attempting to define an ATX inhibitor for clinical testing.

LPA, first described as ovarian cancer ascitic factor, is a growth-promoting lipid isolated from ovarian cancer patient ascites. It induces invasion and metastasis in a wide variety of cancers, including gynecologic cancers (53,56). LPA signals predominantly through G protein-coupled LPA receptors with crosstalk through inflammatory cytokine receptors and receptor tyrosine kinases. These events subsequently activate transcription factors, via the phosphatidylinositol 3-kinase pathway to propagate messages of invasion, angiogenesis, and metastasis (57,58). Wang found that the expression of LPA receptors was significantly increased in ovarian cancer tissues, compared to benign tumors and normal ovarian tissue (59,60). LPA concentrations are elevated in the plasma and/or ascites of ovarian, cervical, and endometrial cancer patients (61); however, the complexity of the relationship between the different LPAs, defined by their lipid substituents, has limited its biomarker development (57).

LPA signaling is central in the progression of most cancers (Fig. 4.3) (53,54,57,62,64). The LPA-Rho-associated kinase pathways have been involved in the course of various cancers,

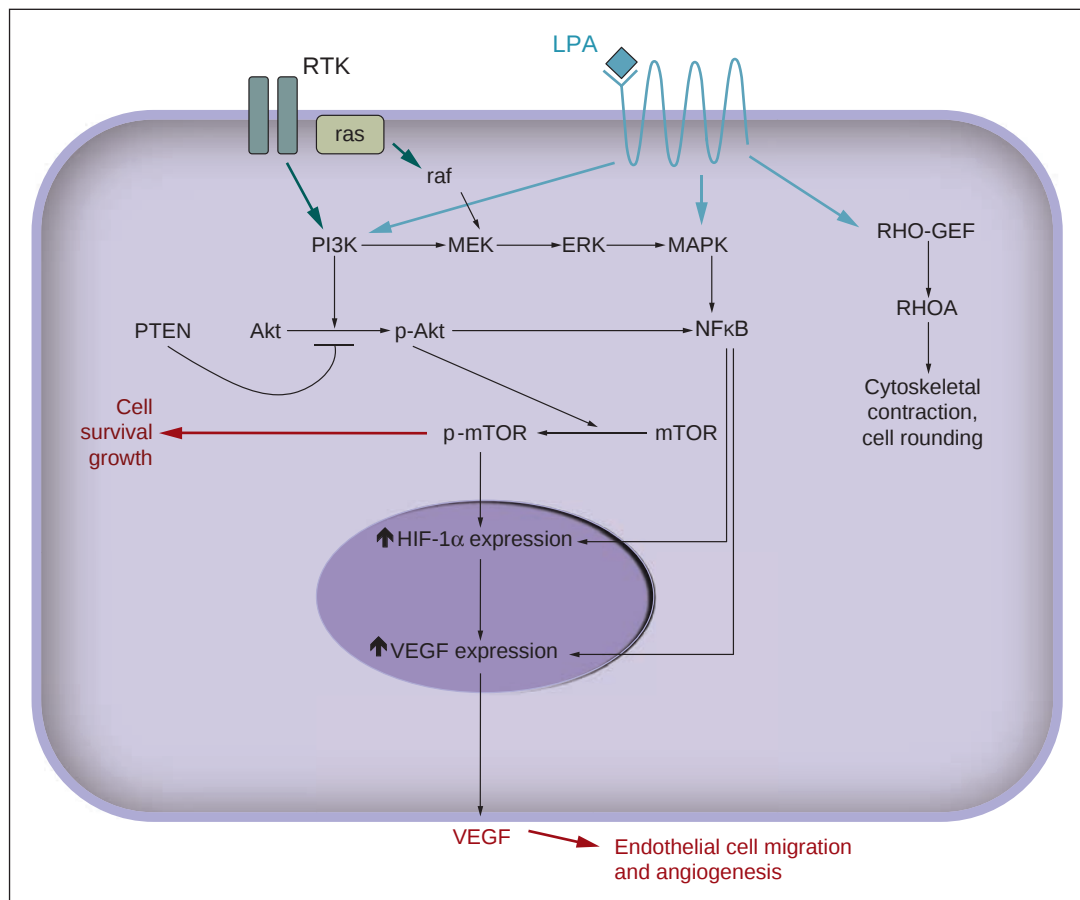


FIGURE 4.3. Molecular pathways. LPA is a well-recognized and potent prosurvival and angiogenic factor produced and secreted by ovarian cancer. LPA signals through the LPA receptor; a 7-pass transmembrane G-protein coupled receptor. LPA promotes expression of VEGF for angiogenesis and cell survival through the PI3K/AKT, NFκB, and MAPK signaling pathways. Receptor tyrosine kinases, RTK, are a broad family of receptors for multiple growth factors. Their activation also promotes cell survival, invasion, angiogenesis, and proliferation through the ras, PI3K/AKT, NFκB, and MAPK pathways. ERK: extracellular regulated kinase; MAPK: mitogen-activated protein kinase; MEK: MAP-ERK kinase; mTOR: mammalian target of rapamycin; NFκB: nuclear factor κB; Rho-GEF and RHO A are Rho family GTPases.

and inhibiting them decreases cancer invasiveness (58). Rho GTPase family members Rho, Rac, and CDC42 have roles in membrane trafficking, cell adhesion, and remodeling of the actin cytoskeleton in gynecologic and other cancers (32). Inhibition of Rho kinase significantly inhibited LPA-induced invasion and motility in human ovarian and cervical cancer cells in a dose-dependent manner *in vitro* and in xenograft models (58,65). Activation of these Rho kinase pathways lead to actin polymerization, followed by formation of membrane protrusions that are required for migration (32). Similar studies are under way for endometrial and cervical cancer (61).

ADHESION

The concept of shedding and spreading in ovarian and other gynecologic cancers underscores the need for cells to attach to secondary sites and initiate secondary tumor masses. The most common sites of such adhesion is the mesothelial lining of the peritoneum, bowel serosa, or vessel walls (63,64). This occurs via adhesion molecules, of which there are four categories: integrins, cadherins, immunoglobulin super family adhesion molecules (CAMs), and selectins. Each class has different structure, functions, and binding partners, and is expressed in various degrees on the surface of different cells (Fig. 4.4). They participate in cell–cell and/or cell–substratum binding, yielding a complexity of adherence and signaling possibilities. When expression or function of adhesion molecules becomes altered

by tumor progression, new signals are propagated that can promote tumor growth, survival, and metastasis (14,66).

Cell–Cell Interactions

Cadherins are calcium-dependent transmembrane glycoproteins that are expressed in the early stages of development of various tissues. There are three primary cadherins: epithelial (E), neural (N), and placental (P) (67). Each, found commonly in desmosomes and cell junctions, activates intra- and intercellular communication (14). The cadherin intracellular portion connects, through α - and/or β -catenin, to actin microfilaments, anchoring cells to one another (2). Additionally, cadherins interact with various cell surface receptors, including receptor tyrosine kinases, such as epidermal growth factor receptor, to propagate intracellular signals resulting in migration, apoptosis, growth control, and differentiation of tumor cells (66).

E-cadherin, a metastasis suppressor molecule, is the most studied member of the cadherin family (68); its downregulation has been associated with transition to a mesenchymal phenotype, increased invasiveness, tumor progression, and poor survival (2,69,70). When E-cadherin expression is decreased, it is countered by upregulation of N- and P-cadherins. This cadherin switch also has been noted during normal development when migration, budding, and other invasive behaviors are necessary, such as during embryogenesis (71). Physiologic cadherin switching occurs when cells have reached their secondary site and the cadherins again switch and cells alter phenotype. This behavior, mimicked in tumor during epithelial–mesenchymal transition

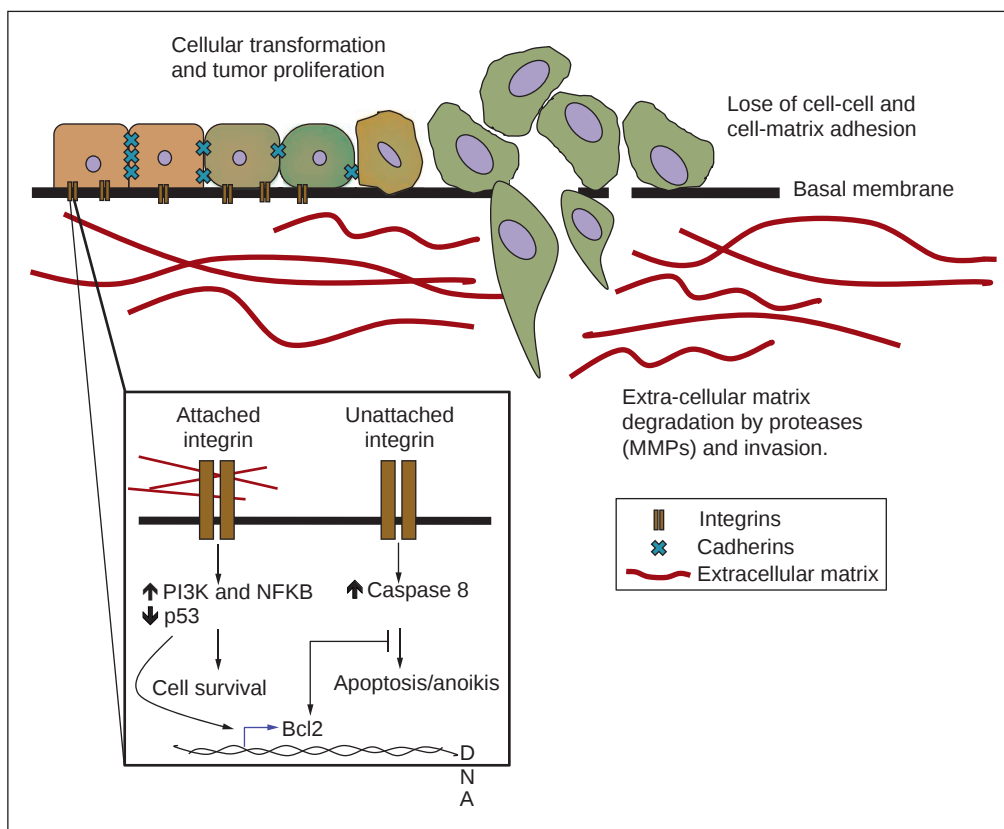


FIGURE 4.4. Invasion. Cancer cells lose their cell-to-cell (cadherin) and cell-to-matrix (integrin) attachment releasing single cells and allowing for cell migration. The release of proteases (MMPs, serine proteases) promotes ECM degradation forming tracks for cancer cells to migrate and invade surrounding tissues. Integrins can initiate pro-survival or pro-apoptotic signals depending on their attachment to the ECM. Metastatic cancer cells have acquired mechanisms to resist anoikis.

albeit without a secondary cadherin switch, leads to release of β -catenin and its translocation to the nucleus (3). β -catenin then activates signaling for proliferation and invasion (72).

E-cadherin downregulation is associated with higher-grade, increased peritoneal seeding, and decreased overall survival in ovarian cancer (73). Sawada et al. demonstrated that when E-cadherin was silenced, it led to an increase adherence to mesothelial cells in an ovarian cancer *in vivo* model (74). E-cadherin expression has been shown to be lower in tumor cells floating in ascites, pleural effusions, and at the metastatic site, than in the primary tumor (2,75). Downregulation of E-cadherin results from upregulation of a series of zinc-finger transcriptional repressors, *Snail*, *Slug*, *ZEB1/2*, *Twist*, and *SIP1*, expression of which is also associated with increased invasive capability of ovarian cancer cells, resistance to chemotherapy, and poor clinical behavior in ovarian cancer (2,3,66,69,70). Therefore, the role of cadherins, particularly sustaining E-cadherin expression, is a critical defense against cancer cell invasion, migration, and adhesion by maintaining tight cell-to-cell connections.

Cell–Matrix Interactions

The ECM is a complex proteinaceous structure surrounding and supporting cells. It is composed of three major classes of biomolecules: proteoglycans, structural proteins such as collagens and elastins, and specialized matrix proteins such as fibronectin and laminins (76). The ECM can serve many functions, including cellular scaffolding support, binding site for growth factors and cofactors, and modulator of intercellular communication (76). ECM remodeling helps determine polarity and growth of tissues and has become a target of interest in cancer treatment. Many adhesion factors such as integrins, selectins, and CD44 interact not only with other cells, but also with the ECM.

Integrins These are transmembrane receptors named for their ability to integrate the microenvironment and cell signaling. They transmit signals bidirectionally, into and out of the cell, incorporating crosstalk with a variety of cell surface receptors and intracellular signaling proteins (66,77). Integrins are composed of eight α and eighteen β chains combining into 24 heterodimers each of which interacts with a specific repertoire of ligands (67). Each subunit contains a large extracellular domain, a single membrane-spanning domain, and a short cytoplasmic tail (78). Common integrin ligands include the major structural ECM molecules, thrombospondin, fibrinogen, and von Willebrand factor, among others (79). Cell-surface ligands for integrins include members of the immunoglobulin CAM superfamily, such as intercellular adhesion molecule-1 (ICAM-1) (79).

The tripeptide sequence, Asp–Gly–Arg (RGD), is the important ligand recognition site for integrins (80). Binding, whether through RGD or other recognition sites, causes integrin clustering or capping, β -subunit phosphorylation, and association of the cytoplasmic tail with cytoskeletal structures. The actin cytoskeleton is connected to the cytoplasmic integrin tail through the ERM proteins, ezrin, radixin, and moesin (81). Ligand binding also initiates intracellular signaling cascades that provide the machinery needed for cell motility and invasion, and to support survival (3,66,82). Although widely distributed throughout the body, integrins appear to be expressed in low and tightly organized quantities in normal tissue, and up- and downregulated in tumors, including in gynecologic cancers (82). The $\alpha 4 \beta 1$, found commonly on mesothelial and endothelial cells, has been associated with increased peritoneal metastasis, and $\alpha \nu \beta 3$, the vitronectin receptor, is both a driver of tumor proliferation and angiogenesis, via crosstalk with the VEGF receptor, in ovarian cancer (83,84). Integrins $\alpha \nu \beta 3$ and $\alpha \nu \beta 6$ have been associated with decreased patient survival in cervical cancer (85,86).

RGD and integrin binding has been used to focus drug and immunotherapy delivery in preclinical models (87,88). Hood et al. took advantage of integrin-facilitated drug delivery using $\alpha \nu \beta 3$ -targeted nanoparticles to deliver a mutant RAF1 gene into tumor vasculature (89). Xiao found that an integrin-targeting peptide, OA02, enhanced the efficiency of the uptake of nanoparticles into ovarian cancer cells (90). Paclitaxel was added to these nanoparticles and enhanced cytotoxicity was observed. This experiment was validated in ovarian tumor-bearing mice, where paclitaxel-loaded OA02-nanoparticles reduced tumor burden with lower systemic toxicity. Additional experiments have shown that integrin-linked doxorubicin-loaded nanoparticles delivered to tumor vasculature caused inhibition of metastasis and eliminated toxicity normally associated with systemic administration (62,77). Combining vascular targeting antagonists with chemotherapy also is hypothesized to cause more direct penetration of the drug into the tumor, while reducing systemic adverse events (77,78). This treatment concept is awaiting clinical validation for gynecologic cancers.

Selectins This class of molecules contains an epidermal growth factor-like motif and binds glycoproteins and glycolipids bearing sialyl Lewis X (sLe^x) in a calcium-dependent manner (80,91). They initiate the recruitment of lymphocytes by tethering and rolling these cells along the endothelium and are expressed predominantly on leukocytes, platelets, and endothelial cells (91). There are three types of selectins (66). Endothelial (E)-selectin, is triggered by cytokines such as TNF α and interleukin-1, and has a role in leukocyte adhesion at sites of inflammation and/or injury. Platelet (P) selectin is stored in endothelial cells and platelet granules and is activated by histamine and/or thrombin during inflammation. Lastly, leukocyte (L)-selectin is constitutively expressed on leukocytes and acts as a homing receptor for these cells to enter secondary lymphoid tissues. Elevated E-selectin has been associated with various diseases and cancers, including ovarian cancer. E7, an HPV-16 oncoprotein, upregulates the expression of E-selectin in cervical cancers (92). Selectins are thought to interact with tumor cells to shield them while in the circulation to enable subsequent extravasation and migration at the secondary site (66).

CD44, an E- and L-selectin ligand, has been correlated with cancer progression, metastasis, and poor overall survival (66,93). CD44 is the major hyaluronic acid receptor and is expressed by all nucleated cells (63,67). The interaction of CD44 expressed on ovarian cells with hyaluronic acid on mesothelial cells is thought to play a role in tumor dissemination and survival in ovarian cancer (3,55,94). Knockdown of CD44 led to a decrease in adhesion and invasion of ovarian cancer cells (63,94). It has been shown to upregulate proteases involved in breakdown of the ECM, a behavior required for invasion (95). Strobel et al. found that an antibody to CD44 inhibited peritoneal implants of ovarian cancer cells in a mouse model (96). Splice variants of CD44 have the ability to connect to the cytoskeleton, activate Src and Rho GTPase signal pathways, bind chemokines and growth factors, and to act as a coreceptor for other adhesion molecules (3,67).

Therefore, migration of cancer cells into or from blood to tissue requires coordinated sequential interactions of tumor cells with numerous adhesion molecules. The loss of E-cadherin leads to the loss of cell–cell junctions releasing single cells and facilitating migration away from the primary tumor and intravasation (97). Next, selectins facilitate tumor cell adhesion to vascular cells allowing them to transmigrate between the endothelium, followed by basement membrane dissolution and migration into the secondary site. Integrin-associated adhesion to basement membrane and ECM is involved in tumor cell exit from the primary tumor, entry into and exit from the vasculature, and attachment and growth at sites of metastasis. Although the basic concept of targeting these elements in therapy has been studied in animal models, translation to human disease has proved difficult to date.

INVASION/PROTEOLYSIS

The initial steps of invasion include activating signal pathways that regulate cell–cell junction breakdown, tumor or other cell-mediated ECM proteolysis, and migration away from the primary site. Local dissolution of the epithelial or endothelial basement membrane and/or ECM is the key event required for successful invasion. After migration from the primary and successful transit, tumor cells activate mechanisms that permit attachment to endothelial cells or endothelial cell basement membrane or local ECM at secondary sites. Success of this multistep process of invasion leads to successful metastasis.

Proteases are crucial for the degradation of the ECM, which places the tumor cells in direct contact with other cells and creates spaces or tracts through which tumor cells can migrate. Both tumor cells and local cells, such as endothelial cells, stromal, and inflammatory cells, can be the source of activated proteases (98). Proteolysis also unmasks ligands to which receptors of endothelial cells interact, such as integrin RGD moieties (20). The breakdown of the ECM also creates protein fragments, some of which promote and some that inhibit adhesion and migration functions; release of ECM-bound growth factors can also occur. Proteases that are secreted or attached to the cell surface can activate other proteases and cell surface receptors, multiplying the invasion stimulus and allowing adaptive changes in the microenvironment (3).

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a family of metalloenzymes that require cleavage for activation. There are 5 categories: interstitial collagenases, gelatinases, stromelysins, membrane-type, and elastases (99,100). Each of these subclasses has selective substrate specificity with elements of the basement membrane and ECM constituting major substrates. MMPs are secreted by a variety of cancers with MMP-2, -7, and -9 described as active in the gynecological cancer microenvironment (101). The source of the MMP in the microenvironment remains a controversy, with data suggesting that both tumor and microenvironmental elements are involved in a cooperative fashion.

Greater quantity of activated MMP2 was observed by immunohistochemistry staining and immunoblots in ovarian cancer than in normal ovarian tissue (102). MMP2 expression was noted to be higher in stromal cells of invasive cervical cancer compared to CIN3. The increased expression was also correlated with increased stage and worse prognosis (103). A MMP7 polymorphism (MMP7-181G/G) has been demonstrated to be a potential risk factor for developing both endometrial and cervical cancers. It also is associated with an increased risk of higher grade and stage tumors and lymphatic metastasis (102,104,105). Overexpression of MMP7 has been shown in a variety of ovarian cancer cell lines and surgical specimens. Additionally, high levels of MMP9 have been found in ovarian xenograft models (106,107). Elevation of MMPs is not specific to malignant tumors. Other benign tumors and conditions and normal remodeling behaviors may have increased quantities of MMPs (108). This may be one of the reasons that targeting MMPs was previously found to be unsuccessful due to inadequate doses and unexpected adverse events (109,110). Therefore, the importance of this class of enzymes is recognized, although the therapeutic usefulness of targeting these elements is questionable.

Serine Proteases

Serine proteases are ubiquitous, in a variety of tissues, both constitutively and by induction. They have roles in wound

healing and immune response, as well as promoting tumor growth, invasion, and metastasis (111). Plasminogen is an inactive proenzyme that is converted to the active enzyme plasmin, a key protease. Among the many functions of plasmin other than clotting is its requirement for propeptide cleavage and activation of MMPs (99). The plasminogen/plasmin system, in concert with the MMPs, helps regulate the tightly controlled process of ECM degradation. Additionally, this system plays a role in thrombolysis, embryogenesis, cell invasion, and angiogenesis (100).

Hepsin is a type II transmembrane serine protease initially shown to be overexpressed in prostate, renal, and ovarian cancers. Its message is upregulated in 90% of prostate cancers and appears to be exclusively expressed by tumor cells (112). More recently, Matsuo et al. found hepsin to have the strongest expression in endometrial cancer, compared with normal tissue and endometrial hyperplasia. They determined that strong hepsin expression was associated with decreased progression-free and overall survival, although not functioning as an independent prognostic factor (111). Ovarian tumors may also overexpress hepsin (113,114). Xuan et al. showed that antihepsin antibodies significantly inhibited invasion of ovarian cancer cell lines (115). Hepsin may be underappreciated in gynecologic cancer biology.

Serine Protease Inhibitors

There is a large complex family of serine protease inhibitors, the SERPINS (116), some of which are upregulated and functional in gynecologic cancer progression (117,118). One such serine protease inhibitor, secretory leukocyte protease inhibitor (SLPI), a whey acidic protein with anti-inflammatory properties, is overexpressed in breast and epithelial ovarian cancers. Paradoxically, SLPI has been shown to have a progrowth and proinvasion role in ovarian cancer, in part through activation of MMP9, and to be associated with a more aggressive tumor phenotype (119,120). More recently, high levels of SLPI were shown to cause paclitaxel resistance in ovarian cancer cell lines (121). These data have credentialed this serine protease inhibitor as a potential molecular target in ovarian cancer.

The serine protease inhibitor maspin, SERPINB5, has been found to have an antiproliferative and antiangiogenic role in breast, lung, and prostate cancers. Its overexpression in ovarian cancer is associated with promotion of invasion and metastasis (122). Localization of maspin is the deciding factor leading to these opposing roles in cancer. Further studies are needed to clarify this issue.

Protease function constitutes a common requirement in any tissue remodeling process, ranging from embryogenesis to cancer. Hence, it was recognized early on that the metastatic potential of cancer cells relies on the ability to invade and degrade basement membranes (123). Cancer cells benefit from proteolysis to manage their attachment to and detachment from the ECM in addition to providing the overall structure of their invasion and interaction with the microenvironment. The ability to regulate matrix proteolysis and invasion is regarded to be essential in the treatment of cancer.

ANGIOGENESIS AND LYMPHANGIOGENESIS

Angiogenesis

Angiogenesis, the development of new blood vessels, has a key role in cancer progression and development of metastases. Its role in tumorigenesis was first described in 1971 by Folkman. He described that a tumor mass larger than 0.125 mm² exceeds its capacity to acquire nutrients by simple diffusion, and that

further expansion of the tumor would require new blood vessel formation (124–126). Not only do these new vessels provide growing tumors with the necessary nutrients, but they also serve as a route for metastatic dissemination (1). Angiogenesis is regulated by a balance of proangiogenic and angiostatic factors that result from the interaction between tumor cells, endothelial cells, and the microenvironment (127). Inhibitors of angiogenesis can help create a dynamic balance in the tumor milieu, from an angiogenic to a quiescent state, favoring the former one when hypoxia and other stresses are present.

Microvessel density is a method used to quantify vessels in cancer, yielding results that correlate with disease relapse and/or survival in cervical cancer (128), ovarian cancer (129–131), and endometrial cancer (132). The microvessel density significantly and independently correlated with progression free survival and overall survival in endometrial cancer (133). The antibody used to stain the microvessels can also give further information as to the quality of the vessels; CD105, staining endoglin, recognizes more immature vessels and CD31, anti-platelet/endothelial (PE)-CAM, recognizing microvessels (134).

New vessels develop in two ways, by sprouting or splitting. During sprouting, endothelial cells are activated by multiple growth factors and proteases are released, remodeling the surrounding ECM (Fig. 4.5) (135). This allows migration of activated endothelial cells through the matrix. Endothelial cell cords are formed, followed by polarization and formation of the lumen in the immature vessels (136,137). The next step, occurring in normal tissues, is the recruitment of pericytes, vascular smooth muscle cells that surround the vessel outside of the basement membrane. They assist in the secretion of matrix molecules and work with the endothelium to create the basement membrane that stabilizes and further matures the neovessels (138). Pericytes are described as either abnormal or absent in tumor vasculature. This is coupled with demonstration that

the basement membrane has defects in its structure leading to immature and leaky vessels (139,140). Splitting is a different method of vessel development in which the lumen of a preexisting vessel is split to form two new vessels from the original one (141). New microvessels keep the tumor cells within a distance of 100 to 200 μm from the blood supply, permitting successful nutrient absorption by diffusion (142).

Some studies suggest that other mechanisms are involved in tumor angiogenesis. One example of this is the recruitment of endothelial progenitors of different lineages that differentiate into endothelial cells in the right milieu. Vascular leukocytes have been described as a subset of cells marked by both CD45, a leukocyte marker, and vasculo-endothelial (VE)-cadherin. These have been demonstrated in ovarian tumors. Their angiogenic ability has been demonstrated both *in vitro* and *in vivo* (143). Vascular leukocytes are a potential target for antiangiogenic therapy (144).

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF), first described as vascular permeability factor in 1983 by Dvorak and colleagues, was isolated from rodent ascites after injection of hepatocellular carcinoma cells and later as key factor in blood vessel development as well as permeability (136,145,146). The VEGF family is comprised of seven glycoproteins (VEGF A–E) and placental growth factor-1 and -2, secreted by tumor cells, endothelial cells, stromal cells, leukocytes, and platelets. VEGF-A, the best characterized, has four in-frame isoforms determined by RNA splicing (147). There are three transmembrane receptor tyrosine kinases, the VEGF receptors (VEGFR 1–3). VEGF-A, -B and -E stimulate angiogenesis via VEGFR1 (VEGF-A and -B) or VEGFR2 (VEGF-A and -E). VEGFR are predominantly found in endothelial cells and bone marrow–derived cells, though can

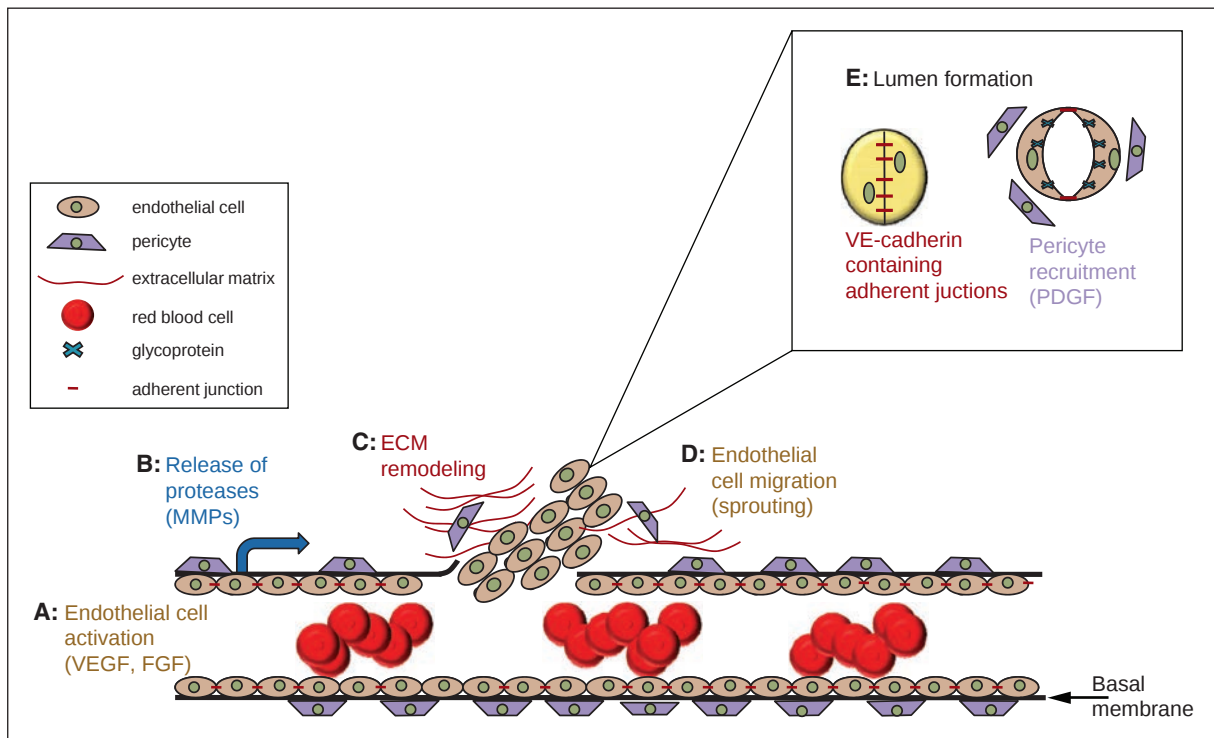


FIGURE 4.5. Angiogenesis sprouting. **A.** Endothelial cells are activated by multiple angiogenic factors secreted by tumor cells and cells of the tumor microenvironment. **B, C.** Proteases are released with the resulting remodeling of the extracellular matrix. **D.** Activated endothelial cells migrate into the stroma forming endothelial cords in the sprouting process. **E.** After cellular polarization, negatively charged glycoproteins and the cytoskeleton retract, forming a vascular lumen. Pericytes are recruited for maturation of the blood vessel, mainly through the action of PDGF.

be found expressed on other cells, including ovarian cancer cells (148). Activation of VEGFR1 and -2 is important for the recruitment, stimulation, and proliferation of endothelial cells, resulting in angiogenesis. Activation of VEGFR2 by VEGF-A has a major permeability-enhancing effect important in the formation of ascites (128,149). VEGF-C and -D activate VEGFR3 and stimulate lymphangiogenesis.

Upregulation of VEGFs is mediated by tissue hypoxia, hypoglycemia, and growth factors. The tumor microenvironment is hypoxic and acidic, both of which stimulate angiogenesis by induction of the hypoxia-inducible factor 1 α (HIF-1 α) (10,150). VEGF and VEGFR-1 are under the transcriptional regulation by HIF-1 α (151). HIF-1 α is overexpressed in several solid tumors, including ovarian carcinomas (152). Tumor growth factor signaling cascades, such as the LPA, NF- κ B, and phosphatidylinositol-3' kinase (PI3K) pathways, are activated by tumor and stromal-induced growth factors and can result in VEGF induction in ovarian cancer (153–156).

Ovarian carcinomas that have high expression of VEGF were found to result in shorter patient survival (157); concordant results were found with serum concentrations of VEGF suggesting poor patient prognosis (158). VEGF is secreted into malignant ascites by ovarian cancer cells, contributing to the increasing ascites burden through its effects on vascular permeability (159–161).

Platelet-Derived Growth Factor

Platelet-derived growth factor (PDGF) stimulates angiogenesis and also activates stromal and tumor cells (162–165). Its expression has been demonstrated in epithelial ovarian carcinomas but not in borderline ovarian tumors (166). PDGF is a dimeric protein composed of two closely related A- and B-chain polypeptides encoded by independent genes (167). Three heterodimers are formed that act in an autocrine and paracrine fashion in ovarian cancer and angiogenesis through two receptors, PDGFR β and α (166). PDGF-BB stimulates migration of endothelial cells by increasing transcription and secretion of VEGF by PDGFR β -expressing endothelial cells; activation of PI3K is important for this response (163,168). PDGF-mediated secretion of VEGF protected endothelial cells *in vitro* from apoptosis caused by serum starvation, indicating an indirect role of PDGF in supporting tumor angiogenesis through activation of survival pathways (168). The presence and potential prognostic value of the PDGFs and PDGFRs in ovarian cancer has not translated to clinical value as most of the multikinase inhibitors tested to date, such as imatinib, with inhibition of PDGFR activity have shown limited activity in gynecologic cancers (166,169–172).

Fibroblast Growth Factor

The fibroblast growth factor (FGF) family includes several ligands interacting with four FGF receptors (FGFR). Gene amplification of FGFR2 has been found in ovarian and endometrial cancer (173). FGFs are involved in proliferation, migration, and differentiation of vascular endothelial cells in a VEGF-independent manner; they also are secreted by and/or effect a wide variety of other cell types in the tumor microenvironment. FGF-1 and -2 are potent direct and indirect angiogenic factors. They also stimulate the secretion of other angiogenic factors including angiopoietin 2 and VEGF (174,175). FGF-2 also interacts with PDGF-BB, stimulating angiogenesis and attraction of vascular smooth muscle to stabilize newly formed vessels (176). FGFR1-IIIc responds to VEGF and is implicated in resistance to anti-VEGFR therapy. The combination of anti-VEGFR and anti-FGFR therapy has been examined in mouse models and was successful after failure of single agent anti-VEGFR treatment (156,177). FGF has been found in high concentrations in ascites of ovarian cancer patients (178). It remains to be determined

whether multitargeted agents will offer greater clinical benefit than specific VEGF pathway inhibitors (179).

Lymphangiogenesis

The lymphatic system is composed of the lymphatic vessels and lymphoid tissue. It has three primary physiologic functions: (a) maintenance of the blood volume through reabsorption of interstitial fluid; (b) immunological surveillance; and (c) transport of fat from the bowel to the liver. The first two functions are involved in cancer progression and metastasis (180). There are three main elements in lymphangiogenesis, VEGF-C, VEGF-D, and their receptor, VEGFR3 (180). These VEGFs also are induced by hypoxia and angiogenic signals, tumor cells, infiltrating inflammatory cells, and stromal cells. Lymph vessels are low-pressure vessels with limited basement membrane and no stromal components, permissive to entry and exit of tumor cells, immune cells, and pathogens and therefore are a ready route for metastasis (181–183). High expression of VEGF-D in epithelial ovarian tumor was associated with higher FIGO stage, intratumoral lymphatic vessels, tumor lymphatic invasion, and lymph node metastasis. VEGF-D, intratumoral lymphatics, and lymphatic invasion are independent prognostic factors for overall survival and disease-free survival in patients with epithelial ovarian carcinoma (184).

METASTASIS

Metastasis, the spread of malignant cells from the primary tumor to other sites, is the culmination of the steps discussed above—gain and loss of cell and matrix adhesion, proteolysis, and migration—and requires cancer cells to overcome many barriers for successful travel and secondary growth. Cancer cells utilize physiologic mechanisms that maintain cellular and tissue homeostasis, to promote tissue invasion, cell survival and proliferation. Survival in alternative microenvironments requires that successful metastasis also use mechanisms to overcome loss of critical stimuli, such as matrix attachment and nutritional restriction (2,3,185).

Anoikis

Anoikis, derived from Greek and meaning homelessness (5,186), is a specific apoptotic process triggered by loss of, or inappropriate cell attachment to the ECM. It is a physiologic phenomenon that maintains cell and tissue homeostasis. Resistance to anoikis is important to cancer cells because it allows them to resist apoptosis during the metastatic process, such as upon single cell release from a primary tumor and migration within the matrix or when floating in effusions (11,187). Cell–cell adhesion prevents anoikis, even in the setting of ECM detachment (188). Ovarian cancer cells shed into the peritoneal fluid form viable clusters, resist anoikis, and later can adhere and invade into serosal mesothelium (189).

The mechanism by which anoikis is triggered relies on the loss of interaction between integrins and the ECM. This causes loss of prosurvival signaling through Akt/PI3K and the raf-ERK pathway (Fig. 4.4) (4,190). Suspended cells and attached cells have very different cytoskeletal structures suggesting that the cytoskeleton also regulates survival signaling in anoikis. The disruption of structural elements or changes in cell shape might trigger anoikis (191) making the cytoskeleton a therapeutic target.

Cancer cells resist anoikis by constitutive activation of survival pathways or inhibitors of apoptosis. In ovarian cancer TrkB, a neurotrophic tyrosine kinase receptor is a potent suppressor of

caspase-associated anoikis that is found to be overexpressed in ovarian cancer (192). TrkB was found overexpressed in high-grade ovarian carcinomas and multicellular spheroids from ascites. OVCAR-3 cell spheroids also overexpressed TrkB compared to monolayer cultures. Overexpression of TrkB was associated to activation of the PI3K-AKT survival pathway in cells that survived anoikis (192). Another mechanism of anoikis resistance is attributed to the deletion or mutation of the tumor and metastasis suppressor, phosphatase and tensin homolog, PTEN. PTEN is prevalent in both endometrioid endometrial and ovarian cancers and negatively regulates AKT signaling pathway by dephosphorylation of phosphatidylinositol-4,5-bisphosphate (193). PTEN mutation removes inhibition of the AKT survival pathway activation and thus promotes anoikis resistance.

Autophagy and Cancer

Autophagy is a physiologic process that occurs in normal cells, but is induced in many types of cancer, including gynecologic cancers. Activation of autophagy can lead to cell survival or cell death depending upon the context and the stimuli, and therefore is likely exploitable for cancer therapy (11). Autophagy is tightly controlled lysosomal auto-digestion activated to maintain cellular homeostasis during the dynamic balance between cell survival and cell death. It participates in invasion, angiogenesis, and metastasis through its role in protein recycling and genome protection (9). When nutrients are deficient due to poor vascularity, intracellular molecules are recycled through autophagy to sustain viability (194,195). Hypoxia induces intracellular reactive oxygen species (ROS) that can injure intracellular proteins and upregulate autophagy (196). ROS are removed by autophagy, protecting the DNA from damage (9).

BIOMARKERS

Biomarkers are important tools to guide treatment and patient care. It is important to differentiate predictive from prognostic markers since they have different application in the management

of patients. Predictive biomarkers function to differentiate outcome to intervention, such as therapy or radiation, whereas prognostic biomarkers are independent of treatment (197). Prognostic biomarkers differentiate overall outcome, such as progression-free and overall survival within a population and have little bearing on individual patients. Despite good response rates to front line treatment of gynecological cancers, relapse rates can be very high in advanced ovarian cancer (198). Predictive and prognostic markers would help to optimize the use of existing therapies and the use of biological targeted therapies and improve quality of life by predicting high risk for toxicities.

Many elements of invasion, angiogenesis, and metastasis have also been examined for predictive, and more commonly, prognostic value. Application of new technologies including the high-throughput extensive genomic, genetic, and proteomic tools are uncovering a plethora of findings that will need to be examined in the context of diagnostics, predictive, and prognostic value and for their relationship to angiogenic, invasive, and metastatic behavior in gynecologic malignancies.

Clinical Application: Therapy Directed Against Invasion, Angiogenesis, and Metastasis

Questions that remain in the clinical arena include the following: (a) the value of specific rather than promiscuous inhibitors; (b) whether therapeutic antibodies that cause antibody-directed cellular cytotoxicity are more active than simple neutralizing antibodies; (c) what the best strategy is for combination development, with other targeted agents and/or chemotherapy; and (d) whether therapy is best in treatment and/or in maintenance of response. In order to have confidence in these targeted inhibitors of angiogenesis, invasion, and tumor dissemination, validation and illustration of the mechanism is key, with demonstration that the activated target is present, affected by the therapeutic, and that modulation of the target by the therapeutic is correlated with outcome (197,199). Many studies have been done with this increasing collection of new agents, some with promise of future benefit (Fig. 4.6).

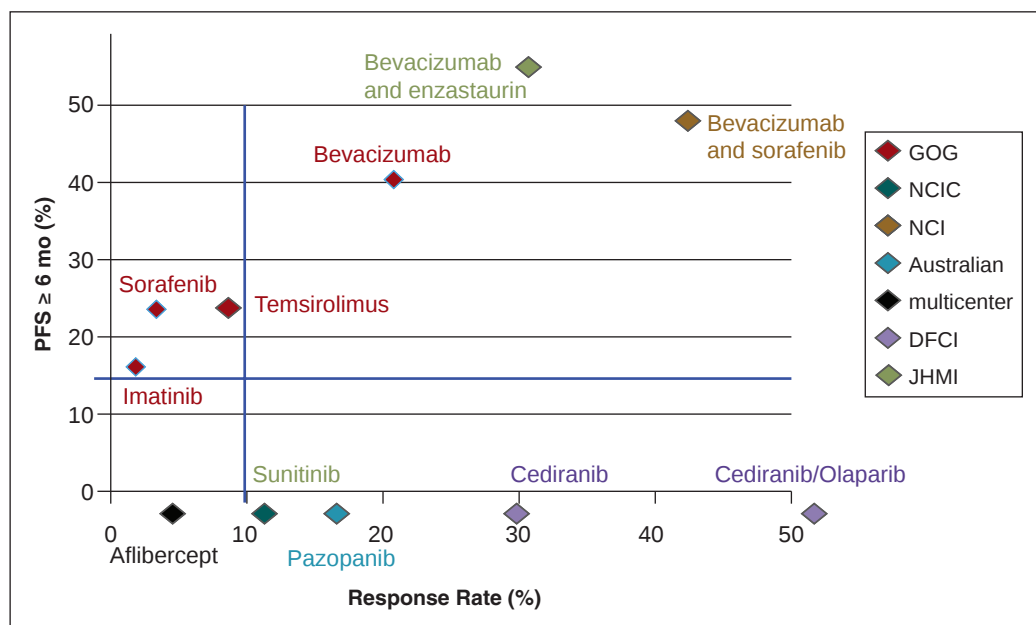


FIGURE 4.6. Angiogenic agents in ovarian cancer. Results of phase I-III trials of antiangiogenic agents alone and in combinations are plotted. Response rate and frequency of 6-month progression-free survival are shown.

Molecular-Targeted Agents: Monoclonal Antibodies

Antiangiogenic antibodies. *Bevacizumab* is a recombinant humanized version of the murine antihuman VEGF monoclonal antibody. This VEGF-neutralizing antibody inhibits VEGF-induced signaling, resulting in reduced angiogenesis and tumor growth. It has been U.S. FDA-approved for renal cell, lung, and colon cancers. In metastatic colon cancer, it prolonged survival when given in combination with chemotherapy; activity has been shown in breast, ovarian, endometrial, and cervical cancers (200–205). One of the first observations of activity of bevacizumab was reduction in gynecologic cancer ascites burden (206–208). Single-agent bevacizumab (GOG 170D) demonstrated a 21% response rate, with 40% surviving progression free at least 6 months (209). Progression-free survival at 6-month rate was 23.9% and 40.4% in cervical (GOG 227C) and endometrial cancer (GOG 229E), respectively (202,205).

The addition of bevacizumab to front-line chemotherapy and to maintenance therapy in epithelial ovarian cancer was evaluated in two pivotal phase III trials, GOG 218 and ICON 7. GOG 218 was a three-arm, placebo-controlled trial of front-line paclitaxel and carboplatin to which either concurrent bevacizumab or concurrent and maintenance bevacizumab were added. A progression-free benefit was seen in women who received both concurrent and maintenance bevacizumab at 15 mg/kg (14.1 vs. 10.3 months; HR, 0.717; $p < 0.0001$) (179). No significant difference in overall survival has been demonstrated (39.7 vs. 39.3 months; $p = 0.45$). ICON 7, a randomized phase III trial, evaluated first-line paclitaxel/carboplatin alone or in combination with bevacizumab followed by bevacizumab maintenance using 7.5 mg/kg (210). Progression-free survival was enhanced in the bevacizumab arm (HR, 0.81; 95% CI, 0.70–0.94; $p = 0.0041$), and interim analysis has revealed no significant improvement in overall survival. A post-hoc exploratory subgroup analysis found a survival improvement for patients with stage IV or stage IIIC disease with >1 cm residual tumor (HR, 0.64; 95% CI, 0.48–0.85; $p = 0.002$).

The addition of bevacizumab to second-line chemotherapy was evaluated in platinum-sensitive recurrent ovarian cancer. The phase III OCEANS trial was a two-arm, placebo-controlled study of gemcitabine and carboplatin, with experimental arms of concurrent and maintenance bevacizumab until disease progression. Patients who received concurrent and maintenance bevacizumab had a longer progression-free survival (12.4 vs. 8.4 months; HR, 0.484; 95% CI, 0.388–0.605; $p < 0.0001$) (211). Again, there was no difference in overall survival. The results of GOG 218, ICON 7, and OCEANS have raised significant questions regarding patient selection, dose, duration, and timing of therapy.

There are several randomized trials evaluating bevacizumab and chemotherapy in recurrent (GOG 213 and AURELIA) and newly diagnosed (GOG 241, 252, and 262) ovarian cancer, cervical cancer (GOG 240), and endometrial cancer (86P). Bevacizumab is also being evaluated in combination with a variety of agents including mTOR, PARP, VEGFR, and SRC inhibitors, as well as with vascular disrupting agents.

Anti-EGFR family antibodies. *Cetuximab* is a recombinant chimeric antibody to EGFR that is presently approved for treatment of metastatic colon cancer and unresectable head and neck cancer, with activity in breast and non-small cell lung cancer. However, cetuximab has minimal activity as a single agent and lacks significant activity in combination with chemotherapy or radiation in patients with recurrent ovarian (GOG 146P) or cervical cancer (GOG 227E, 76DD) (212–215). The high incidence of gastrointestinal and metabolic toxicity has precluded further development. Similar minimal activity of other methods

of inhibition of EGFR has been seen. Currently, there is no role for EGFR interruption in gynecologic malignancies.

Trastuzumab is a monoclonal antibody against EGFR-2 (Her2) that prolongs survival in Her2-positive breast cancer in both the adjuvant and metastatic settings (216,217). The only role for trastuzumab in gynecologic cancers to date appears to be in combination with chemotherapy and/or other HER2/EGFR inhibitors in uterine papillary serous cancers (218). Rare cases of true mucinous ovarian cancer have been found expressing very high Her2 and responding to trastuzumab. This observation is being followed.

Molecular Targeted Agents: Kinase Inhibitors

Antiangiogenic Agents. A number of small-molecule inhibitors of the VEGF receptors and other angiogenic pathways have been developed and reached clinical trials. VEGFR2 is most commonly targeted with preclinical data showing this approach to be active in reducing endothelial cell proliferation, migration, and vascular development, and xenograft models have confirmed activity in a number of solid tumors (219).

Selective VEGFR Inhibitors. *Cediranib* is an oral tyrosine kinase inhibitor (TKI) that targets all three VEGFRs and c-kit. Two phase II single-agent studies in recurrent EOC have been conducted. Partial response frequency ranged from 13% to 17%, with hypertension and fatigue being the most common grade 3 adverse events (220). Cediranib is being evaluated in combination with carboplatin and paclitaxel in a phase III trial (ICON6) in women with recurrent disease (221).

Mixed Kinase Inhibitors, Including VEGFRs. *Sorafenib* is an oral Raf-kinase and VEGFR-2 inhibitor that has been approved for treatment of metastatic renal cell and hepatocellular cancers (222,223). Single-agent sorafenib in women with recurrent ovarian cancer resulted in partial response in 2 patients, 20 with stabilization, and 6-month progression-free survival was 24% (GOG 170F) (224). A randomized phase II study comparing maintenance sorafenib 400 mg twice daily to placebo in advanced ovarian or primary peritoneal cancer in complete remission following surgery and one previous chemotherapy regimen has been reported as negative (IGCS, 2012). A phase I trial of *sorafenib* and *bevacizumab* in combination yielded a response rate of 47% in heavily pretreated ovarian cancer patients (197,225); evaluation of tumor biopsies, cytokine concentrations, and vascular imaging confirm an antiangiogenic signaling effect of the combination. A phase II trial of bevacizumab combined with sorafenib is presently accruing at the National Cancer Institute.

Nintedanib (BIBF1120) inhibits VEGFRs 1, 2, and 3, PDGFR- α and - β , and FGFRs 1, 2, and 3. A phase 2 placebo-controlled nintedanib maintenance trial in patients who responded to previous (at least second-line) chemotherapy reported a 36-week progression-free survival of 16.3% versus 5.0% with placebo ($p = 0.06$) (226). The most common significant adverse effects in the nintedanib arm included elevated transaminases and diarrhea. A phase III randomized placebo-controlled trial of nintedanib in combination with carboplatin and paclitaxel followed by maintenance nintedanib or placebo (AGO-OVAR12/LUME-Ovar1) in first-line treatment of EOC has completed enrollment.

Pazopanib is a TKI that targets all three VEGFRs, both PDGFRs, and c-kit. The phase II trial of pazopanib in ovarian cancer patients with initial complete CA125 response yielded a CA-125 response rate of 31%, where 29% of patients with measurable disease had stabilization (227). A phase III randomized placebo-controlled maintenance trial of pazopanib 800 mg daily (AGO-OVAR16) has completed enrollment and is maturing. Pazopanib has also been evaluated in cervical cancer (228) with improved progression-free survival (HR, 0.66; 90% CI, 0.48–0.91;

$p = 0.013$) and overall survival (HR, 0.67; 90% CI, 0.46–0.99; $p = 0.045$) compared to lapatinib, an EGFR/Her2 TKI. There was no benefit of combination lapatinib and pazopanib.

Sunitinib, an inhibitor of VEGFRs and PDGFRs (229,230), resulted in a response rate of 16.7% in a noncontinuous arm and 5.4% with continuous dosing in a phase II trial in platinum-refractory EOC (AGO-OVAR-2.11) (231). Sunitinib has minimal activity as a single agent in cervical cancer (232). The GOG has activated a phase 2 trial to evaluate sunitinib in patients with recurrent clear cell ovarian cancer (GOG254). Other VEGFR inhibitors that also target the PDGFRs and/or c-kit include vatalanib and axitinib. All are under investigation in ovarian cancers and some in other gynecologic malignancies.

Cabozantinib is an oral TKI that inhibits c-Met, ALK, and VEGFR2, and has been shown to reduce tumor growth and angiogenesis (233). Simultaneous targeting of the MET and VEGF signaling pathways may be a promising strategy to improve anti-tumor activity by blocking alternative stimulatory pathways. Reported in abstract only, a phase II randomized discontinuation trial of XL184/cabozantinib showed an overall clinical benefit defined as partial response and stable disease of 58%. The most common significant adverse effects were hand-foot syndrome (10%), diarrhea (8%) and fatigue (4%). The agent continues to be evaluated in women with refractory ovarian cancer.

Vandetanib, a dual VEGFR and EGFR inhibitor, was examined in lung and ovarian cancers because of the recognized presence and activity of both targets. A phase II study with tissue acquisition was negative (234). However, examination of signaling pathways, cytokine concentrations, and functional vascular imaging demonstrated that only EGFR was successfully inhibited at tolerable oral doses. VEGFR2 was not inhibited, nor were there changes in circulating VEGF, hypertension, or contrast changes in MRI. Vandetanib is currently being evaluated in a randomized phase II trial in combination with docetaxel in patients with recurrent ovarian cancer.

Alternative Antiangiogenesis Therapies. *Aflibercept* (VEGF-trap) is a unique fusion protein that acts as a high-affinity soluble VEGFR decoy, inhibiting VEGF-mediated events (235). Unlike bevacizumab, aflibercept has the ability to bind to other VEGF family members, including placental growth factor. A multicenter phase II study of aflibercept in recurrent ovarian cancer yielded objective response rates of 7.3% and 3.8% with 4 mg/kg and 2 mg/kg doses, respectively. The study did not achieve its primary endpoint; however, results from a phase 1 or 2 trial of aflibercept in combination with docetaxel in patients with recurrent ovarian cancer reported substantial antitumor activity (236). Aflibercept is also being evaluated in patients with endometrial cancer.

AMG 386 is a peptide-Fc fusion protein that inhibits angiogenesis by binding angiopoietin-1 and -2 and blocking interaction with the Tie2 receptor. A phase II trial of weekly paclitaxel with AMG 386 or placebo for patients with recurrent ovarian, fallopian tube, or primary peritoneal carcinoma was conducted. The median progression-free survival with paclitaxel plus placebo and 3 or 10 mg/kg of AMG386, respectively, was 4.6, 5.7 (HR vs. placebo, 0.75; 95% CI, 0.56–1.00; $p = 0.21$), and 7.2 months (HR vs. placebo, 0.76; 95% CI, 0.57–1.02; $p = 0.23$) (237). The side-effect profile was acceptable. Continued studies are ongoing to further evaluate the activity of AMG 386 in women with recurrent and newly diagnosed ovarian cancer and endometrial cancer.

COMBINATION THERAPY

Further refinement of targeted therapy is focused on the hypothesis that inhibiting biologic targets in combination may be more

effective than alone. Both targeted agents with cytotoxics and multitargeted agent studies have been initiated. To date, these approaches have not borne out promise in the phase III trials that have been completed. This underscores the importance of biological material acquisition for proof of mechanism to understand the successes and more importantly the failures of such studies. These results challenge the use of this strategy in an unselected patient population and indicate the need to develop clinical nomograms or predictive biomarkers to direct anticancer therapies. Adverse events have also limited targeting some elements of angiogenesis, invasion, and metastasis.

Drug Schedules

It has long been recognized that some drugs may have altered mechanisms of action or better pharmacokinetics when the drug schedule is modified. Paclitaxel and docetaxel have been shown to have antiangiogenic activity *in vitro* and *in vivo* (238,239). The concentrations used in those preclinical studies were at or lower than the concentration range used in the clinic; cisplatin, the control, was shown to have little effect on angiogenesis. Several chemotherapeutic agents have been shown to have antiangiogenic activity when administered in small doses in a continuous exposure approach (240). A phase II trial revealed activity of bevacizumab in combination with low-dose oral cyclophosphamide in recurrent ovarian cancer with a response rate of 24%, median progression-free survival of 7.2 months, and median overall survival 16.9 months (241); it is unknown if this is superior to single-agent low-dose daily cyclophosphamide. Weekly scheduling of topotecan, paclitaxel, or docetaxel combined with bevacizumab also have been reported to have activity in patients with ovarian cancer (242,243). Whether the effects are due to modulation of angiogenesis, invasion, and metastasis rather than using the cytotoxic effect another way is yet to be demonstrated.

CONCLUSIONS

Continued scientific, epidemiologic, and clinical advances are critically needed until successful, reproducible, and accurate early detection of gynecologic tumors becomes routine. Understanding the biology, regulation, and implications of the process of invasion and angiogenesis will continue to drive new biomarker and therapeutic target identification and intervention. The similarity between dysregulated invasion and angiogenesis and unregulated motility of metastasis allows the potential for a dual-purpose intervention. The tumor's interaction with its microenvironment becomes the focus for scientific dissection and therapeutic application (1). Here, the process of autocrine and paracrine regulation, signal pathway activation, and cell-cell conversation are critical. The use of the newer and high-throughput technologies to identify collections of biologic targets rather than one gene or protein at a time can make the process more streamlined and provide a broader view of the interaction of events. In addition, it is clear that there are numerous convergent and divergent angiogenic processes. New targets are emerging that may overcome angiogenesis escape, including novel endothelial cell and pericyte targets. Several small molecules including vascular disrupting agents, DLL4-NOTCH pathway inhibitors, and endoglin (CD105) are in clinical trials or presently under development. Together, improved understanding, study of events in the patient populations, and cooperative and collaborative progress will allow us to overcome invasion and metastasis, the major causes of morbidity and mortality associated with gynecologic cancers.

REFERENCES

- Liotta LA, Kohn EC. The microenvironment of the tumour-host interface. *Nature*. 2001; 411(6835):375–379.
- Lengyel E. Ovarian cancer development and metastasis. *Am J Pathol*. 2010;177(3):1053–1064.
- Friedl P, Alexander S. Cancer invasion and the microenvironment: plasticity and reciprocity. *Cell*. 2011;147(5):992–1009.
- Frisch SM, Screaton RA. Anoikis mechanisms. *Curr Opin Cell Biol*. 2001;13(5):555–562.
- Frisch SM, Francis H. Disruption of epithelial cell–matrix interactions induces apoptosis. *J Cell Biol*. 1994;124(4):619–626.
- Yuan SY, Rigor RR. *Regulation of Endothelial Barrier Function*. San Rafael, CA: Morgan & Claypool Life Sciences; 2010.
- Mierke CT. Role of the endothelium during tumor cell metastasis: is the endothelium a barrier or a promoter for cell invasion and metastasis? *J Biophys*. 2008;2008:183516. doi: 10.1155/2008/183516.
- Kenific CM, Thorburn A, Debnath J. Autophagy and metastasis: another double-edged sword. *Curr Opin Cell Biol*. 2010;22(2):241–245.
- Mah LY, Ryan KM. Autophagy and cancer. *Cold Spring Harb Perspect Biol*. 2012;4(1):a008821.
- Sakurai T, Kudo M. Signaling pathways governing tumor angiogenesis. *Oncology*. 2011;81(suppl. 1): 24–29.
- Coates JM, Galante JM, Bold RJ. Cancer therapy beyond apoptosis: autophagy and anoikis as mechanisms of cell death. *J Surg Res*. 2010;164(2):301–308.
- Saad AF, Hu W, Sood AK. Microenvironment and pathogenesis of epithelial ovarian cancer. *Horm Cancer*. 2010;1(6):277–290.
- Kim YN, Koo KH, Sung JY, et al. Anoikis resistance: an essential prerequisite for tumor metastasis. *Int J Cell Biol*. 2012;2012:306879.
- Mareel M, Leroy A. Clinical, cellular, and molecular aspects of cancer invasion. *Physiol Rev*. 2003;83(2):337–376.
- Psaila B, Kaplan RN, Port ER, et al. Priming the ‘soil’ for breast cancer metastasis: the premetastatic niche. *Breast Dis*. 2006;26:65–74.
- Paget S. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev*. 1989;8(2):98–101.
- Ribatti D, Mangialardi G, Vacca A. Stephen paget and the ‘seed and soil’ theory of metastatic dissemination. *Clin Exp Med*. 2006;6(4):145–149.
- Modugno F, Ness RB, Chen C, et al. Inflammation and endometrial cancer: a hypothesis. *Cancer Epidemiol Biomarkers Prev*. 2005;14(12):2840–2847.
- Demaria S, Pikarsky E, Karin M, et al. Cancer and inflammation: promise for biologic therapy. *J Immunother*. 2010;33(4):335–351.
- Calvo F, Sahai E. Cell communication networks in cancer invasion. *Curr Opin Cell Biol*. 2011; 23(5):621–629.
- Munkarah A, Ali-Fehmi R. Cox-2: a protein with an active role in gynecological cancers. *Curr Opin Obstet Gynecol*. 2005;17(1):49–53.
- Hougardy BM, Maduro JH, van der Zee AG, et al. Clinical potential of inhibitors of survival pathways and activators of apoptotic pathways in treatment of cervical cancer: changing the apoptotic balance. *Lancet Oncol*. 2005;6(8):589–598.
- Lo-Ciganic WH, Zgibor JC, Bunker CH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology*. 2012;23(2):311–319.
- Maccio A, Madeddu C. Inflammation and ovarian cancer. *Cytokine*. 2012;58(2):133–147.
- Pejovic T, Nezhat F. Missing link: inflammation and ovarian cancer. *Lancet Oncol*. 2011;12(9):833–834.
- Hawes SE, Kiviat NB. Are genital infections and inflammation cofactors in the pathogenesis of invasive cervical cancer? *J Natl Cancer Inst*. 2002;94(21):1592–1593.
- Kiviat NB, Paavonen JA, Wolner-Hanssen P, et al. Histopathology of endocervical infection caused by chlamydia trachomatis, herpes simplex virus, trichomonas vaginalis, and neisseria gonorrhoeae. *Hum Pathol*. 1990;21(8):831–837.
- Schwelke JR, Zajackowski ME. Effect of concurrent lower genital tract infections on cervical cancer screening. *Genitourin Med*. 1997;73(5):383–386.
- Choi DS, Kim HJ, Yoon JH, et al. Endometrial cancer invasion depends on cancer-derived tumor necrosis factor- α and stromal derived hepatocyte growth factor. *Int J Cancer*. 2009;124(11):2528–2538.
- Chen H, Yang WW, Wen QT, et al. TGF- β induces fibroblast activation protein expression; fibroblast activation protein expression increases the proliferation, adhesion, and migration of ho-8910pm [corrected]. *Exp Mol Pathol*. 2009;87(3):189–194.
- Yoshida S, Harada T, Iwabe T, et al. Induction of hepatocyte growth factor in stromal cells by tumor-derived basic fibroblast growth factor enhances growth and invasion of endometrial cancer. *J Clin Endocrinol Metab*. 2002;87(5):2376–2383.
- Kedrin D, van Rheenen J, Hernandez L, et al. Cell motility and cytoskeletal regulation in invasion and metastasis. *J Mammary Gland Biol Neoplasia*. 2007;12(2–3):143–152.
- Kaplan RN, Rafii S, Lyden D. Preparing the ‘Soil’: the premetastatic niche. *Cancer Res*. 2006;66(23):11089–11093.
- Hiratsuka S, Nakamura K, Iwai S, et al. Mmp9 induction by vascular endothelial growth factor receptor-1 is involved in lung-specific metastasis. *Cancer Cell*. 2002;2(4):289–300.
- Arya M, Patel HR, Williamson M. Chemokines: key players in cancer. *Curr Med Res Opin*. 2003;19(6):557–564.
- Kulbe H, Chakravarty P, Leinster DA, et al. A dynamic inflammatory cytokine network in the human ovarian cancer microenvironment. *Cancer Res*. 2012;72(1):66–75.
- Ray P, Lewin SA, Mihalko LA, et al. Noninvasive imaging reveals inhibition of ovarian cancer by targeting cxcl12-cxcr4. *Neoplasia*. 2011; 13(12):1152–1161.
- Scotton CJ, Wilson JL, Milliken D, et al. Epithelial cancer cell migration: a role for chemokine receptors? *Cancer Res*. 2001;61(13):4961–4965.
- Jiang YP, Wu XH, Shi B, et al. Expression of chemokine cxcl12 and its receptor cxcr4 in human epithelial ovarian cancer: an independent prognostic factor for tumor progression. *Gynecol Oncol*. 2006;103(1):226–233.
- Donzella GA, Schols D, Lin SW, et al. Amd3100, a small molecule inhibitor of hiv-1 entry via the cxcr4 co-receptor. *Nat Med*. 1998;4(1):72–77.
- Scotton CJ, Wilson JL, Scott K, et al. Multiple actions of the chemokine cxcl12 on epithelial tumor cells in human ovarian cancer. *Cancer Res*. 2002;62(20):5930–5938.
- Wang Y, Xu RC, Zhang XL, et al. Interleukin-8 secretion by ovarian cancer cells increases anchorage-independent growth, proliferation, angiogenic potential, adhesion and invasion. *Cytokine*. 2012;59(1):145–155.
- Coward J, Kulbe H, Chakravarty P, et al. Interleukin-6 as a therapeutic target in human ovarian cancer. *Clin Cancer Res*. 2011;17(18):6083–6096.
- Xie K. Interleukin-8 and human cancer biology. *Cytokine Growth Factor Rev*. 2001;12(4):375–391.
- Bellone S, Watts K, Cane S, et al. High serum levels of interleukin-6 in endometrial carcinoma are associated with uterine serous papillary histology, a highly aggressive and chemotherapy-resistant variant of endometrial cancer. *Gynecol Oncol*. 2005;98(1):92–98.
- Duan Z, Foster R, Bell DA, et al. Signal transducers and activators of transcription 3 pathway activation in drug-resistant ovarian cancer. *Clin Cancer Res*. 2006;12(17):5055–5063.
- Uslu R, Sanli UA, Dikmen Y, et al. Predictive value of serum interleukin-8 levels in ovarian cancer patients treated with paclitaxel-containing regimens. *Int J Gynecol Cancer*. 2005;15(2):240–245.
- Houben AJ, Mooleenaar WH. Autotaxin and lpa receptor signaling in cancer. *Cancer Metastasis Rev*. 2011;30(3–4):557–565.
- Stracke ML, Krutzsch HC, Unsworth EJ, et al. Identification, purification, and partial sequence analysis of autotaxin, a novel motility-stimulating protein. *J Biol Chem*. 1992;267(4):14528–14529.
- Shuyu E, Lai YJ, Tsukahara R, et al. Lysophosphatidic acid 2 receptor-mediated supramolecular complex formation regulates its antiapoptotic effect. *J Biol Chem*. 2009;284(21):14558–14571.
- Gotoh M, Fujiwara Y, Yue J, et al. Controlling cancer through the autotaxin-lysophosphatidic acid receptor axis. *Biochem Soc Trans*. 2012; 40(1):31–36.
- Vidot S, Witham J, Agarwal R, et al. Autotaxin delays apoptosis induced by carboplatin in ovarian cancer cells. *Cell Signal*. 2010;22(6): 926–935.
- Mills GB, May C, Hill M, et al. Ascitic fluid from human ovarian cancer patients contains growth factors necessary for intraperitoneal growth of human ovarian adenocarcinoma cells. *J Clin Invest*. 1990;86(3):851–855.
- Mills GB, May C, McGill M, et al. A putative new growth factor in ascitic fluid from ovarian cancer patients: identification, characterization, and mechanism of action. *Cancer Res*. 1988; 48(5):1066–1071.
- Naora H, Montell DJ. Ovarian cancer metastasis: integrating insights from disparate model organisms. *Nat Rev Cancer*. 2005;5(5):355–366.
- Xu Y, Gaudette DC, Boynton JD, et al. Characterization of an ovarian cancer activating factor in ascites from ovarian cancer patients. *Clin Cancer Res*. 1995;1(10):1223–1232.
- Liu S, Murph M, Panupinthu N. Atx-lpa receptor axis in inflammation and cancer. *Cell Cycle*. 2009;8(22):3695–3701.
- Ogata S, Morishige K, Sawada K, et al. Fasudil inhibits lysophosphatidic acid-induced invasiveness of human ovarian cancer cells. *Int J Gynecol Cancer*. 2009;19(9):1473–1480.
- Sedlakova I, Vavrova J, Tosner J. Lysophosphatidic acid (lpa)—a perspective marker in ovarian cancer. *Tumour Biol*. 2011;32(2):311–316.
- Wang P, Wu X, Chen W, et al. The lysophosphatidic acid (lpa) receptors their expression and significance in epithelial ovarian neoplasms. *Gynecol Oncol*. 2007;104(3):714–720.
- Hope JM, Wang FQ, Whyte JS, et al. Lpa receptor 2 mediates lpa-induced endometrial cancer invasion. *Gynecol Oncol*. 2009;112(1):215–223.
- Murphy EA, Majeti BK, Barnes LA, et al. Nanoparticle-mediated drug delivery to tumor vasculature suppresses metastasis. *Proc Natl Acad Sci USA*. 2008;105(27):9343–9348.
- Bast RC Jr, Hennessy B, Mills GB. The biology of ovarian cancer: new opportunities for translation. *Nat Rev Cancer*. 2009;9(6):415–428.

64. Freedman RS, Deavers M, Liu J, et al. Peritoneal inflammation – a microenvironment for epithelial ovarian cancer (eoc). *J Transl Med*. 2004;2(1):23.
65. Sun H, Zhu Q, Ren J, et al. [Influence of lysophosphatidic acid on proliferation, adhesion, migration and apoptosis of cervical cancer cells]. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi*. 2009;25(8):702–705.
66. Zigler M, Dobroff AS, Bar-Eli M. Cell adhesion: implication in tumor progression. *Minerva Med*. 2010;101(3):149–162.
67. Gritsenko PG, Ilina O, Friedl P. Interstitial guidance of cancer invasion. *J Pathol*. 2012; 226(2):185–199.
68. Christofori G, Semb H. The role of the cell-adhesion molecule e-cadherin as a tumour-suppressor gene. *Trends Biochem Sci*. 1999;24(2):73–76.
69. Cheng JC, Chang HM, Leung PC. Egr-1 mediates epidermal growth factor-induced downregulation of e-cadherin expression via slug in human ovarian cancer cells. *Oncogene*. 2012 [Epub ahead of print].
70. Elloul S, Elstrand MB, Nesland JM, et al. Snail, slug, and smad-interacting protein 1 as novel parameters of disease aggressiveness in metastatic ovarian and breast carcinoma. *Cancer*. 2005;103(8):1631–1643.
71. Vergara D, Merlot B, Lucot JP, et al. Epithelial-mesenchymal transition in ovarian cancer. *Cancer Lett*. 2010;291(1):59–66.
72. Cianfrocca R, Tocci P, Spinella F, et al. The endo-thelin a receptor and epidermal growth factor receptor signaling converge on beta-catenin to promote ovarian cancer metastasis. *Life Sci*. 2012; 91(13–14):500–506.
73. Cho EY, Choi Y, Chae SW, et al. Immunohistochemical study of the expression of adhesion molecules in ovarian serous neoplasms. *Pathol Int*. 2006;56(2):62–70.
74. Sawada K, Mitra AK, Radjabi AR, et al. Loss of e-cadherin promotes ovarian cancer metastasis via alpha 5-integrin, which is a therapeutic target. *Cancer Res*. 2008;68(7):2329–2339.
75. Kim G, Davidson B, Henning R, et al. Adhesion molecule protein signature in ovarian cancer effusions is prognostic of patient outcome. *Cancer*. 2012;118(6):1543–1553.
76. Lu P, Weaver VM, Werb Z. The extracellular matrix: a dynamic niche in cancer progression. *J Cell Biol*. 2012;196(4):395–406.
77. Desgrosellier JS, Cheresh DA. Integrins in cancer: biological implications and therapeutic opportunities. *Nat Rev Cancer*. 2010;10(1):9–22.
78. Wang Z, Chui WK, Ho PC. Integrin targeted drug and gene delivery. *Expert Opin Drug Deliv*. 2010;7(2):159–171.
79. Humphries JD, Byron A, Humphries MJ. Integrin ligands at a glance. *J Cell Sci*. 2006;119 (Pt 19):3901–3903.
80. Smith CW. 3. Adhesion molecules and receptors. *J Allergy Clin Immunol*. 2008;121(suppl. 2): S375–S379; quiz S414.
81. Liu Y, Belkina NV, Park C, et al. Constitutively active ezrin increases membrane tension, slows migration, and impedes endothelial transmigration of lymphocytes in vivo in mice. *Blood*. 2012;119(2):445–453.
82. Sawada K, Ohayagi-Hara C, Kimura T. Integrin inhibitors as a therapeutic agent for ovarian cancer. *J Oncol*. 2012;2012:915140.
83. Landen CN, Kim TJ, Lin YG, et al. Tumor-selective response to antibody-mediated targeting of alphavbeta3 integrin in ovarian cancer. *Neoplasia*. 2008;10(11):1259–1267.
84. Slack-Davis JK, Atkins KA, Harrer C, et al. Vascular cell adhesion molecule-1 is a regulator of ovarian cancer peritoneal metastasis. *Cancer Res*. 2009;69(4):1469–1476.
85. Gruber G, Hess J, Stiefel C, et al. Correlation between the tumoral expression of beta3-integrin and outcome in cervical cancer patients who had undergone radiotherapy. *Br J Cancer*. 2005; 92(1):41–46.
86. Hazelbag S, Kenter GG, Gorter A, et al. Overexpression of the alpha v beta 6 integrin in cervical squamous cell carcinoma is a prognostic factor for decreased survival. *J Pathol*. 2007;212(3):316–324.
87. Nagy JA, Brown LF, Senger DR, et al. Pathogenesis of tumor stroma generation: a critical role for leaky blood vessels and fibrin deposition. *Biochim Biophys Acta*. 1989;948(3):305–326.
88. Ribatti D. The contribution of Harold F. Dvorak to the study of tumor angiogenesis and stroma generation mechanisms. *Endothelium*. 2007; 14(3):131–135.
89. Hood JD, Bednarski M, Frausto R, et al. Tumor regression by targeted gene delivery to the neovasculature. *Science*. 2002;296(5577):2404–2407.
90. Xiao K, Li Y, Lee JS, et al. “Oa02” Peptide facilitates the precise targeting of paclitaxel-loaded micellar nanoparticles to ovarian cancer in vivo. *Cancer Res*. 2012;72(8):2100–21010.
91. McEver RP. Selectins: lectins that initiate cell adhesion under flow. *Curr Opin Cell Biol*. 2002; 14(5):581–586.
92. D’Anna R, Le Buanec H, Bizzini B, et al. Human papillomavirus-16-e7 oncoprotein enhances the expression of adhesion molecules in cervical endothelial cells but not in human umbilical vein endothelial cells. *J Hum Virol*. 2001;4(2):85–95.
93. Rodriguez-Rodriguez L, Sancho-Torres I, Mesonero C, et al. The cd44 receptor is a molecular predictor of survival in ovarian cancer. *Med Oncol*. 2003;20(3):255–263.
94. Cannistra SA, Kansas GS, Niloff J, et al. Binding of ovarian cancer cells to peritoneal mesothelium in vitro is partly mediated by cd44h. *Cancer Res*. 1993;53(16):3830–3838.
95. Mareel M, Oliveira MJ, Madani I. Cancer invasion and metastasis: interacting ecosystems. *Virchows Arch*. 2009;454(6):599–622.
96. Strobel T, Swanson L, Cannistra SA. In vivo inhibition of cd44 limits intra-abdominal spread of a human ovarian cancer xenograft in nude mice: a novel role for cd44 in the process of peritoneal implantation. *Cancer Res*. 1997;57(7):1228–1232.
97. Ramis-Conde I, Chaplain MA, Anderson AR, et al. Multi-scale modelling of cancer cell intravasation: the role of cadherins in metastasis. *Phys Biol*. 2009;6(1):016008.
98. Barbolina MV, Moss NM, Westfall SD, et al. Microenvironmental regulation of ovarian cancer metastasis. *Cancer Treat Res*. 2009; 149:319–334.
99. Chakraborti S, Mandal M, Das S, et al. Regulation of matrix metalloproteinases: an overview. *Mol Cell Biochem*. 2003;253(1–2):269–285.
100. Lijnen HR. Plasmin and matrix metalloproteinases in vascular remodeling. *Thromb Haemost*. 2001;86(1):324–333.
101. Davidson B, Goldberg I, Gotlieb WH, et al. Coordinated expression of integrin subunits, matrix metalloproteinases (mmp), angiogenic genes and ets transcription factors in advanced-stage ovarian carcinoma: a possible activation pathway? *Cancer Metastasis Rev*. 2003;22(1):103–115.
102. Wu S, Lu S, Tao H, et al. Correlation of polymorphism of IL-8 and mmp-7 with occurrence and lymph node metastasis of early stage cervical cancer. *J Huazhong Univ Sci Technolog Med Sci*. 2011;31(1):114–119.
103. Fernandes T, de Angelo-Andrade LA, Morais SS, et al. Stromal cells play a role in cervical cancer progression mediated by mmp-2 protein. *Eur J Gynaecol Oncol*. 2008;29(4):341–344.
104. Singh H, Jain M, Mittal B. Mmp-7 (-181a>g) promoter polymorphisms and risk for cervical cancer. *Gynecol Oncol*. 2008;110(1):71–75.
105. Yi YC, Chou PT, Chen LY, et al. Matrix metalloproteinase-7 (mmp-7) polymorphism is a risk factor for endometrial cancer susceptibility. *Clin Chem Lab Med*. 2010;48(3):337–344.
106. Planaguma J, Liljestrom M, Alameda F, et al. Matrix metalloproteinase-2 and matrix metalloproteinase-9 codistribute with transcription factors runx1/aml1 and etv5/erm at the invasive front of endometrial and ovarian carcinoma. *Hum Pathol*. 2011;42(1):57–67.
107. Wang FQ, So J, Reierstad S, et al. Matrilysin (mmp-7) promotes invasion of ovarian cancer cells by activation of progelatinase. *Int J Cancer*. 2005;114(1):19–31.
108. Brun JL, Cortez A, Lesieur B, et al. Expression of mmp-2, -7, -9, mt1-mmp and timp-1 and -2 has no prognostic relevance in patients with advanced epithelial ovarian cancer. *Oncol Rep*. 2012;27(4):1049–1057.
109. Wojtowicz-Praga S, Low J, Marshall J, et al. Phase I trial of a novel matrix metalloproteinase inhibitor batimastat (bb-94) in patients with advanced cancer. *Invest New Drugs*. 1996; 14(2):193–202.
110. Nemunaitis J, Poole C, Primrose J, et al. Combined analysis of studies of the effects of the matrix metalloproteinase inhibitor marimastat on serum tumor markers in advanced cancer: Selection of a biologically active and tolerable dose for longer-term studies. *Clin Cancer Res*. 1998;4(5):1101–1109.
111. Matsuo T, Nakamura K, Takamoto N, et al. Expression of the serine protease hepsin and clinical outcome of human endometrial cancer. *Anticancer Res*. 2008;28(1A):159–164.
112. Miao J, Mu D, Ergel B, et al. Hepsin colocalizes with desmosomes and induces progression of ovarian cancer in a mouse model. *Int J Cancer*. 2008;123(9):2041–2047.
113. Sakanari JA, Staunton CE, Eakin AE, et al. Serine proteases from nematode and protozoan parasites: isolation of sequence homologs using generic molecular probes. *Proc Natl Acad Sci USA*. 1989;86(13):4863–4867.
114. Tanimoto H, Yan Y, Clarke J, et al. Hepsin, a cell surface serine protease identified in hepatoma cells, is overexpressed in ovarian cancer. *Cancer Res*. 1997;57(14):2884–2887.
115. Xuan JA, Schneider D, Toy P, et al. Antibodies neutralizing hepsin protease activity do not impact cell growth but inhibit invasion of prostate and ovarian tumor cells in culture. *Cancer Res*. 2006;66(7):3611–3619.
116. Goulet B, Chan G, Chambers AF, et al. An emerging role for the nuclear localization of maspin in the suppression of tumor progression and metastasis. *Biochem Cell Biol*. 2012;90(1):22–38.
117. Normandin K, Peant B, Le Page C, et al. Protease inhibitor serpin1 expression in epithelial ovarian cancer. *Clin Exp Metastasis*. 2010;27(1):55–69.
118. Whitley BR, Beaulieu LM, Carter JC, et al. Phosphatidylinositol 3-kinase/akt regulates the balance between plasminogen activator inhibitor-1 and urokinase to promote migration of skov-3 ovarian cancer cells. *Gynecol Oncol*. 2007; 104(2):470–479.
119. Simpkins FA, Devoogdt NM, Rasool N, et al. The alarm anti-protease, secretory leukocyte protease inhibitor, is a proliferation and survival factor for ovarian cancer cells. *Carcinogenesis*. 2008;29(3):466–472.

120. Hoskins E, Rodriguez-Canales J, Hewitt SM, et al. Paracrine sli secretion upregulates mmp-9 transcription and secretion in ovarian cancer cells. *Gynecol Oncol.* 2011;122(3):656–662.
121. Rasool N, LaRochelle W, Zhong H, et al. Secretory leukocyte protease inhibitor antagonizes paclitaxel in ovarian cancer cells. *Clin Cancer Res.* 2010;16(2):600–609.
122. Bauerschlag DO, Habermann M, Weimer J, et al. Heterogeneous expression of serine protease inhibitor maspin in ovarian cancer. *Anticancer Res.* 2010;30(7):2739–2744.
123. Kirmse R, Otto H, Ludwig T. The extracellular matrix remodeled: interdependency of matrix proteolysis, cell adhesion, and force sensing. *Commun Integr Biol.* 2012;5(1):71–73.
124. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971;285(21):1182–1186.
125. Folkman J, Merler E, Abernathy C. Isolation of a tumor factor responsible for angiogenesis. *J Exp Med.* 1971;133(2):275–288.
126. Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. *Cell.* 1994;79(2):185–188.
127. Maitland ML, Lou XJ, Ramirez J, et al. Vascular endothelial growth factor pathway. *Pharmacogenet Genomics.* 2010;20(5):346–349.
128. Cantu De Leon D, Lopez-Graniel C, Frias Mendivil M, et al. Significance of microvascular density (mvd) in cervical cancer recurrence. *Int J Gynecol Cancer.* 2003;13(6):856–862.
129. Hollingsworth HC, Kohn EC, Steinberg SM, et al. Tumor angiogenesis in advanced stage ovarian cancer. *Am J Pathol.* 1995;147:33–41.
130. Raspollini MR, Amunni G, Villanucci A, et al. Prognostic significance of microvessel density and vascular endothelial growth factor expression in advanced ovarian serous carcinoma. *Int J Gynecol Cancer.* 2004;14(5):815–823.
131. Taskiran C, Erdem O, Onan A, et al. The prognostic value of endoglin (cd105) expression in ovarian carcinoma. *Int J Gynecol Cancer.* 2006;16(5):1789–1793.
132. Ozalp S, Yalcin OT, Acikalin M, et al. Microvessel density (mvd) as a prognosticator in endometrial carcinoma. *Eur J Gynaecol Oncol.* 2003;24(3–4):305–308.
133. Kaku T, Kamura T, Kinukawa N, et al. Angiogenesis in endometrial carcinoma. *Cancer.* 1997;80(4):741–747.
134. Rubatt JM, Darcy KM, Hutson A, et al. Independent prognostic relevance of microvessel density in advanced epithelial ovarian cancer and associations between cd31, cd105, p53 status, and angiogenic marker expression: a gynecologic oncology group study. *Gynecol Oncol.* 2009;112(3):469–474.
135. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell.* 1996;86(3):353–364.
136. Ferrara N, Gerber HP, LeCouter J. The biology of vegf and its receptors. *Nat Med.* 2003;9(6):669–676.
137. Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. *Cell.* 2011;146(6):873–887.
138. Jain RK. Molecular regulation of vessel maturation. *Nat Med.* 2003;9(6):685–693.
139. Raza A, Franklin MJ, Dudek AZ. Pericytes and vessel maturation during tumor angiogenesis and metastasis. *Am J Hematol.* 2010;85(8):593–598.
140. Kalluri P, Crowe C, Reller M, et al. An outbreak of foodborne botulism associated with food sold at a salvage store in texas. *Clin Infect Dis.* 2003;37(11):1490–1495.
141. Ribatti D, Djonov V. Intussusceptive microvascular growth in tumors. *Cancer Lett.* 2012;316(2):126–131.
142. Fakhrejahani E, Toi M. Tumor angiogenesis: pericytes and maturation are not to be ignored. *J Oncol.* 2012;2012:261750.
143. Conejo-Garcia JR, Buckanovich RJ, Benencia F, et al. Vascular leukocytes contribute to tumor vascularization. *Blood.* 2005;105(2):679–681.
144. Balint K, Conejo-Garcia JR, Buckanovich R, et al. Role of vascular leukocytes in ovarian cancer neovascularization. *Adv Exp Med Biol.* 2008;622:273–280.
145. Senger DR, Galli SJ, Dvorak AM, et al. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science.* 1983;219(4587):983–985.
146. Gavard J, Gutkind JS. Vegf controls endothelial-cell permeability by promoting the beta-arrestin-dependent endocytosis of ve-cadherin. *Nat Cell Biol.* 2006;8(11):1223–1234.
147. Biselli-Chicote PM, Oliveira AR, Pavarino EC. Vegf gene alternative splicing: pro- and anti-angiogenic isoforms in cancer. *J Cancer Res Clin Oncol.* 2012;138(3):363–370.
148. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev.* 1997;18(1):4–25.
149. Eliceiri BP, Paul R, Schwartzberg PL, et al. Selective requirement for src kinases during vegf-induced angiogenesis and vascular permeability. *Mol Cell.* 1999;4(6):915–924.
150. Semenza G. Signal transduction to hypoxia-inducible factor 1. *Biochem Pharmacol.* 2002;64(5–6):993–998.
151. Azuma M, Shi M, Danenberg KD, et al. Serum lactate dehydrogenase levels and glycolysis significantly correlate with tumor vegfa and vegfr expression in metastatic crc patients. *Pharmacogenomics.* 2007;8(12):1705–1713.
152. Talks KL, Turley H, Gatter KC, et al. The expression and distribution of the hypoxia-inducible factors hif-1alpha and hif-2alpha in normal human tissues, cancers, and tumor-associated macrophages. *Am J Pathol.* 2000;157(2):411–421.
153. Dutta S, Wang FQ, Wu HS, et al. The nf-kappab pathway mediates lysophosphatidic acid (lpa)-induced vegf signaling and cell invasion in epithelial ovarian cancer (eoc). *Gynecol Oncol.* 2011;123(1):129–137.
154. Hu YL, Tee MK, Goetzel EJ, et al. Lysophosphatidic acid induction of vascular endothelial growth factor expression in human ovarian cancer cells. *J Natl Cancer Inst.* 2001;93(10):762–768.
155. Hsieh CY, Chen CA, Chou CH, et al. Overexpression of her-2/neu in epithelial ovarian carcinoma induces vascular endothelial growth factor c by activating nf-kappa b: implications for malignant ascites formation and tumor lymphangiogenesis. *J Biomed Sci.* 2004;11(2):249–259.
156. Casanovas O, Hicklin DJ, Bergers G. Drug resistance by evasion of antiangiogenic targeting of vegf signaling in late-stage pancreatic islet tumors. *Cancer Cell.* 2005;8(4):299–309.
157. Hartenbach EM, Olson TA, Goswitz JJ, et al. Vascular endothelial growth factor (vegfr) expression and survival in human epithelial ovarian carcinomas. *Cancer Lett.* 1997;121(2):169–175.
158. Li L, Wang L, Zhang W, et al. Correlation of serum vegf levels with clinical stage, therapy efficacy, tumor metastasis and patient survival in ovarian cancer. *Anticancer Res.* 2004;24(3b):1973–1979.
159. Zebrowski BK, Liu W, Ramirez K, et al. Markedly elevated levels of vascular endothelial growth factor in malignant ascites. *Ann Surg Oncol.* 1999;6(4):373–378.
160. Kraft A, Weindel K, Ochs A, et al. Vascular endothelial growth factor in the sera and effusions of patients with malignant and nonmalignant disease. *Cancer.* 1999;85(1):178–187.
161. Hu L, Ferrara N, Jaffe RB. Paracrine vegf/ve-cadherin action on ovarian cancer permeability. *Exp Biol Med (Maywood).* 2006;231(10):1646–1652.
162. Ostman A. Pdgfr receptors-mediators of autocrine tumor growth and regulators of tumor vasculature and stroma. *Cytokine Growth Factor Rev.* 2004;15(4):275–286.
163. Wang D, Huang HJ, Kazlauskas A, et al. Induction of vascular endothelial growth factor expression in endothelial cells by platelet-derived growth factor through the activation of phosphatidylinositol 3-kinase. *Cancer Res.* 1999;59(7):1464–1472.
164. Hellstrom M, Kalen M, Lindahl P, et al. Role of pdgf-b and pdgfr-beta in recruitment of vascular smooth muscle cells and pericytes during embryonic blood vessel formation in the mouse. *Development.* 1999;126(14):3047–3055.
165. Sundberg C, Ljungstrom M, Lindmark G, et al. Microvascular pericytes express platelet-derived growth factor-beta receptors in human healing wounds and colorectal adenocarcinoma. *Am J Pathol.* 1993;143(5):1377–1388.
166. Henriksen R, Funa K, Wilander E, et al. Expression and prognostic significance of platelet-derived growth factor and its receptors in epithelial ovarian neoplasms. *Cancer Res.* 1993;53(19):4550–4554.
167. Helden CH, Westermarck B. Mechanism of action and in vivo role of platelet-derived growth factor. *Physiol Rev.* 1999;79(4):1283–1316.
168. Reinmuth N, Liu W, Jung YD, et al. Induction of vegf in perivascular cells defines a potential paracrine mechanism for endothelial cell survival. *FASEB J.* 2001;15(7):1239–1241.
169. Versnel MA, Haarbrink M, Langerak AW, et al. Human ovarian tumors of epithelial origin express pdgf in vitro and in vivo. *Cancer Genet Cytogenet.* 1994;73(1):60–64.
170. Posadas EM, Kwitkowski V, Kotz HL, et al. A prospective analysis of imatinib-induced c-kit modulation in ovarian cancer: a phase ii clinical study with proteomic profiling. *Cancer.* 2007;110(2):309–317.
171. Matei D, Chang DD, Jeng MH. Imatinib mesylate (gleevec) inhibits ovarian cancer cell growth through a mechanism dependent on platelet-derived growth factor receptor alpha and akt inactivation. *Clin Cancer Res.* 2004;10(2):681–690.
172. Coleman RL, Broaddus RR, Bodurka DC, et al. Phase ii trial of imatinib mesylate in patients with recurrent platinum- and taxane-resistant epithelial ovarian and primary peritoneal cancers. *Gynecol Oncol.* 2006;101(1):126–131.
173. Katoh M. Cancer genomics and genetics of fgfr2 (review). *Int J Oncol.* 2008;33(2):233–237.
174. Fujii T, Kuwano H. Regulation of the expression balance of angiopoietin-1 and angiopoietin-2 by shh and fgf-2. *In Vitro Cell Dev Biol Anim.* 2010;46(6):487–491.
175. Pepper MS, Ferrara N, Orci L. Potent synergism between vascular endothelial growth factor and basic fibroblast growth factor in the induction of angiogenesis in vitro. *Biochem Biophys Res Commun.* 1992;189(2):824–831.
176. Nissen LJ, Cao R, Hedlund EM, et al. Angiogenic factors fgf2 and pdgfr-bb synergistically promote murine tumor neovascularization and metastasis. *J Clin Invest.* 2007;117(10):2766–2777.

177. Allen BL, Filla MS, Rapraeger AC. Role of heparan sulfate as a tissue-specific regulator of fgf-4 and fgf receptor recognition. *J Cell Biol.* 2001;155(5):845–858.
178. Barton DP, Cai A, Wendt K, et al. Angiogenic protein expression in advanced epithelial ovarian cancer. *Clin Cancer Res.* 1997;3(9):1579–1586.
179. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473–2483.
180. Albrecht I, Christofori G. Molecular mechanisms of lymphangiogenesis in development and cancer. *Int J Dev Biol.* 2011;55(4–5):483–494.
181. Nathanson SD. Insights into the mechanisms of lymph node metastasis. *Cancer.* 2003;98(2):413–423.
182. Tanis PJ, Nieweg OE, Valdes Olmos RA, et al. Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. *J Am Coll Surg.* 2001;192(3):399–409.
183. Robison K, Holman LL, Moore RG. Update on sentinel lymph node evaluation in gynecologic malignancies. *Curr Opin Obstet Gynecol.* 2011;23(1):8–12.
184. Li L, Liu B, Li X, et al. Vascular endothelial growth factor d and intratumoral lymphatics as independent prognostic factors in epithelial ovarian carcinoma. *Anat Rec (Hoboken).* 2009;292(4):562–569.
185. Geiger TR, Peeper DS. Metastasis mechanisms. *Biochim Biophys Acta.* 2009;1796(2):293–308.
186. Ma Z, Liu Z, Myers DP. Mechanotransduction and anoikis: death and the homeless cell. *Cell Cycle.* 2008;7(16):2462–2465.
187. He X, Ota T, Liu P, et al. Downregulation of htra1 promotes resistance to anoikis and peritoneal dissemination of ovarian cancer cells. *Cancer Res.* 2010;70(8):3109–3118.
188. Hofmann C, Lippert E, Falk W, et al. Primary human colonic epithelial cells are transiently protected from anoikis by a src-dependent mechanism. *Biochem Biophys Res Commun.* 2009;390(3):908–914.
189. Iwanicki MP, Davidowitz RA, Ng MR, et al. Ovarian cancer spheroids use myosin-generated force to clear the mesothelium. *Cancer Discov.* 2011;1(2):144–157.
190. Chiarugi P. From anchorage dependent proliferation to survival: lessons from redox signalling. *IUBMB Life.* 2008;60(5):301–307.
191. Flusberg DA, Numaguchi Y, Ingber DE. Cooperative control of akt phosphorylation, bcl-2 expression, and apoptosis by cytoskeletal microfilaments and microtubules in capillary endothelial cells. *Mol Biol Cell.* 2001;12(10):3087–3094.
192. Yu X, Liu L, Cai B, et al. Suppression of anoikis by the neurotrophic receptor trkb in human ovarian cancer. *Cancer Sci.* 2008;99(3):543–552.
193. Merritt MA, Cramer DW. Molecular pathogenesis of endometrial and ovarian cancer. *Cancer Biomark.* 2011;9(1–6):287–305.
194. Kuma A, Hatano M, Matsui M, et al. The role of autophagy during the early neonatal starvation period. *Nature.* 2004;432(7020):1032–1036.
195. Lum JJ, Bauer DE, Kong M, et al. Growth factor regulation of autophagy and cell survival in the absence of apoptosis. *Cell.* 2005;120(2):237–248.
196. Degenhardt K, Mathew R, Beaudoin B, et al. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. *Cancer Cell.* 2006;10(1):51–64.
197. Lee JM, Sarosy GA, Annunziata CM, et al. Combination therapy: intermittent sorafenib with bevacizumab yields activity and decreased toxicity. *Br J Cancer.* 2010;102(3):495–499.
198. Cannistra SA. Cancer of the ovary. *N Engl J Med.* 2004;351(24):2519–2529.
199. Hays JL, Kim G, Giuriou I. Proteomics and ovarian cancer: integrating proteomics information into clinical care. *J Proteomics.* 2010;73(10):1864–1872.
200. Miller KD. E2100: a phase iii trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. *Clin Breast Cancer.* 2003;3(6):421–422.
201. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase ii trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol.* 2004;22(11):2184–2191.
202. Aghajanian C, Sill MW, Darcy KM, et al. Phase ii trial of bevacizumab in recurrent or persistent endometrial cancer: a gynecologic oncology group study. *J Clin Oncol.* 2011;29(16):2259–2265.
203. Burger RA. Experience with bevacizumab in the management of epithelial ovarian cancer. *J Clin Oncol.* 2007;25(20):2902–2908.
204. Cannistra SA, Matulonis UA, Penson RT, et al. Phase ii study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol.* 2007;25(33):5180–5186.
205. Monk BJ, Willmott LJ, Sumner DA. Anti-angiogenesis agents in metastatic or recurrent cervical cancer. *Gynecol Oncol.* 2010;116(2):181–186.
206. Cohn DE, Valmadre S, Resnick KE, et al. Bevacizumab and weekly taxane chemotherapy demonstrates activity in refractory ovarian cancer. *Gynecol Oncol.* 2006;102(2):134–139.
207. Gerber HP, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. *Cancer Res.* 2005;65(3):671–680.
208. Numnum TM, Rocconi RP, Whitworth J, et al. The use of bevacizumab to palliate symptomatic ascites in patients with refractory ovarian carcinoma. *Gynecol Oncol.* 2006;102(3):425–428.
209. Burger RA, Sill MW, Monk BJ, et al. Phase ii trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a gynecologic oncology group study. *J Clin Oncol.* 2007;25(33):5165–5171.
210. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011;365(26):2484–2496.
211. Aghajanian C, Blank SV, Goff BA, et al. Oceans: a randomized, double-blind, placebo-controlled phase iii trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30(17):2039–2045.
212. Schilder RJ, Pathak HB, Lokshin AE, et al. Phase ii trial of single agent cetuximab in patients with persistent or recurrent epithelial ovarian or primary peritoneal carcinoma with the potential for dose escalation to rash. *Gynecol Oncol.* 2009;113(1):21–27.
213. Secord AA, Blessing JA, Armstrong DK, et al. Phase ii trial of cetuximab and carboplatin in relapsed platinum-sensitive ovarian cancer and evaluation of epidermal growth factor receptor expression: a gynecologic oncology group study. *Gynecol Oncol.* 2008;108(3):493–499.
214. Santin AD, Sill MW, McMeekin DS, et al. Phase ii trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a gynecologic oncology group study. *Gynecol Oncol.* 2011;122(3):495–500.
215. Farley J, Sill MW, Birrer M, et al. Phase ii study of cisplatin plus cetuximab in advanced, recurrent, and previously treated cancers of the cervix and evaluation of epidermal growth factor receptor immunohistochemical expression: a gynecologic oncology group study. *Gynecol Oncol.* 2011;121(2):303–308.
216. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in her2-positive breast cancer. *N Engl J Med.* 2005;353(16):1659–1672.
217. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from nctg n9831 and nsabp b-31. *J Clin Oncol.* 2011;29(25):3366–3373.
218. El-Sahwi K, Bellone S, Cocco E, et al. In vitro activity of pertuzumab in combination with trastuzumab in uterine serous papillary adenocarcinoma. *Br J Cancer.* 2010;102(1):134–143.
219. Adjei AA. Novel small-molecule inhibitors of the vascular endothelial growth factor receptor. *Clin Lung Cancer.* 2007;8(suppl. 2):S74–S78.
220. Matulonis UA, Berlin S, Ivy P, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. *J Clin Oncol.* 2009;27(33):5601–5606.
221. Raja FA, Griffin CL, Qian W, et al. Initial toxicity assessment of icon6: a randomised trial of cediranib plus chemotherapy in platinum-sensitive relapsed ovarian cancer. *Br J Cancer.* 2011;105(7):884–889.
222. Eisen T, Sternberg CN, Robert C, et al. Targeted therapies for renal cell carcinoma: review of adverse event management strategies. *J Natl Cancer Inst.* 2012;104(2):93–113.
223. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356(2):125–134.
224. Matei D, Sill MW, Lankes HA, et al. Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: a gynecologic oncology group trial. *J Clin Oncol.* 2011;29(1):69–75.
225. Azad NS, Posadas EM, Kwitkowski VE, et al. Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. *J Clin Oncol.* 2008;26(22):3709–3714.
226. Ledermann JA, Hackshaw A, Kaye S, et al. Randomized phase ii placebo-controlled trial of maintenance therapy using the oral triple angiogenesis inhibitor bibf 1120 after chemotherapy for relapsed ovarian cancer. *J Clin Oncol.* 2011;29(28):3798–3804.
227. Friedlander M, Hancock KC, Rischin D, et al. A phase ii, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. *Gynecol Oncol.* 2010;119(1):32–37.
228. Monk BJ, Mas Lopez L, Zarba JJ, et al. Phase ii, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. *J Clin Oncol.* 2010;28(22):3562–3569.
229. Reidy-Lagunes D, Thornton R. Pancreatic neuroendocrine and carcinoid tumors: what's new, what's old, and what's different? *Curr Oncol Rep.* 2012;14(3):249–256.
230. Stadler WM. Effective therapy for metastatic renal cancer, which4er to now. *J Clin Oncol.* 2009;27(22):3573–3574.

231. Baumann KH, du Bois A, Meier W, et al. A phase ii trial (ago 2.11) in platinum-resistant ovarian cancer: a randomized multicenter trial with sunitinib (su11248) to evaluate dosage, schedule, tolerability, toxicity and effectiveness of a multitargeted receptor tyrosine kinase inhibitor monotherapy. *Ann Oncol.* 2012;23(9):2265–2271.
232. Mackay HJ, Tinker A, Winqvist E, et al. A phase ii study of sunitinib in patients with locally advanced or metastatic cervical carcinoma: Ncic ctg trial ind.184. *Gynecol Oncol.* 2010;116(2):163–167.
233. Yakes FM, Chen J, Tan J, et al. Cabozantinib (xl184), a novel met and vegfr2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther.* 2011;10(12):2298–2308.
234. Annunziata CM, Walker AJ, Minasian L, et al. Vandetanib, designed to inhibit vegfr2 and egfr signaling, had no clinical activity as monotherapy for recurrent ovarian cancer and no detectable modulation of vegfr2. *Clin Cancer Res.* 2010;16(2):664–672.
235. Byrne AT, Ross L, Holash J, et al. Vascular endothelial growth factor-trap decreases tumor burden, inhibits ascites, and causes dramatic vascular remodeling in an ovarian cancer model. *Clin Cancer Res.* 2003;9(15):5721–5728.
236. Coleman RL, Duska LR, Ramirez PT, et al. Phase 1–2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. *Lancet Oncol.* 2011;12(12):1109–1117.
237. Karlan BY, Oza AM, Richardson GE, et al. Randomized, double-blind, placebo-controlled phase ii study of amg 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer. *J Clin Oncol.* 2012;30(4):362–371.
238. Belotti D, Vergani V, Drudis T, et al. The microtubule-affecting drug paclitaxel has anti-angiogenic activity. *Clin Cancer Res.* 1996;2(11):1843–1849.
239. Hotchkiss KA, Ashton AW, Mahmood R, et al. Inhibition of endothelial cell function in vitro and angiogenesis in vivo by docetaxel (taxotere): association with impaired repositioning of the microtubule organizing center. *Mol Cancer Ther.* 2002;1(13):1191–1200.
240. Bocci G, Nicolaou KC, Kerbel RS. Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective anti-angiogenic window for various chemotherapeutic drugs. *Cancer Res.* 2002;62(23):6938–6943.
241. Garcia AA, Hirte H, Fleming G, et al. Phase ii clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the california, chicago, and princess margaret hospital phase ii consortia. *J Clin Oncol.* 2008;26(1):76–82.
242. McGonigle KE, Muntz HG, Vuky J, et al. Combined weekly topotecan and biweekly bevacizumab in women with platinum-resistant ovarian, peritoneal, or fallopian tube cancer: results of a phase 2 study. *Cancer.* 2011;117(16):3731–3740.
243. O'Malley DM, Richardson DL, Rheaume PS, et al. Addition of bevacizumab to weekly paclitaxel significantly improves progression-free survival in heavily pretreated recurrent epithelial ovarian cancer. *Gynecol Oncol.* 2011;121(2):269–272.

5

Development and Identification of Tumor Serum Markers

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Tumor markers are defined as molecules or substances produced by malignant tumors that enter the circulation in detectable amounts. They indicate the likely presence of cancer or provide information about its behavior. In management of cancer, the most useful biochemical markers are the macromolecular tumor antigens, including enzymes, hormones, receptors, growth factors, biologic response modifiers, and glycoconjugates. A substantial number of substances have been investigated as potential tumor markers over the past decade and the list is continually growing owing to new technology employed in biomarker discovery.

Tumor markers can be used for risk stratification, screening, differential diagnosis, prognosis, predicting, and monitoring response to therapy and detecting recurrence (Table 5.1). The performance of a tumor marker depends on its sensitivity (percentage of patients with cancer correctly identified as a result of a positive test), specificity (percentage of the population without cancer correctly identified as a result of a negative test),

and positive predictive value (PPV, percentage of patients with positive test that have the cancer, true positives) (Table 5.2). An ideal tumor marker should have a 100% sensitivity, specificity, and PPV. However, in practice such a marker does not exist. As the majority of markers are tumor-associated rather than tumor-specific, and are elevated in multiple cancers, benign and physiologic conditions, they lack specificity. In addition, if sensitivity is low, a normal result may not exclude malignancy. Tumor markers discovered thus far contribute to differential diagnosis but are not themselves diagnostic. This restricts their use, with few exceptions, to monitoring therapeutic response and follow-up. Tumor markers currently used in nongynecologic malignancies include:

1. Carcinoembryonic Antigen (CEA), the most commonly elevated marker in colorectal cancer, whose preoperative assessment is recommended by the American Society of Clinical Oncology (ASCO) as it may complement surgical staging and help in choosing the most appropriate surgical treatment. Abnormal preoperative levels may also indicate higher risk of recurrence but there is no concrete evidence as to whether patients with colorectal cancer would benefit from adjuvant therapy based on preoperative CEA alone (1). CEA is, however, not used in screening or early diagnosis.
2. CA-15-3, measurements of which have been advocated (ASCO) in monitoring response to treatment in breast cancer when the disease is not measurable.
3. Prostate-specific antigen (PSA) is used in screening for prostate cancer but its use as a stand-alone marker is not recommended. Most guidelines recommend a PSA test followed by digital rectal examination with definitive diagnosis always requiring a biopsy. PSA may have a role in detecting disease recurrence and monitoring treatment in patients with prostate cancer (2).

Table 5.1 Tumor Markers and Their Potential Uses**1. Risk stratification**

Adjusting risk categorization for an individual without the disease. The marker could then be used in screening or prevention if these are proven to be effective

2. Screening

Screening to detect cancer earlier than it would have been using clinical signs and symptoms

3. Differential diagnosis

Use of serum and tissue tumor markers to establish the tissue of origin of a newly diagnosed cancer by differentiating between the cancer and benign conditions

4. Prognosis

Markers used to determine prognosis in a patient, i.e., risk of invasion and metastasis in the absence of therapy

5. Prediction

Ability of a marker to determine the likelihood of sensitivity or resistance to specific therapy

6. Monitoring

Monitoring patients either during or after therapy to determine the status of the cancer. Patients are usually monitored during primary therapy but also during therapy for metastatic disease to determine if the patient is responding to the treatment or if an alternative therapy is needed

Table 5.2 Parameters of Tumor Marker Assays

Tumor Marker Result	True Tumor Status	
	Positive	Negative
Positive	A (True positives)	B (False positives)
Negative	C (False negatives)	D (True negatives)

Sensitivity = True positives / All with tumor = $A / A + C$

Specificity = True negatives / All tumor free = $D / D + B$

Positive predictive value (PPV) = True positives / All with positive tumor-marker result = $A / A + B$

This chapter focuses on those markers that are clinically relevant to female genital tract malignancies.

OVARIAN AND FALLOPIAN TUBE CANCERS

Women have approximately a 1% to 2% lifetime risk of developing ovarian cancer (OC) and it accounts for 4% of cancers diagnosed in women, with over 225,000 new cases diagnosed worldwide each year (3). Incidence rates are highest in the U.S. and Northern Europe and lowest in Africa and Asia. It is associated with the highest mortality rates of all female genital tract malignancies. Around 85% of cases occur over the age of 50, and 80% to 85% of cancers are epithelial in origin. Epithelial ovarian cancer (EOC) may be serous, mucinous, endometrioid, clear cell, transitional, and undifferentiated. The most common histologic subtype of EOC is serous OC, which usually presents at advanced stages and has the poorest outcomes (4). However, in the reproductive age group germ cell tumors, granulosa cell/sex-cord tumors, mucinous, and endometrioid tumors are more common. Only a few tumor markers have been validated for clinical use with the best known among them being cancer antigen 125 (CA-125).

CA-125

CA-125 was first described by Bast et al. in 1981. It is a 200-kDa glycoprotein recognized by the OC-125 murine monoclonal antibody (5). CA-125 carries two major antigenic domains: domain A (binds monoclonal antibody OC-125) and domain B (binds monoclonal antibody M11) (6). The current second-generation heterologous CA-125-II assay incorporates M11 and OC125 antibodies, while the original homologous assay was with OC125 alone. Currently there are a number of CA-125 assays that correlate well with each other (7,8).

CA-125 is expressed by amniotic and coelomic epithelium during fetal development. It is widely distributed in adult tissues (mesothelial cells of the pleura, pericardium and peritoneum, tubal, endometrial and endocervical epithelium) but is not expressed by the surface epithelium of normal fetal and adult ovaries with the exception of inclusion cysts, areas of metaplasia, and papillary excrescences (9). It therefore lacks complete specificity for OC.

The level of CA-125 in body fluids or ovarian cysts does not correlate well with serum levels. This is probably due to the serum concentration being reflective not only of the production of the antigen by the tumor but other factors that affect its release into the circulation. The widely adopted cut-off at 35 kU/L routinely used in clinical practice is based upon the distribution of values in 99% of 888 healthy men and women (10). However, levels of CA-125 tend to be lower in postmenopausal women or in patients who have undergone hysterectomy; levels of 20 U/mL and 26 U/mL have been suggested (11–13). Approximately 85% of patients with epithelial ovarian cancer have CA-125 levels of greater than 35 U/mL (10,14). Raised serum levels are found in 50% Stage I and greater than 90% Stage II–IV cancer (15) (Table 5.3). CA-125 levels are more frequently elevated in serous compared to mucinous, clear cell, and borderline tumors (15–17). CA-125 can be elevated in other malignancies (pancreas, breast, colon, and lung cancer) (Table 5.4) and in benign conditions (Table 5.3) and in physiologic states such as pregnancy, endometriosis, and menstruation (15). Diagnostic accuracy of raised CA-125 in postmenopausal women is improved by absence of many of these nonmalignant conditions (Table 5.3).

Table 5.3 CA-125 Elevations in Benign Disorders and Ovarian Cancer

		Cut-off
Healthy women	Premenopausal ^a	35 kU/L
	Postmenopausal ^b	20 kU/L
Disease	Condition	CA-125 elevations over 35 kU/L (%)
Benign ovarian disease	Overall (all benign tumours) ^c	29%
	Ovarian cysts ^c	14%
	Germ cell tumours (mature teratoma) ^c	21%
	Sex cord stromal tumours (thecoma, fibrothecoma) ^c	52%
	Cystadenoma, adenofibroma, cystadenofibroma ^c	20%
	Serous epithelial tumours ^c	20%
	Mucinous epithelial tumours ^c	18%
	Benign, NOS ^c	27%
	Benign, other (normal ovaries) ^c	22%
Benign disorders of the female genital tract	Abscess/hydrosalpinx/POD ^c	37%
	Fibroid (leiomyomas) ^c	26%
	Acute salpingitis ^d	40.4%
	Chronic salpingitis ^d	8.3%
	Pelvic inflammatory disease ^e	29.4%
	Endometriosis/endometrioma ^c	67%
	Endometriosis (Stage I) ^d	8.0%
	Endometriosis (Stage II) ^d	19.6%
	Endometriosis (Stage I/II combined) ^d	11.5%
	Endometriosis (Stage III) ^d	44.7%
	Endometriosis (Stage IV) ^d	86.7%
	Endometriosis (Stage III/IV combined) ^d	50.4%
	Endometriosis (overall) ^d	24.3%
Other disorders ^d	Cirrhosis ^d	67.1%
	Cirrhosis + ascites ^d	100.0%
	Acute pancreatitis ^d	32.2%
	Chronic active hepatitis ^d	9.1%
	Chronic pancreatitis ^d	1.9%
	Renal failure ^d	14.6%
	Heart failure ^f	14.7%
	Diabetes ^d	0.0%
Ovarian cancer ^d	<i>According to histology</i>	
	Serous	80.0%
	Mucinous	69.0%
	Endometrioid	75.0%
	Clear cell	78.0%
	Undifferentiated	88.0%

(Continued)

Table 5.3 CA-125 Elevations in Benign Disorders and Ovarian Cancer (Continued)

	Cut-off
Ovarian cancer ^d	
According to FIGO Stage	
Stage I	50.0%
Stage II	90.0%
Stage III	92.1%
Stage IV	93.9%
All stages	85.1%
According to tumor diameter	
Microscopic	21%
<1 cm	38%
<2 cm	46%
>1 cm	79%
>2 cm	70%
>10 cm	100%

^aBast RC Jr, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med* 1983;309(15):883–887.

^bBon GG, et al. Serum tumor marker immunoassays in gynecologic oncology: establishment of reference values. *Am J Obstet Gynecol* 1996;174(1 Pt 1):107–114.

^cMoore et al. Comparison of HE4 and CA125 levels in benign gynaecological disease. *Am J Obstet Gynecol* 2012.

^dJacobs I, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. *Human Reprod* 1989;4(1):1–12.

^eMuyldermans M, Cornillie FJ, Koninckx PR. CA125 and endometriosis. *Human Reprod Update* 1995;1(2):173–187.

^fMiralles C, et al. Cancer antigen 125 associated with multiple benign and malignant pathologies. *Ann Surg Oncol* 2003;10(2):150–154.

Screening

Screening is the identification of unrecognized disease in apparently asymptomatic population by use of tests, examinations, or other procedures that allow earlier diagnosis of the disease than if it had presented clinically. The main goal of cancer screening is to reduce mortality from the disease by either preventing it (if a premalignant condition exists) or diagnosing it earlier when treatment is more effective. Just detection of the cancer of interest before it is symptomatic cannot justify screening.

There are cancer-specific criteria detailing which cancers could most benefit from screening which build on the WHO criteria for all diseases (Table 5.5) (18). To be effective and applicable to the population at large, screening needs to achieve high sensitivity/specificity, PPV, and negative predictive value (NPV) (Table 5.6), and be acceptable to the populations to be tested. The PPV depends on the prevalence of the disease within the population, with more false positives detected if disease prevalence is low. Well-organized national screening programs, such as for cervical screening, are required to realize the true potential of screening in reducing disease-specific mortality.

In a national screening program, issues that have to be considered include frequency of screening, age of the population to be screened, well-defined mechanisms for referral and treatment of screen-detected abnormalities, comprehensive information systems that not only send invitations at predefined intervals but also recall those with abnormalities for assessment and schedule follow-up of those treated, and quality assurance protocols to monitor and evaluate the efficacy of the screening program. Furthermore, for a screening strategy to be successful, uptake and compliance with screening has to be high.

Table 5.4 CA-125 Elevations in Nonovarian Malignancies

Cancer	CA-125 elevations over 35 k U/L (%)
Nongynecologic malignancies	
Breast ^a	17.6%
Colorectal ^a	15.1%
Pancreas ^a	52.6%
Lung ^a	29.5%
Gastric ^a	30.9%
Biliary tract ^a	45.8%
Liver ^a	49.0%
Oesophageal ^a	10.5%
Nonovarian gynecologic malignancies	
Endometrial cancer ^{b,c}	21%
Endometrial cancer ^d	25%
Stage III	55%
Stage IV	86%
Cervical cancer ^e	30%

^aJacobs I, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. *Human Reprod* 1989;4(1):1–12.

^bGinath S, et al. Tissue and serum CA125 expression in endometrial cancer.

Int J Gynecol Cancer 2002;12(4): 372–375.

^cDuk JM, et al. CA 125: a useful marker in endometrial carcinoma. *Am J Obstet Gynecol* 1986;155(5):1097–1102.

^dBonfrer JM, et al. Clinical evaluation of the Byk LIA-mat CA125 II assay: discussion of a reference value. *Clin Chem* 1997;43(3):491–497.

^eGupta D, et al. Performance of serum CA125 as a prognostic biomarker in patients with uterine papillary serous carcinoma. *Int J Gynecol Ca* 2011;21(3):529–534.

The first cancer screening program to be implemented was for cervical cancer in 1940. However, its impact on mortality has only been evident since the introduction of organized screening programs. Breast cancer screening began in the 1960s

Table 5.5 World Health Organization Criteria for a Screening Program

1. The condition sought should be an important health problem
2. There should be accepted treatment for patients with recognized disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognizable latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10. Case finding should be a continuing process and not a “once and for all” project

Source: From Wilson J, Jungner G. WHO principles and practice of screening for disease. Geneva: World Health Organization, 1968:66–67 (5).

Table 5.6 Parameters Crucial when Evaluating Screening Tests**1. Test validity**

Accuracy/Validity of the screening test is evaluated by sensitivity and specificity of the screening test. Sensitivity is the correct identification of the individuals with disease out of all with positive screening results, whereas specificity is the proportion of people with negative screening test who do not have the disease

2. Measuring test performance

Easier to measure in research setting than in a screening program. The proportion of the population with detectable preclinical disease is an important factor judging the effectiveness of a screening strategy. An ideal test would detect the disease early; those that can only detect advanced disease indicate a long screening interval or poor sensitivity of the test

3. Positive Predictive Value (PPV)

Proportion of individuals with a positive screening test that will have the disease. A PPV of 10% means that only one out of ten individuals investigated had the disease, the other nine were investigated unnecessarily

4. Negative Predictive Value (NPV)

Proportion of individuals with a negative test result who are correctly diagnosed as not having the disease. In clinical setting, high NPV means that the test only rarely misclassifies a sick person as being healthy

5. Test sensitivity versus program sensitivity

Test sensitivity (screening test applied once) can be different from program sensitivity (screening test applied multiple times to the same population). Program sensitivity is higher in cases where population adherence to screening is high, because if the cancer was missed in the first round of screening, it is very likely it would be picked up on the second round. However, if adherence with screening is poor, there will be cancers that will be missed and diagnosed only when symptomatic

6. Validity

RCTs are the gold standard for evaluating effectiveness of a screening strategy but need a large number of participants and take a long time to complete (at least 15 years). Case-control studies have been used to evaluate screening tests but suffer due to potential selection bias

7. Lead time bias

Screening advances the time of diagnosis, therefore the duration of time between when a cancer is detected by screening and when it would have been detected due to symptoms is referred to as lead-time. However, if there is no effect on survival, i.e., the cancer is diagnosed through screening, but the individual dies at the same time as if detected by symptoms, it would falsely appear that the survival is longer in the screened population when it is not. This is called lead-time bias

8. Length-bias sampling

Screening tends to pick up less aggressive, slow-growing cancers and less likely to pick up more aggressive, faster-growing cancers. Length-time bias refers to the greater likelihood of screen-detected cancers to be slow-growing—this would give the false impression of improved survival of screen detected cancers

9. Overdiagnosis

Screening can result in overdiagnosis, detection of the cancer that would not have been detected during that person's lifetime if it were not for screening. These lesions are not easy to distinguish from those that become clinically significant. There may be serious consequences for these patients. However, overdiagnosis probably contributes a small percentage of harm compared to the benefits of screening

10. Selection bias

Individuals who participate in screening programs are usually more health conscious, healthier, more aware of signs and symptoms of the disease, have better access to treatment, and are more likely to adhere to treatment. Hence, they might have better outcomes if they develop cancer than the unscreened population. Selection bias is higher in clinical trials than in screening programmes that are associated with high uptake

when mammography became available. The initial study of 62,000 women aged between 40 to 64 years lasted over 25 years and provided the first experimental evidence of the efficacy of the breast cancer screening strategy (19). In the 1970s, lung cancer screening trials using chest radiograph and sputum cytology were initiated, followed by the first colorectal cancer screening trial in 1975. Trials of prostate and ovarian cancer screening started in the 1990s (20).

Screening can also contribute to primary prevention, as in colorectal cancer screening, where removal of adenomas substantially reduces the incidence of colorectal cancer. However, there are downsides to screening too. Breast cancer screening has had a lot of criticism in recent years as it picks up less aggressive forms of the disease, ductal carcinoma *in situ* (DCIS) that would have otherwise gone unnoticed during an individual's lifetime. Compliance with colorectal cancer screening is an issue probably due to the nature of the test. Prostate screening has been hampered by low sensitivity of the PSA test when used alone.

Screening for ovarian cancer continues to be investigated in the research setting with CA-125 the only tumor marker currently being explored in large trials. When it is interpreted using a cut-off, 2.9% of healthy postmenopausal women will have elevated CA-125 levels, limiting its use as a stand-alone test (21). In the multimodal screening strategy, this is overcome by use of transvaginal ultrasound (TVS) as a second-line test in women with elevated CA-125 levels so that high specificity (99.9%) and four or less operations for each OC detected can be achieved (22,23). Ovarian morphology has been used to refine algorithms for interpreting TVS in postmenopausal women with elevated CA-125 (24,25). Over the last decade, CA-125 interpretation in the context of screening has been further improved by a more sophisticated approach incorporating age, menopausal status, and the rate of change of CA-125 values over time (26–28). This statistical algorithm (Risk of Ovarian Cancer, ROC), based on the age-specific risk of the disease and the behavior of CA-125 with time in women with ovarian cancer versus normal controls, has improved both the sensitivity and specificity of CA-125

interpretation (28). Prospective evaluation of the ROC algorithm in a randomized controlled trial (RCT) of 13,582 postmenopausal women aged over 50 demonstrated high specificity (99.8%; 95% CI, 99.7–99.9) and PPV (19%; 95% CI, 4.1–45.6) for primary invasive EOC (26). Algorithms, such as the ROC, rely on modeling the behavior of a biomarker from disease onset to clinical presentation and use data that may take years to accumulate.

Four large trials on OC screening (OCS) have reported in the past decade. The Kentucky Screening Study (29), a single-arm annual ultrasound screening study of 25,327 women, reported a sensitivity for primary epithelial ovarian cancer of 81% with 9.3 operations carried out per case detected. For primary invasive OC, sensitivity decreased to 76.3%. Encouragingly, the majority of the primary ovarian cancers (82%) were early stage (I/II). Recently, the study reported that at a mean follow-up of 5.8 years, the women in the trial (primary invasive OCs, screen positives and interval cancers) had a longer 5-year survival ($74.8\% \pm 6.6\%$) compared to the women from the same institution treated by the same surgical and chemotherapeutic protocols that were not screened ($53.7\% \pm 2.3\%$) ($p < 0.001$). Moreover, 70% of the screen-detected OCs were at early stage (I/II) (30), but this was not a RCT and there may be a range of factors responsible for the apparent impact of screening.

The Japanese Shizuoka Cohort Study of Ovarian Cancer Screening (31) was an RCT of 82,487 low-risk postmenopausal women who were screened using an annual ultrasound and CA-125 using a cut-off. Sensitivity of 77.1% and specificity of 99.9% was reported for this trial with OC detection rates of 0.31 per 1000 women at prevalent screen and 0.38–0.74 per 1000 women at subsequent screens. Proportion of stage I OC was higher in the screened group (63%) than in the control group (38%) but did not reach statistical significance (31). The effect on mortality has not yet been reported.

The U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial enrolled 78,237 women aged 55 to 74 years, with 34,202 women randomized to OCS. Women were screened using serum CA-125, using a cut-off of 35 kU/L, and transvaginal ultrasonography for 3 years followed by CA-125 alone for a further 2 years. Evaluation and management of positive screening tests was at the discretion of participants' clinicians. Women were followed up for a median of 12.4 years (25th to 75th centile, 10.9–13.0) (32). During the prevalence screen in 28,816 women, 29 ovarian, tubal, and peritoneal cancers were detected, of which 20 were invasive, and nine were borderline. A total of 4.7% women had an abnormal scan and 1.4% an abnormal CA-125. The PPV for invasive cancer was 3.7% for abnormal CA-125, 1% for abnormal transvaginal scanning and 23.5% if both tests were abnormal (33). The results of the first 4 rounds of screening in 34,261 postmenopausal women reported 89 invasive ovarian/peritoneal cancers, of which 60 were screen detected. Only 28% of screen-detected cases were stage I/II. The overall ratio of surgeries per screen-detected cancers was 19.5:1, having decreased over the years from 34% in the first year of screening to 15% to 20% in subsequent years (34).

In The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), 202,638 postmenopausal women aged between 50 and 74 years were randomized to either control or annual screening with ultrasound or a multimodal strategy in a 2:1:1 fashion (35,36) (www.ukctocs.org.uk) (Fig. 5.1). In the multimodal group, CA-125 is interpreted using the ROC algorithm (that takes into account the absolute value of CA-125 and serial levels over time) to triage the women into low, intermediate, and elevated risk. Those at intermediate risk have a repeat CA-125 in 12 weeks, whereas those with elevated risk are referred for a transvaginal scan and repeat CA-125 in 6 weeks. In addition to assessing the effect of ovarian cancer on mortality, the trial will also address acceptability, compliance, costs, performance characteristics of the 2 screening strategies, and the physical and psychological morbidity of screening. The prevalence screen suggests that multimodal strategy has superior sensitivity (89.4%) and specificity (99.8%) to ultrasound screening alone (sensitivity 84.9%; specificity 98.2%) for primary ovarian cancer.

For primary invasive ovarian cancers, the sensitivity of multimodal screening remained at 89%, whereas that of the ultrasound-based strategy decreased to 75.0% (36). Results are expected in 2015.

Currently, there is lack of evidence whether screen-detected cancers include a significantly high proportion of high-grade serous carcinomas in early stage or only those subtypes that confer better prognosis.

Although it has been shown that screening can detect ovarian cancer early (31) and provide a survival benefit in the screened group, only two randomized trials have so far reported on the impact of OCS on survival or mortality. The first one, involving 22,000 women carried out in the 1980s, which used sequential CA-125 and Transvaginal scanning (TVS), reported improved survival of 72.9 months in the screened versus 41.8 months in the control group (22). Recently, the PLCO trial (32) reported no mortality benefit with OCS with 118 and 100 deaths in the screening and control arm, respectively (mortality rate ratio of 1.18 (95% CI, 0.91–1.54) (Fig. 5.2). These data did not demonstrate a mortality benefit from simultaneous screening with CA-125 (using an absolute cut-off) and TVS scanning. Moreover, excess morbidity of carrying out surgery in women with false-positive results was 5.1% (32). However, the mortality data from PLCO needs to be interpreted with caution as concerns have been raised about the trial design, as 40.6% of women were diagnosed after screening ended, CA-125 was interpreted using an absolute cut-off (rather than a time series algorithm), and management of screen positives was at the discretion of the treating clinician (rather than via a well-defined protocol) (37). UKCTOCS, the largest OCS trial (38), will report in 2015, and should address some of these issues. On the basis of current evidence, women from the general population should only be screened in the context of research trials.

Women who have a strong family history of ovarian cancer constitute only 5% to 10% of women with ovarian cancer. These women (from families with multiple first-degree relatives affected by breast and ovarian cancer, or Lynch syndrome) have a greater than 10% lifetime risk of developing ovarian cancer, and are considered to be high-risk. Most of this risk is attributable to mutations in the *BRCA1*, *BRCA2*, and *MMR* genes with cumulative risks by the age of 70 years for ovarian cancer of 40% (35% to 46%) in *BRCA1*-mutation carriers, 18% (13% to 23%) in *BRCA2* mutation carriers (39), and 10% to 12% in women with mutations in the *MMR* genes (40). These women often seek screening, but the current recommendation is that they should consider risk-reducing bilateral salpingo-oophorectomy once they have completed their families.

There are a number of studies evaluating OC screening in the familial context (41,42). There is some evidence that a strategy based on annual screening is not effective in detecting early stage disease in this population. An approach based on 3 to 4 monthly screening is currently being evaluated in the UK Familial Ovarian Cancer Screening Study (UKFOCSS, prospective screening study based on annual TVS and CA-125 interpreted using the ROC algorithm, with over 5700 women) (43) and trials are under way under the auspices of the Cancer Genetics Network and Gynecological Oncology Group (44). Both trials are using the ROC algorithm with a screening interval of 3 to 4 months. One of the trials in the high-risk group has reported so far; the U.S.-based Cancer Genetics Network (CGN) (45) used the ROC algorithm to screen 2,343 high-risk women at 3 monthly intervals. Thirty-eight women underwent surgery following 6,284 screens; 5 ovarian cancers were detected, of which 2 were prevalent (1 early, 1 late stage) and 3 were incident (all early) cases resulting in a PPV of 13%. Three further occult cancers were detected at risk-reducing salpingo-oophorectomy and 1 woman developed an interval (late stage) cancer (46). The results of the UK trial are anticipated in 2013.

There are some recent developments with immediate implications for OC screening. These include novel insights into tumor biology, as reflected in the proposed classification of OCs into

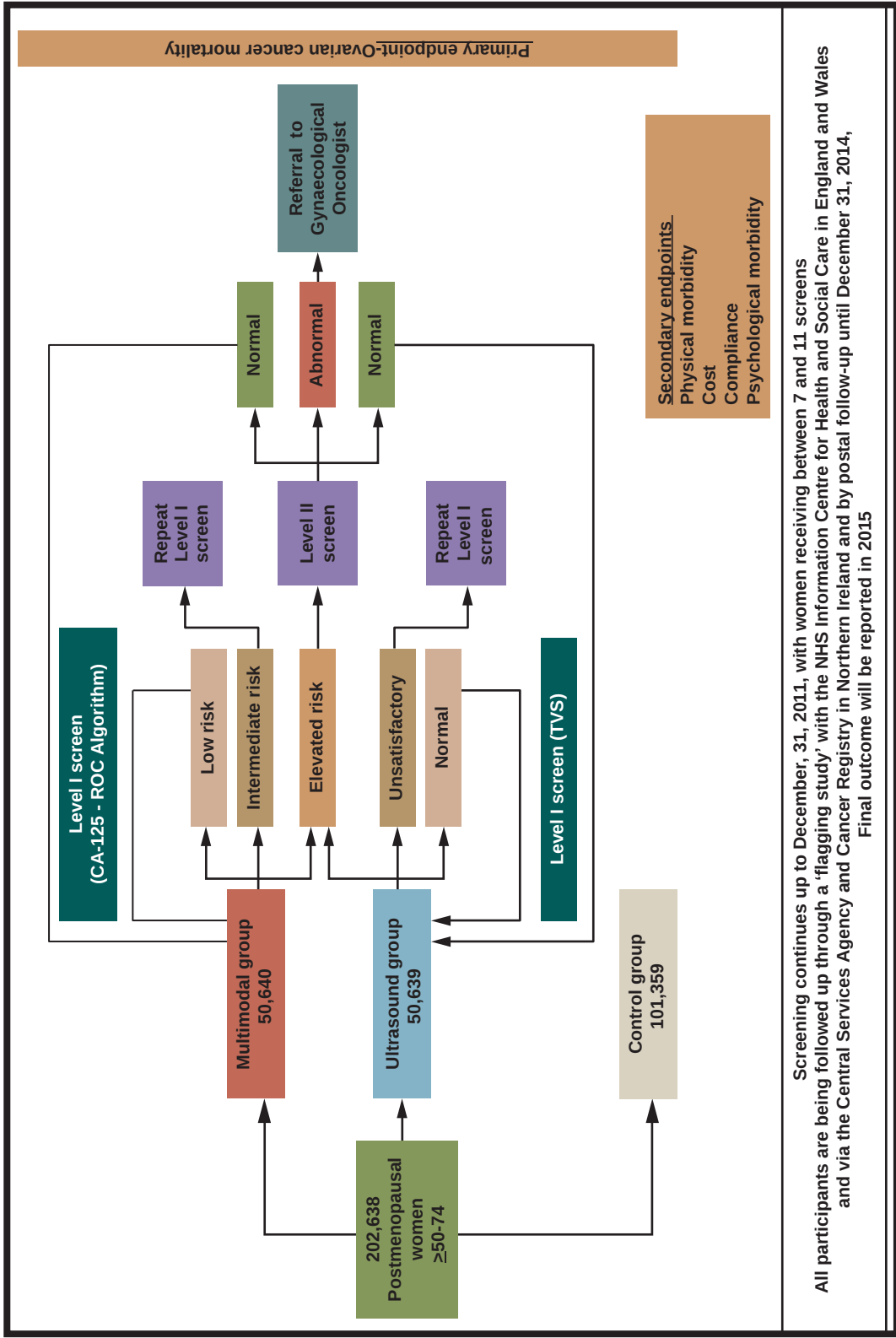


FIGURE 5.1. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Women in the trial, based on the risk of ovarian cancer (ROC) value, are stratified into **low risk** (ROC: $<1 / 3,500$), and returned to annual screening with the next blood test in one year; **intermediate risk** ($<1 / 1,000$ and $<1 / 3,500$) with a repeat CA-125 in 12 weeks; and **elevated risk** ($>1 / 1,000$) with Level II screen (CA-125 and TVS) scheduled in 6-8 weeks, with earlier screens arranged where there was a high index of suspicion. Those with persistent abnormalities on Level II screen are referred to a gynecologic oncologist. The screening protocol has been described in detail elsewhere. Roc, risk of ovarian cancer; TVS, transvaginal ultrasound.

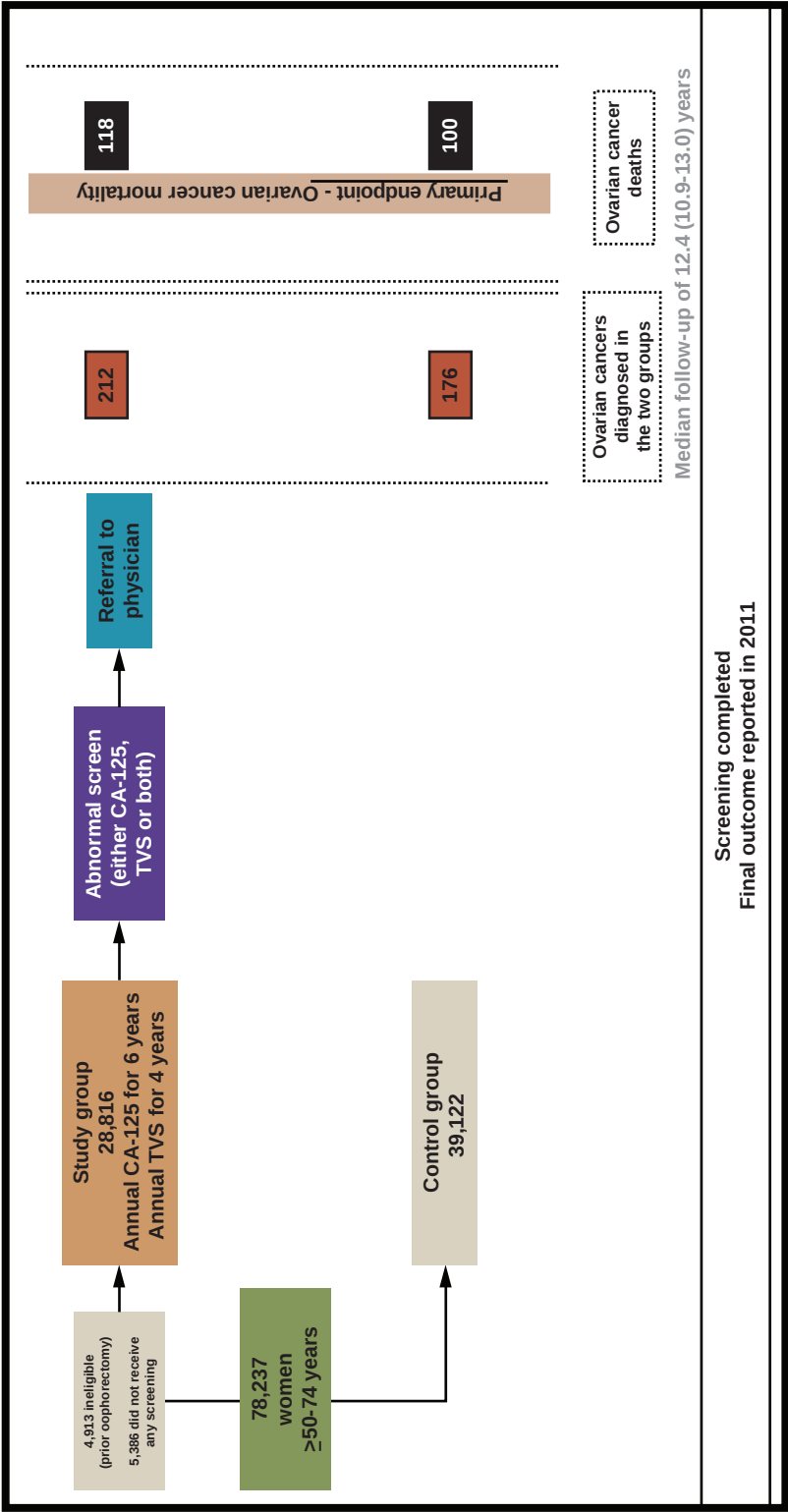


FIGURE 5.2. Prostate Lung Colorectal and Ovarian (PLCO) Cancer Screening Trial. Women in the trial underwent 4 annual screens with CA-125 (interpreted using a cut-off of 35 kU/L) and TVS and 2 further screens with CA-125 alone. If an abnormality was detected on screening, the women underwent referral to their physician. Final outcome (OC mortality) was reported in 2011. TVS, transvaginal ultrasound.

Type I, slow growing cancers with good prognosis such as low-grade serous, low-grade endometrioid, clear cell, mucinous, and transitional (Brenner) carcinomas, and more aggressive Type II, which include high-grade serous, high-grade endometrioid, undifferentiated tumors and carcinosarcomas (47). Screening strategies including biomarker discovery and refining of ultrasound indices need to take into account both types with a focus on detection of type II cancers, which account for over 80% of OC mortality. To date, the goal of screening was limited to detection of early-stage disease (48,49) but the work of Crum et al. supports a model of “fimbrial-ovarian” serous neoplasia, with a proportion of serous OCs starting as premalignant serous tubal intraepithelial cancer (STIC) lesions in the distal fallopian tube and spreading to the ovary (50). This raises the possibility of primary prevention in the future.

In a 1980s biobank study, CA-125 was found to be raised in 59 out of 236 (25%) stored serum samples collected from women with ovarian cancer 5 years before diagnosis (13). Data from a Japanese OCS study indicate that, in serous-type ovarian cancer, first elevation of CA-125 to diagnosis has a shorter interval compared with those with nonserous-type disease (1.4 vs. 3.8 years; $p = 0.011$). Although 47% of nonserous-type ovarian cancers developed from slightly elevated CA-125 levels between 35 and 65 kU/L, 75% of serous ovarian cancers developed suddenly from a normal CA-125 level (<35 kU/L) (51). A model of natural history of OC developed by Brown and Palmer suggests that on average, it takes over 4 years for *in situ*, stage I or stage II cancers to become clinically apparent, and approximately 1 year for stage III/IV cancers (52). Serous cancers are less than 1 cm in diameter during the occult period. The model suggests that for a screening strategy to be able to detect 50% of the cancers before they progress to stage III, an annual screen would have to detect tumors 1.3 cm in diameter (53). Unpublished data from UKCTOCS suggest that detecting such small high-grade serous cancers may be feasible using the ROC algorithm.

Recently, using samples from 112 OC patients and 706 controls from PLCO, Urban et al. demonstrated that Human Epididymis protein 4 (HE4) had higher sensitivity of confirming Type II cancers (40% vs 20%) than Type I cancers (18.8% vs 56.2%) compared to TVS. HE4 had higher sensitivity (35.7%) than TVS (28.6%) as a first-line test. The sensitivity of HE4 was improved by using TVS as a second-line test. Combination of HE4 and CA-125 (32.1%) had a better sensitivity than TVS alone (20.2%). However, the authors stress that diagnosing HE4-associated tumors is not necessarily better than diagnosing TVS-associated tumors in terms of outcome (54).

Whether a raised CA-125 in asymptomatic postmenopausal women is a predictor of nongynecologic cancer is not yet clear. Data from the RCT of 22,000 postmenopausal women (22) reported that elevated serum CA-125 was not a predictor of a nongynecologic malignancy on mean follow-up of 2,269 days (55). However, it was associated with significantly increased risk of death from all causes in the next 5 years (56). In contrast, data from the Norwegian OCS trial of 5,500 women showed that breast and lung cancer were overrepresented among women with elevated CA-125 (57). Both trials indicate that elevated CA-125 is a risk factor for death from malignant disease. These data indicate that steps should be taken to rule out other malignancies such as breast, lung, and pancreas in asymptomatic postmenopausal women with rising CA-125 levels with no evidence of gynecologic malignancy.

One of the limitations of CA-125 is that 15% to 20% of ovarian cancers do not express the antigen. This may partly be caused by CA-125 forming circulating immune antibodies containing complexes bound to the free antigen (58). Rosen et al. (59) explored 10 potential serum markers that could complement CA-125 in 65 ovarian cancers with weak or absent CA-125 tissue expression. All specimen lacking CA-125 expressed human kallikrein 10 (HK10), human kallikrein 6 (HK6), osteopontin, and claudin 3. A small proportion of CA-125 negative ovarian cancers expressed DF3 (95%),

vascular endothelial growth factor (VEGF) (81%), MUC1 (62%), mesothelin (MES) (34%), HE4 (32%), and CA-19-9 (29%). MES and HE4 showed the greatest specificity when reactivity with normal tissues was considered. Differential expression was also found for HK10, osteopontin, DF3, and MUC1 (59). Several of these markers are currently being assessed in nested case control studies using serum samples from ovarian cancer screening trials.

The screening trials in the general population have focused on postmenopausal women as around 90% of ovarian cancers are sporadic and occur in women from the general population over the age of 50. A number of risk factors affect ovarian cancer risk in the general population, such as oral contraceptive use, parity, and hysterectomy, which can be used to determine an individual's risk. Recent efforts have focused on identification of low- and moderate-penetrance genes that predispose women to ovarian cancer (60–63). It is therefore very likely that population-screening strategies in the future will use a risk-stratification tool that combines these factors.

Additional Markers

In the past few years, major efforts have been made to identify either a better marker or a panel of markers that would improve the performance of CA-125 in the context of screening. However, most of the studies used clinical samples (rather than preclinical samples), so their findings are more relevant to differential diagnosis of benign from malignant masses, avoiding unnecessary operations in women with benign lesions and ensuring that surgery, where there is high suspicion of ovarian cancer, is undertaken by trained gynecologic oncologists in tertiary-care centers (64–66). Using a CA-125 cut-off of 35 kU/L combined with imaging has been shown to achieve a sensitivity of 94% and specificity of 90% for differential diagnosis of ovarian cancer from benign disease (67). The performance of various other markers to detect ovarian cancer has been evaluated: Interleukin-6 (IL-6), Interleukin-7 (IL-7), soluble Interleukin-2 receptor (sIL-2R), Tumor Necrosis Factor (TNF), Soluble receptors of TNF (sTNF-R), Macrophage Colony-Stimulating Factor (M-CSF), CA-15-3, CA-72-4 or TAG-72, CA-19-9, OVX1, CASA/OSA, Growth factors, Tetranectin, Tumor-Associated Trypsin Inhibitor (TATI), GAT (Galactosyltransferase associated with tumor), LASA (lipid-associated sialic acid), VEGF (vascular endothelial growth factor), IAP (immunosuppressive acid protein), Lyso-phosphatidic Acid (LPA), Prostatin, Cadherin, Shed glycans, Dipeptase 1; however, despite a plethora of studies, none been shown to be useful in clinical practice. Limited sensitivities and specificities constrain their use in screening.

The only promising marker in the last decade has been serum human epididymis protein 4 (HE4). Preclinical samples from asymptomatic women from the PLCO trial were used to assess the performance of 49 ovarian cancer biomarkers using the ProBE design (68) of a prospective-specimen collection, with retrospective-blinded evaluation study design (69). The performance of “standard” tumor markers, such as CA-125, HE4, CA-72.4, and CA-15.3, in prediagnostic samples drawn within 6 months of cancer diagnosis was comparable to that in clinical samples. Performance was poorer for markers such as prolactin, transthyretin, or apolipoprotein A1, which may reflect the individual response to the cancer, in prediagnostic specimens. Serum CA-125 remained the single best biomarker for ovarian cancer, with sensitivity of 86% (95% CI, 0.76–0.97) in cases where blood was drawn within 6 months of diagnosis, with the second best marker being HE4, with sensitivity of 73% (95% CI, 0.60–0.86). For all markers, sensitivity declined in specimens more remote than 6 months from diagnosis. However, the limitation of this study was that CA-125 was used in “real time” for triaging women for diagnostic work up for ovarian cancer (70). A recent study by Anderson et al. (71) using specimens from the

Carotene and Retinol Efficacy Trial showed that a panel including CA-125, HE4, mesothelin may provide signal for ovarian cancer 3 years before diagnosis; this is consistent with data from the UK screening trials.

Another recent study using a nested case-control design in laboratory-blinded samples obtained before cancer diagnosis and matched controls from the (PLCO) Cancer Screening Trial demonstrated that none of the 5 predictive models, each containing 6 to 8 biomarkers, nor a model derived from all of the 28 markers evaluated, showed improvement over CA-125 alone (72). There are 2 possibilities why studies have failed to show improvement over CA-125; either the current technologies are unable to identify biomarkers with greater or complementary potential for screening, or the available technologies, powerful as they are, have not yet been applied appropriately either in discovery or in validation, with one of the main obstacles being use of clinical as opposed to prediagnostic/preclinical samples (69).

A limited number of studies have investigated the utility of proteomic markers in preclinical diagnosis of ovarian cancer. The most recent study of preclinical samples from 118 OC cases and 951 age-matched controls from the PLCO trial collected less than 12 months before cancer diagnosis showed that although CA-125 was elevated in 61.5% of the 65 OC cases that had CA-125 data available, a combination of CA-125 and apolipoprotein A1, truncated transthyretin, transferrin, hepcidin, β_2 microglobulin, connective tissue activating protein III, and interalpha-trypsin inhibitor heavy-chain 4 did not improve sensitivity of using CA-125 alone (73).

To ascertain the optimal biomarker panel to distinguish early-stage OC from healthy women, Yurgovetsky et al. had used multiple xMAP bead-based immunoassays using 96 serum biomarkers and applied it to samples from 139 patients with early-stage ovarian cancer, 149 patients with late-stage ovarian cancer, and 1,102 healthy women. The highest sensitivity (86%) and specificity (98%) was achieved using a 4-marker panel consisting of CA-125, HE4, CEA, and VCAM-1. In an independent blinded validation set (44 patients with early-stage ovarian cancer, 124 patients with late-stage ovarian cancer, and 929 healthy women), sensitivity for early stage (I/II) disease remained at 86% but increased to 95% for late stage disease (III/IV) while maintaining high specificity (98%) (74). This panel justifies evaluation in a screening context.

Although limited progress has been made in identifying new biomarkers, it is likely that novel algorithms that incorporate serial change over time of some of these markers alongside CA-125 may significantly improve screening performance.

Differential Diagnosis of an Adnexal Mass

The factors that influence whether a tumor marker is incorporated into clinical practice are outlined in Table 5.7. Serum CA-125 is of value in differential diagnosis of benign and malignant adnexal masses, especially in postmenopausal women. Using an upper limit of 35 U/mL, sensitivity of 78%, specificity of 95%, and PPV of 82% were achieved for malignant disease in women with palpable adnexal masses (75). This has since been confirmed by numerous studies (76–78). Further improvements in specificity were achieved by using a panel of markers (CA-125 II, CA-72-4, CA-15-3, and LASA) and an artificial neural network approach to differentiate malignant from benign pelvic masses (79).

The Risk of Malignancy Index (RMI) has been the most valuable clinical tool used in the past two decades. It combines serum CA-125 values with ultrasound findings and menopausal status. The initial study demonstrated a sensitivity of 85% and a specificity of 97%. Patients with an elevated RMI score had on average a 42-fold increase in the background risk of ovarian cancer (80).

Table 5.7 Criteria for Incorporating Tumor Marker into Clinical Practice

1. The intended use of the tumor marker must be clearly outlined
 2. The difference between ‘positive’ and ‘negative’ populations must be sufficient to guide change in clinical management
 3. The estimate of difference must be reliable and validated
- Assay must be technically stable, reproducible and accurate
- Clinical study must have been suitably designed and have a sufficient power to address the utility of intended use
- Statistically analysis must be rigorous

Source: Hayes D.F. (2011). Biomarkers. In V.T. DeVita Jr, T.S. Lawrence, S.A. Rosenberg, R.A. DePinho, R.A. Weinberg (Eds), *Cancer: Principles and Practice of Oncology*. (pp. 694–701). Wolters Kluwer Health; Lippincott, Williams & Wilkins.

Since then, the RMI has been validated extensively. A systematic review of 109 eligible studies assessing accuracy of models for predicting malignancy in ovarian masses showed that while all models had acceptable sensitivity and specificity, RMI was the best predictor. Using 200 as the cut-off, the pooled estimate for sensitivity for preoperative assessment of an adnexal mass was 78% for a specificity of 87% (81). Varying the RMI cut-off (25 to 1,000) in combination with specialist ultrasound (US), magnetic resonance imaging (MRI), and radioimmunoscintigraphy (RS) provided a sensitivity of 94% and a specificity of 90%, therefore suggesting this approach rather than using an RMI cut-off value of 250 alone to improve correct referral of cancer patients to a cancer center (67).

RMI over 200 has recently been evaluated in a Danish study of 1,159 women with pelvic mass referred to a tertiary center for further preoperative investigations, showing that using this cut-off, a sensitivity and specificity for ovarian cancer versus benign pelvic mass of 92% and 82%, respectively, and PPV and NPV of 62% and 97% could be achieved therefore indicating that RMI ≥ 200 is a reliable tool in OC diagnosis (82). RMI has also been investigated in an Asian population, in a retrospective study of 209 women undergoing surgery for adnexal mass. Using a cut-off of 200, RMI 1 gave sensitivity of 70.6%, specificity of 83.9%, PPV of 75%, and NPV of 80.6%, while RMI 2 improved sensitivity to 80% with a specificity of 78.2%, PPV of 71.6%, and NPV of 85.1%, thus favoring RMI 2 as the index better suited at predicting malignancy (83). In differential diagnosis of borderline tumors from benign adnexal masses, RMI IV (based on preoperative serum CA-125 and CA-19-9 levels, ultrasound findings and menopausal status) cut-off of 200, the Receiver Operator Characteristic area under the curves for serum CA-125, CA-19-9, ultrasound score, RMI IV(CA-125), and RMI IV(CA-19-9) were 0.580, 0.625, 0.548, 0.694, 0.734, and 0.711, respectively (84).

RMI when combined with subjective ultrasound was shown to be superior to a combination of CA-125 and HE4 and menopausal status (in the risk of ovarian malignancy assay, ROMA), in a single-center prospective cohort study of 432 women with a pelvic mass who were scheduled to have surgery (85).

Despite lower accuracy in borderline, stage I invasive, and nonepithelial ovarian cancers, the RMI is a simple, easily applicable method in the primary evaluation of patients with adnexal masses which identifies ovarian cancers more accurately than any other criterion used in diagnosis of this disease (86).

Prognosis

Preoperative serum CA-125 levels are related to tumor stage, tumor volume, and histologic grade of OC. Although initial studies did not find preoperative CA-125 to be an independent prognostic factor (87–89), it may be of value in localized/early-stage

disease (90). In a study of 118 patients with FIGO stage I epithelial OC, compared to those with stage I and preoperative serum CA-125 levels <65 U/mL, stage I patients with preoperative serum CA-125 ≥ 65 U/mL had a significantly longer survival (91). This finding has been confirmed in a study of 600 patients from gynecologic cancer centers in Australia, USA, and Europe with stage I epithelial ovarian cancer. On multivariate analysis, preoperative serum CA-125 greater than 30 U/mL and age greater than 70 years at diagnosis were the only independent predictors for overall survival (OS). Levels of CA-125 of ≤ 30 U/mL (over histologic cell type, sub-stage and grade) were able to identify a subgroup of FIGO stage I patients with a genuinely good prognosis and survival who could possibly be spared from adjuvant chemotherapy (92). Additional parameters such as cyclooxygenase-2 overexpression in combination with preoperative CA-125 level of under 30 U/mL have been recently found to be independent predictors of survival in univariate and multivariate analyses (93). However, CA-125 does not appear to be an independent prognostic factor in advanced ovarian cancer (90).

Postoperative CA-125 levels have been found to be significant prognostic factors (87). Patients with a low CA-125 prognostic score composed of two CA-125 values, one taken preoperatively and the other taken 1 month after surgery, have significantly better prognosis than patients with high scores (94). In the immediate postoperative period, CA-125 levels can be elevated as a result of the abdominal surgery and irritation of the peritoneal cavity; therefore, measurements are best postponed for at least 4 weeks (95).

During primary chemotherapy, serum CA-125 half-life is an independent prognostic factor in patients with advanced epithelial ovarian cancer, both for complete remission and survival (96–98). The most commonly used cut-off is a CA-125 half-life of 20 days (98–100). In patients with CA-125-positive tumors, other useful prognostic indicators of survival are the serum CA-125 levels prior to third course of chemotherapy (96,101,102) and the slope of the CA-125 exponential regression curve. In patients treated on maintenance chemotherapy and achieving a clinically defined complete response to primary chemotherapy with a baseline CA-125 level of ≤ 35 U/mL, the baseline CA-125 level before initiation of maintenance chemotherapy strongly predicts the risk of subsequent relapse. Patients with pre-maintenance baseline CA-125 values ≤ 10 U/mL have a superior progression free survival compared to those with higher levels even if in the normal CA-125 range (103).

Serum CA-125 continues to be of prognostic significance when ovarian cancer recurs, with patients with normal serum CA-125 levels (≤ 35 U/mL) at relapse having a better prognosis than patients with elevated levels (104).

Apart from CA-125, other markers have been evaluated as those with prognostic value. More recently, soluble MUC1 and serum MUC1-specific antibodies have been shown to be prognostic for poor clinical response and reduced OS in both platinum-resistant as well as platinum-refractory OC treated with interleukin 2 (IL-2) (105). The mean levels of anti-MUC1 IgG was higher in patients with progressive disease, both at early ($p = 0.025$) and late ($p = 0.052$) time points during the IL-2 treatment.

Another marker, survivin, with levels higher in serous OC than in benign epithelial tumors, could not be used for differential diagnosis of OC from benign masses but could be used as a prognostic marker for OC as its levels were positively correlated with age, advanced stage, and poor disease-free survival (106).

Monitoring Response to Treatment

It is now established that serum CA-125 levels reflect progression or regression of disease in over 90% of ovarian cancer patients with elevated preoperative levels (107) (Fig. 5.1). These findings have resulted in the widespread use of serum CA-125 levels to

monitor the clinical course of ovarian cancer and its response to chemotherapy (108). However, CA-125 should not be used as the sole criterion to determine clinical response (109) as studies involving second-look laparotomy have confirmed that CA-125 values of less than 35 U/mL do not exclude active disease (110). The pattern of CA-125 over time is a more useful parameter than using an arbitrary cut-off level (100,101,111,112). Precise mathematical definitions to evaluate response to treatment have been suggested with 50% response corresponding to a 50% decrease in CA-125 after 2 samples, confirmed by a third sample collected at least 28 days later and a 75% response defined as a serial decrease over 3 samples of greater than 75% (113,114). Prechemotherapy CA-125, its half-life, nadir concentration, and time to nadir have a univariate prognostic value for disease-free and OS in a multicenter French study (115).

Detecting Recurrence

Among patients with elevated CA-125 levels at diagnosis, serial monitoring following initial chemotherapy can lead to the early detection of recurrent disease. Median lead-time prior to clinical progression of 63 to 99 days has been demonstrated between marker detection of disease progression and clinically apparent progressive disease (116,117). The value of marker lead-time depends ultimately on a patient's remaining therapeutic options, and the clinical value of this approach is unclear (118).

In a study of 39 patients with elevated serum CA-125 at time of diagnosis and complete clinical and radiographic response to initial treatment with normalization of serum, Santillan et al. reported that a relative increase in CA-125 of 100% (odds ratio [OR] = 23.7; 95% CI, 2.9–192.5) was significantly predictive of recurrence. From baseline CA-125 nadir levels, an absolute increase in CA-125 of 5 U/mL (OR = 8.4; 95% CI, 2.2–32.6) and 10 U/mL (OR = 71.2; 95% CI, 4.8 to >999.9) were also significantly associated with the likelihood of concurrent disease recurrence. These data suggest that for patients in complete clinical remission, a progressive low-level increase in serum CA-125 levels is strongly predictive of disease recurrence (119).

CA-125 measurements together with thin-section computer tomography (CT) and careful review of the clinical history have been recommended in follow-up of patients with ovarian carcinomas (120). However, a study of 58 patients with recurrent ovarian cancer revealed that 98% of recurrences were identified by physical examination and CA-125, with ultrasound and CT not providing additional clinically relevant information during follow-up (121).

In a population-based study of 331 Dutch EOC patients, van Altena et al. showed a significant association of CA-125 nadir ≤ 5 kU/L with both longer PFS and longer OS (log-rank test $p < 0.01$ and $p = 0.03$, respectively). It was also an independent prognostic variable (HR = 1.51; 95% CI, 1.04–2.31) for PFS next to histologic type, FIGO stage, and residual tumor after surgery (122). However, the MRC OVO5/EORTC55955 trial has shown no value in CA-125 monitoring in the follow-up of ovarian cancer patients. The trial included 1,442 patients with normal CA-125 level following platinum-based therapy. Patients whose levels rose to twice the upper limit of normal (529 women) were randomized to immediate (based on CA-125 levels) or delayed chemotherapy (the latter when signs and symptoms of recurrence were present). The women randomized to monitoring started chemotherapy at a median of 4.8 months earlier than those in the delayed arm but this did not result in difference in survival between the arms (early arm: median 25.7 months, 95% CI 23.0–27.9; delayed arm: median 27.1, 95% CI 22.8–30.9; HR: median 0.98, 95% CI 0.80–1.20; $p = 0.85$). Therefore, Rustin suggests that CA-125 should only be measured if there is a suspicion of relapse or at patient's request (123). The pattern of CA-125 throughout a patient's clinical course of the disease is presented in Figure 5.3.

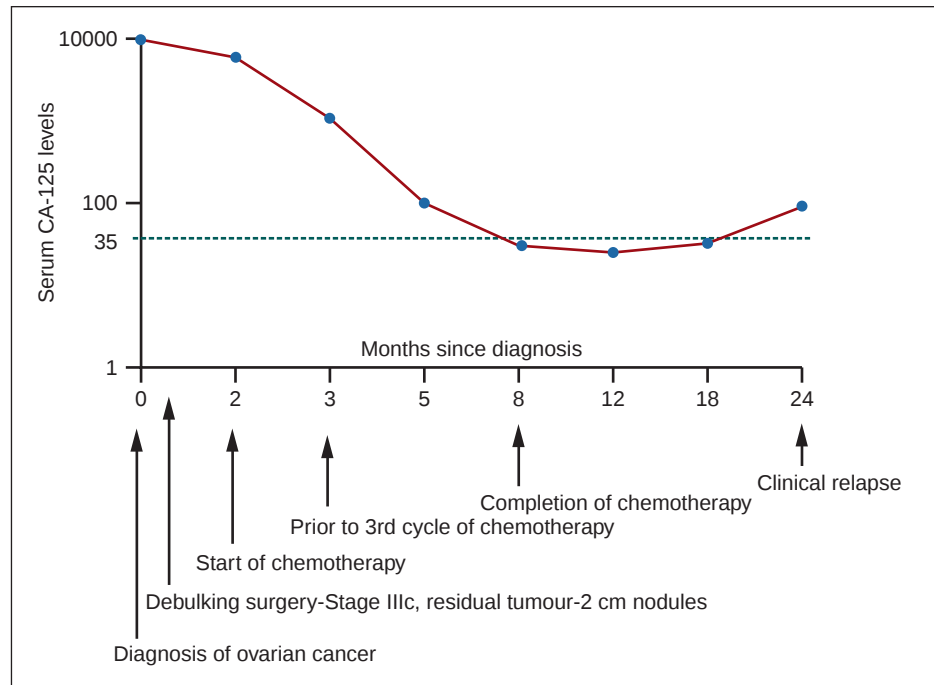


FIGURE 5.3. Correlation between serum CA-125 and clinical course in ovarian cancer.

HE4

Human epididymis protein 4 (HE4) is a glycoprotein in the epithelial cells of the epididymis. In ovarian cancer, increased serum levels and expression of the HE4 WAP four-sulphide core domain 2 (*WFCD2*) gene have been demonstrated (124).

Mean serum HE4 in patients with malignant ovarian lesions (248.7 pM) is much higher than in controls (34.1 pM) or women with benign lesions (39.1 pM) (Table 5.8). HE4 levels are decreased in pregnancy (median levels of 30.5 pmol/L) (125) and levels around 50 and 60 have been demonstrated in pre- and postmenopausal women, respectively (126), which increase with age (median 109.5 pmol/L in women over 80). HE4 levels are lower in many of the benign conditions that usually elevate CA-125 levels (Table 5.9), especially in women with endometriosis.

HE4 can also be elevated in other cancers (Table 5.10). Initial report stated that its specificity is superior to CA-125 (124) and of particular value for early-stage disease (127). Combining CA-125 with HE4 has been found to increase sensitivity while maintaining high specificity (127); but more recently, it has been reported not to be superior to CA-125 in clinical setting (128).

More recently, the superiority of HE4 in differential diagnosis of ovarian cancer as a single marker was reported. Moreover, the diagnostic prediction (AUC 0.864) was improved by Risk of Malignancy (ROMA) index (AUC 0.897) (129). Serum HE4 has

lower sensitivity than CA-125 for early stage disease, but has better sensitivity and specificity in differential diagnosis of benign from malignant pelvic masses, especially in premenopausal patients (124). Although HE4 has recently been shown to improve the performance of CA-125 (129), in a Swedish study of 114 OC, 45 borderline and 215 patients with benign ovarian tumors, Partheen et al. showed that HE4 did not out-perform CA-125 (benign vs. malignant AUC 86.8% for CA-125 and 84.4% for HE4; benign versus Stage I OC 72% for HE4 and 76% for CA-125) (130). Very recently, Schummer et al. demonstrated that in patients who are developing a recurrence, HE4 rises earlier than CA-125 with a lead-time of up to 4.5 months (131). It can also be elevated in patients who do not express CA-125 at sufficient levels to make a clinical decision. MMP7 and Mesothelin are, however, not as useful in predicting recurrence to add to CA-125. However, as HE4 levels fail to normalize at the end of treatment, it is possible that it can be used as a marker predicting poor prognosis.

Recent developments with regard to the HE4 marker include its commercial availability (when combined with CA-125) as a test for preoperative prediction of low/high risk of epithelial OC as well as being approved by the U.S. Food and Drug Administration for monitoring recurrence or progression of epithelial ovarian cancer. For the former, it is included in the Risk of Ovarian Malignancy Algorithm (ROMA), a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA-125 II and menopausal status into a numerical score. In premenopausal women, ROMA value $\geq 13.1\%$ predicts high risk of epithelial OC; ROMA value $\geq 27.7\%$ is deemed to represent high risk of OC in postmenopausal women (132).

When looking at new biomarkers/combination of markers, it is important to establish the normal range in healthy individuals, especially if the marker has been shown to be very promising, such as HE4. The normal range for HE4 has recently been established in serum samples from 1101 healthy women and 67 pregnant women. HE4 concentration increased with advancing age (>40). Median serum HE4 levels in premenopausal women (46.6 pmol/L) were significantly lower than in postmenopausal women (57.6 pmol/L; $p < 0.001$). The upper 95th percentile for HE4 levels was 89 pmol/L for premenopausal women, 128 pmol/L for postmenopausal women, and 115 pmol/L for

Table 5.8 Mean Levels of Serum HE4 in Normal Controls and Benign and Malignant Lesions

Condition	Serum HE4 level (mean)
Normal Control	34.1 pM
Benign Lesions	39.1 pM
Malignant Lesions	248.7 pM

Source: Wang S, et al. The Application of HE4 in Diagnosis of Gynecological Pelvic Malignant Tumor. Clin Oncol Cancer Res. 2009; 6: 72-74.

Table 5.9 Elevations of HE4 and CA-125 in Women with Benign Disease and Ovarian Cancer

		HE4 > 89.1 pM (premenopausal women); HE4 > 128 pM (postmenopausal women)	CA-125 > 35 U/mL
Benign disease ^a	Overall (all benign tumors)	8%	29%
	Ovarian cysts	8%	14%
	Germ cell tumors (mature teratoma)	1%	21%
	Sex cord stromal tumors (thecoma, fibrothecoma)	24%	52%
	Cystadenoma, adenofibroma, cystadenofibroma	20%	20%
	Serous epithelial tumors	8%	20%
	Mucinous epithelial tumors	13%	18%
	Benign, NOS	9%	27%
	Endometriosis/endometrioma	3%	67%
	Abscess/hydrosalpinx/POD	13%	37%
	Fibroid (leiomyomas)	8%	26%
	Benign, other (Normal ovaries)	5%	22%
		HE4 > 140 pmol/L	CA-125 > 35 U/mL
Ovarian cancer ^b	Overall	75.2%	80%
	Stage I–II	58.3%	54.2%
	Stage III	78.8%	86.5%
	Stage IV	79.6%	85.7%
	Serous papillary	84.4%	84.4%
	Mucinous	43.8%	68.8%
	Other histologies	57.9%	68.5%

^aMoore et al. Comparison of HE4 and CA-125 levels in benign gynaecological disease. *Am J Obstet Gynecol* 2012.

^bEscudero JM, et al. Comparison of serum human epididymis protein 4 with cancer antigen 125 as a tumor marker in patients with malignant and nonmalignant diseases. *Clin Chem* 2011;57(11):1534–1544.

all women. In pregnant women, median HE4 concentrations were significantly lower than their premenopausal counterparts ($p < 0.001$) (133). HE4 levels appear to be lower in the Asian population (HE4 of 33.2 pmol/L) (134). This has implication for further clinical application of the test in different populations.

Glycodelin

Glycodelin was first described as a marker with a role in OC in 2001 (135). Since then, limited studies reported evaluating its expression mainly in tissue rather than serum. Tissue expression data suggests that in serous OC, glycodelin expression carries a better prognosis (136). An ELISA-based assay was only introduced in 2005 (137). A panel including HE4, Glycodelin, MMP7, SLPI, Plau-R, MUC1, Inhibin A, PAI-1, and CA-125 evaluated in serum samples from women with OC and healthy controls showed a sensitivity ranging from 59.5% to 80.5% while maintaining high specificity. However, for detecting disease recurrence, a panel consisting of HE4, Glycodelin, MMP7, and CA-125 had a sensitivity of 100% when compared to CA-125 alone (96%) (138). Although this data is promising, further evaluation of glycodelin is required.

DNA Methylation Profile

Circulating methylated DNA may represent a new generation of tumor marker (139), as changes in DNA methylation are one of the most common alterations in human neoplasia (140). Hypermethylation of tumor-derived DNA can be found in serum and

plasma of cancer patients (141,142). Recently, in colorectal cancer the pattern of methylation of serum DNA has been shown to be a prognostic factor (143).

In OC, DNA methylation profiles have been shown to predict active disease (144), predict response to treatment (components of the WNT pathway has shown that methylation of NKD1 and DVL1 were independent predictors of progression free survival, whilst DVL1 and NFATC3 methylation were significantly associated with response to treatment) (145) and OS, as secreted frizzled-related proteins sFRP5 promoter was shown to be significantly methylated in OC and was associated with worse 5-year OS when compared to unmethylated sFRP5 (52% vs. 88%, $p = 0.03$) (146).

Salivary Transcriptomes as Novel Markers

Novel biomarker strategy, using salivary transcriptomes as possible biomarkers for OC, has been recently been evaluated in 11 OC patients and 11 controls. In a validation set of 21 OC patients and 35 healthy controls, combination of 5 biomarkers (AGPAT1, B2M, BASP2, IER3, and ILI1) yielded high sensitivity (85.7%) and specificity (91.4%) (147).

Cell-Free DNA as a Novel Marker

Cell-free DNA has increasingly been investigated as a potential biomarker reflecting the release of both normal and tumor-derived DNA into the circulation through cellular necrosis and apoptosis.

Table 5.10 Elevations of HE4 in Women with Cancers Other Than Ovarian

Cancer Group		HE4 > 140 pmol/L
Non gynecologic malignancies	Breast	5.6%
	Digestive tract malignancy	11.3%
	Small cell lung cancer (SCLC)	26.9%
	Non-small cell lung cancer (NSCLC)	29.3%
	Liver	16.3%
	Melanoma	11.1%
	Urologic malignancies	21.5%
	Hematologic malignancies	10.0%
	Mesenchymal tumours	0.0%
	Nonovarian/endometrial/NSCLC malignancies (without effusion or liver metastases)	6.5%
	Nonovarian/endometrial/NSCLC malignancies (with effusion or liver metastases)	18.5%
Non ovarian gynecologic malignancies	Endometrial cancer	28%
	Cervical cancer	0%

Source: Escudero JM, et al. Comparison of serum human epididymis protein 4 with cancer antigen 125 as a tumor marker in patients with malignant and nonmalignant diseases. *Clin Chem* 2011;57(11):1534–1544.

Preoperative total plasma cell-free DNA levels were assayed in 164 women with invasive epithelial ovarian carcinoma (EOC), 49 with benign ovarian neoplasms, and 75 age-matched controls, divided equally in training and validation set. Elevated levels of cell-free DNA were observed in OC patients, but, more notably, levels of more than 22,000 GE/mL were significantly associated with decreased patient survival ($p < 0.001$). Validation set data indicated a 2.83-fold increased risk of death from disease ($p < 0.001$) (148).

Metabolite Profiling

Metabolites are the end products of cellular regulatory processes. Alterations in their levels can be regarded as response to genetic or environmental changes. Analysis of 66 invasive ovarian carcinomas and 9 borderline ovarian tumors by gas chromatography/time-of-flight mass spectrometry (GC-TOF MS) using a novel contamination-free injector was undertaken to assess if quantitative signatures of primary metabolites can be used to characterize molecular changes in ovarian tumor tissues. A total of 291 metabolites were detected, and 114 were already annotated compounds. Principal component analysis as well as additional supervised predictive models allowed a separation of 88% of the borderline tumors from the carcinomas. The data suggests that metabolomics is a promising high-throughput, automated approach in addition to functional genomics and proteomics for analyses of molecular changes in malignant tumors (149).

MICRORNA-BASED OVARIAN CANCER BIOMARKERS

MicroRNAs (miRNAs) are noncoding RNAs that regulate gene expression by translational inhibition or mRNA degradation.

They are involved in diverse biologic processes including development, proliferation, differentiation, and apoptosis. As they encode around 3% of the genome and up to 30% of human protein coding genes may be regulated by miRNAs, they have become interesting potential biomarkers to study. Their study has also been helped by a microarray approach. In the past 5 years, several miRNA expression profiles have been published, reporting a decrease in expression in OCs compared to normal tissues. Initial studies looked at tissue profiling of ovarian cancers and normal ovaries and showed upregulation (miR-200a, miR-200b, miR-200c, miR-141) or downregulation (miR-199a, miR-140, miR-145 or miR-125b1) of certain miRNAs (150). One advantage of using miRNAs as biomarkers is that they are generally stable and can be detected in serum and plasma. More recently, 8 miRNAs extracted from serum (e.g., miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205 or miR-214) were compared in exosomes isolated from sera of women with benign disease and OC and demonstrated that exosomal microRNA profile in OC patients is distinct from those with benign disease (151). Resnick et al. have shown other miRNAs being up- (miR-21, miR-92, miR-93, miR-126, miR-29a) or downregulated (miR-155, miR-127, miR-99b), but more interestingly demonstrated upregulation of miR-21, miR-92, and miR-93 in 3 cancer patients with normal CA-125 levels (152). Although miRNA signature/profile is not of established value in diagnosis, prognosis, or response to treatment, further understanding of miRNA in OC is warranted.

Carcinoembryonic Antigen

CEA was first identified in 1965 in serum of rabbits immunized with colon carcinoma (153). It is an oncofetal antigen, which is found in small amounts in adult colon. Elevated levels are associated with colon and pancreatic cancer but CEA levels are also raised in benign diseases of the liver, gastrointestinal tract and lung, and in smokers. In ovarian cancer, CEA is expressed by most endometrioid and Brenner tumors and in areas of intestinal differentiation in mucinous tumors. In contrast to CA-125, this marker is not expressed in normal and inflammatory conditions of the adnexa. Around 25% to 50% of ovarian cancer patients have elevated levels of CEA and the correlation with ovarian cancer is not as well established as with the other markers (154,155).

In a small study of 21 patients, CEA, CA-19-9 and red blood cells, hematocrit, and hemoglobin were shown to be of benefit in identifying women with late stage (IB-IV) borderline ovarian tumors (156).

Preoperative CEA and CA-125 serum levels (CA-125/CEA ratio > 25) in a study of 640 patients of whom 355 had OC diagnosis, have shown a sensitivity of 82%. When the CA-125/CEA cut-off was increased to 100, specificity increased to around 85% (157).

In a tissue expression study of 189 women diagnosed with borderline ovarian tumors and 571 women with OC, using 30% as a cut-off level for CEA over-expression indicated that 18% of LMPs and 4% of OCs were positive but mucinous tumors being more likely to be positive than other histologic subtypes ($p < 0.00001$). CEA was shown to be an independent marker of prognostic value as patients with CEA expression over 30% had a shorter disease specific survival (158).

Alpha-Fetoprotein

Alpha-Fetoprotein (AFP) is an oncofetal protein produced by the fetal yolk sac, liver, and upper gastrointestinal tract. Elevated levels of AFP occur in pregnancy and benign liver disease. Serum levels are raised in most patients with liver tumors and in some patients with gastric, pancreatic, colon, and bronchogenic malignancies have elevated AFP levels (154). AFP levels were

investigated in 135 patients with germ cell tumors and elevated levels were found in all patients with endodermal sinus tumors, 62% with immature teratomas and 12% with dysgerminoma (159). AFP also accurately predicts the presence of yolk sac elements in mixed germ-cell tumors (160). Although AFP production in epithelial ovarian cancers is extremely rare, a case of ectopic production of AFP by an ovarian endometrioid tumor has been described in the literature (161).

In women with endodermal sinus tumors, AFP is a reliable marker for monitoring therapeutic response and detecting recurrence (162,163). On univariate analysis, AFP levels of over 1,000 ng/mL, age over 22, and histology were found to be major prognostic factors in 43 patients with ovarian and extragonadal germ-cell tumors (164).

Recently, a sensitive chemiluminescence (CL) imaging immunoassay method for detection of multiple tumor markers with high throughput, easy operation, and low cost was developed. The proof of concept study included 5 markers (alpha-fetoprotein, CA-125, CA-153, and CEA) to screen patients with liver, breast, or ovarian cancers. The method showed very good reproducibility, accuracy, and wide detection range, thus making it an ideal platform to study the performance of the panel in clinical and preclinical sets of samples from OC patients (165).

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is synthesized in pregnancy by the syncytiotrophoblast. It is a glycoprotein hormone made up of 2 dissimilar covalently linked subunits α and β . Production of hCG by the tumor is accompanied by varying degrees of release of the free subunits into circulation. Recent advances in our understanding of hCG/hCG- β synthesis by trophoblastic and nontrophoblastic tissues alongside an improvement in techniques measuring hCG have helped define its role in the clinical practice. hCG is elevated in virtually all cases of gestational trophoblastic disease (hydatidiform mole, invasive mole, and choriocarcinoma) and serves as an ideal tumor marker. There is a close correlation between hCG levels and tumor burden and hCG levels are used in staging and clinical management. Serum hCG can also be detected in patients with nontrophoblastic cancers. Although gynecologic cancers are prominent in this group, the sensitivity of using hCG is lower than for other markers in current use except in germ-cell tumors with a chorionic component (166).

In a retrospective analysis of 113 patients with stage IC to IV malignant ovarian germ cell tumors, both on univariate and multivariate analyses, stage of disease and elevation of serum hCG- β and AFP were significant predictors of OS, whereas age at diagnosis was of no prognostic value (167). It is worth noting that this is the first study to demonstrate stage and tumor markers as prognostic parameters in patients with malignant ovarian germ cell tumors and may help in deciding on therapeutic regimen.

In a series of 424 pediatric patients with a mean age 12.5 years, tumor markers were elevated in 54% of the cases with elevated β -human chorionic gonadotropin (β -hCG), alpha fetoprotein (AFP), and CA-125 being significantly associated with malignancy ($p < 0.02$), but an elevated CEA was not ($p = 0.1880$). However, the best indicators of malignancy in these young patients were complaint of a mass or precocious puberty, a mass exceeding 8 cm or a mass with solid imaging characteristics (168).

In 2012, Lenhard et al. showed that 67% of OC and 26.7% of benign ovarian tumors had hCG-positivity in the serum with significantly higher hCG serum concentrations in patients with OC compared to benign ovarian tumors ($p = 0.000$). Ovarian cancer tissue was positive for hCG expression in 68%. Although the hCG tissue expression differed by grade, it did not by histologic subtype. Increased hCG expression was found in mucinous OCs at Stage II compared to stage I ($p = 0.018$). Although there

was no significant correlation between tissue hCG expression and overall ovarian cancer patient survival, a subgroup analysis revealed an increased 5-year survival in LH-R positive/FSH-R negative and hCG positive tumors (hCG positive 75% vs. hCG negative 50.5%) (169). LH-R has previously been shown to be of prognostic value. This study highlights that both hCG and LH-R may be useful targets in novel cancer therapies.

Muller and Cole have comprehensively reviewed the literature on hCG and its role in cancer. With regard to gynecologic malignancies, they state that the serum free β -subunit or its urinary degradation product β -core fragment is produced by 68% of ovarian, 51% of endometrial and 46% of cervical malignancies. The free β -subunit enhances growth and invasion in all these malignancies and is therefore associated with poor prognosis. However, they stress that in clinical practice, confusion arises when a patient presents with persistent low positive hCG in the absence of pregnancy and absence of obvious malignancies (170). The first aim is to rule out a tumor then consider a false positive test by assaying hCG in the urine. A further possibility in women aged over 35 with oligomenorrhea, amenorrhea or following bilateral salpingo-oophorectomy is pituitary hCG.

Inhibin and Related Peptides

Inhibins and activins are structurally related dimeric proteins first isolated from ovarian follicular fluid on the basis of their ability to modulate pituitary follicle-stimulating-hormone secretion. They are members of a larger group of diverse proteins, the transforming growth factor- β (TGF- β) superfamily, which are involved in cell growth and differentiation. Inhibin is a heterodimeric glycoprotein composed of a common α -subunit and one of two β -subunits, resulting in either inhibin A ($\alpha\beta_A$) and inhibin B ($\alpha\beta_B$), for which specific immunoassays are now available. The serum also contains immunoreactive forms of the α -subunit not attached to the β -subunit, the most abundant of which is pro- α_C and pro- α_N - α_C . The pro- α_C assay measures these precursor forms of inhibin. The original Monash assay detected immunoreactive inhibin that included a range of inhibin-related peptides in addition to biologically active inhibin dimers.

In 1989, Lappohn et al. (171) reported elevated serum immunoreactive inhibin concentration in women with granulosa-cell tumors. Numerous studies have since confirmed serum inhibin elevation in ovarian sex cord/stromal tumors and established its role in differential diagnosis and surveillance of these malignancies (172–174). The major molecular forms detected are bioactive dimeric inhibins A and B (175,176). Antimüllerian hormone, or müllerian inhibitory factor, is another member of the TGF- β superfamily that is being investigated as a marker for granulosa-cell tumor (175,177,178).

In epithelial ovarian cancer, the role of the inhibin peptides remains to be determined. Using the initial nonspecific Monash assay, elevated serum inhibin levels were reported in 25% to 90% of women with epithelial ovarian cancer (179–181). In 2004, an ELISA for total inhibin was developed (182). Tsigkou et al. investigated the sensitivity/specificity of serum total inhibin for epithelial ovarian cancer in 89 postmenopausal women with stage II to III epithelial ovarian cancer and found that patients with serous or mucinous tumors showed the highest total inhibin levels. At 95% specificity, the total inhibin assay detected 93% of serous and 94% of mucinous tumors (183). Mucinous ovarian cancers are most likely to be associated with increased inhibin levels (173,184). In contrast, using specific assays that measure bioactive dimeric inhibin A, elevated serum levels were only found in 5% to 31% of women with epithelial ovarian cancer (173,184,185). Overall, the picture is emerging that dimeric inhibin A and B levels are not informative in epithelial ovarian cancer, and total inhibin/pro- α_C immunoreactive forms are the most commonly elevated

of the inhibin-related peptides (183,185,186). Furthermore, although there is preferential secretion of precursor forms of the α -subunit rather than dimeric inhibin A by epithelial ovarian cancer, pro- α C is unlikely to be a useful marker if used alone (187). Combining pro- α C with CA-125 may improve the sensitivity for detection of epithelial ovarian cancer (185). Combination of total inhibin and CA-125 detected all cases of serous and mucinous tumors and the overall sensitivity for epithelial ovarian cancers was 99% at 95% specificity, respectively. On further follow-up, it became clear that an increase of total inhibin levels was associated with recurrence. This recent data suggest that total inhibin is a sensitive and specific marker of epithelial ovarian cancer in postmenopausal women and may therefore be combined with CA-125 for noninvasive diagnosis of epithelial ovarian cancer. Furthermore, it may also be a useful serum marker to monitor disease-free intervals (183). The elevation of inhibin in patients with ovarian malignancies is presented in Table 5.11.

In conclusion, the data suggest that functional inhibin is secreted by most ovarian granulosa-cell tumors and may be superior to estradiol in assessing therapeutic response and predicting recurrence. For epithelial ovarian cancer, dimeric inhibin A and B levels are probably not informative. While the role of total inhibin/pro- α C needs further investigation, most recent data suggests that total inhibin displays high sensitivity and specificity for serous and mucinous cancer, which is improved when total inhibin is combined with CA-125. More recently, a combination of inhibin and antimüllerian hormone has shown to be useful in diagnosis and follow-up of granulosa cell tumors (188).

Activin is a dimer of the two- β -subunits of inhibin and exists as activin A ($\beta A\beta A$), activin B ($\beta B\beta B$), and activin AB ($\beta A\beta B$). Serum activin A has been shown to be significantly elevated in epithelial ovarian cancer (175,189,190), with highest levels detected in undifferentiated tumors. High concentrations of activin A in peritoneal fluid of women with serous ovarian carcinoma has been shown to be useful in distinguishing serous ovarian cancer from cystadenoma (191). Preliminary data suggest a poor correlation of activin levels and the clinical course of the disease (175). It is possible that activin A could play a role in ovarian cancer but further investigation is needed. This may be possible with the recent introduction in 2009 of a reliable and specific ELISA for activin B (192).

Kallikreins

The human kallikrein gene family currently consists of 15 members. There is accumulating evidence that in addition to prostate-specific antigen (PSA, hK3) and human glandular kallikrein (hK2) (both prostate cancer biomarkers), many other members of the human kallikrein gene family are differentially regulated in

breast, ovarian, and testicular cancers. Recently it has been shown that the malignant phenotype of ovarian cancer cells can be enhanced by over expression of the human tissue kallikrein genes 4, 5, 6, and 7 (193). Potential biomarkers for ovarian cancer include kallikreins 5, 6, 7, 8, 10, 11, and 14 (194–197). Kallikrein 4 is upregulated in epithelial ovarian carcinoma cells in effusions (196) and kallikrein expression may have some value in differentiating ascites resulting from ovarian cancer from other malignant and nonmalignant causes (198). Human kallikrein 8 seems to be an independent marker of favorable prognosis in ovarian cancer (199), while kallikrein 7, although not an independent prognosticator for ovarian cancer, has been found to be associated with unfavorable characteristics of the disease (200). Kallikrein-related peptidase, KLK5, was found to be significantly elevated in the serum and ascitic fluid (41/41) of OC patients (42/52) with increased levels associated with poor patient outcome (201).

Osteopontin

Osteopontin is a biomarker that has been identified using gene-expression profiling techniques. The initial investigation showed osteopontin tissue expression to be weak or absent in 93% of ovarian adenocarcinomas compared to positive expression in 81.5% in borderline tumors and 50% in omental and lymph node implants. Its expression did not correlate with histologic type, grade, or clinical stage (202). In 2002, Kim et al. showed an increased expression of this marker in ovarian cancer cell lines, microdissected tissues, and plasma of epithelial ovarian cancer patients (203). Preoperative plasma osteopontin and CA-125 levels were investigated in patients with ovarian cancer, benign ovarian tumor, other gynecologic cancers and in healthy women and showed significantly higher levels in patients with ovarian cancer than the other groups. Higher plasma osteopontin levels were detected in late stage ovarian cancer patients (stage IV) and ovarian cancer patients with ascites with no correlation with histologic type. Sensitivity of preoperative plasma osteopontin in detecting ovarian cancer was 81.3%, which increased to 93.8% when combined with CA-125, suggesting that preoperative osteopontin may be a useful biomarker for differential diagnosis of ovarian cancer, particularly when combined with CA-125 (59,204). Osteopontin levels have been shown to correlate with presence of ascites, bulky disease, and recurrence (205). In predicting clinical response to therapy, osteopontin is inferior to CA-125. However, levels increase earlier in 90% of patients developing recurrent disease leading the authors to suggest that it may be useful as a complementary marker in detecting recurrent ovarian cancer (206). Recently, a study by Matsuura et al. showed that statins can inhibit OC proliferation by up to 50%, and the effect is mediated by changes in osteopontin gene expression. Simvastatin-treated

Table 5.11 Elevations in Inhibin or CA-125 Levels in Women with Ovarian Cancer

	Cancer Group	Elevations in Inhibin ^a Levels (%)	CA-125 > 35 kU/L (%)	Inhibin + CA-125 (%)
Malignant ovarian tumors	Serous	18	94	97
	Mucinous	84	71	94
	Endometrioid	54	91	90
	Other ovarian cancers	33–44	78–100	89–100
	Granulosa cell tumor	100	30	100
	All ovarian cancers	50	82	95

^aTotal inhibin.

Source: Robertson DM, Pruyers E, Jobling T. Inhibin as a diagnostic marker for ovarian cancer. *Cancer Lett* 2007;249(1):14–17.

mice survived significantly longer compared to the controls. This is an important new area that needs further exploration in OC, as a possible new drug therapy (207).

Mesothelin

Mesothelin is a marker that was initially identified in mesotheliomas and ovarian cancers in 1996 (208). Serum levels are higher in ovarian cancer patients when compared to women with benign ovarian tumors or from the normal population. The levels increase significantly from early to advanced stages. Elevated mesothelin levels before therapy are associated with poor OS both in patients with optimal debulking surgery and in those with advanced disease (209). As mentioned previously, Schummer et al. in addition to CA-125 and HE4 examined MMP7 and Mesothelin but found that the latter two are not as useful in predicting recurrence to add to CA-125 when compared to HE4 (131). Although it is possible that mesothelin may prove to be a useful tumor marker in the future, both for differential diagnosis of epithelial ovarian cancer as well as for prognosis, there is currently little data to highlight its significance.

Cytokines

Cytokines are soluble mediator substances produced by cells that exercise a specific effect on other target cells. Their importance in tumor biology has increased since the demonstration that many cytokines are produced by cancer cells and can influence the malignant process in a positive and a negative manner (190). However, cytokines do not fulfill the classic criteria for tumor markers, as they may be elevated in a number of pathologic conditions, are invariably produced by nonmalignant surrounding tissue rather than the tumor itself and are not specific for one cell type. Despite this, their measurement in malignant conditions may provide valuable clinical information regarding prognosis and response to treatment.

Details of some of the cytokines and their role as tumor markers in ovarian malignancy are discussed shortly below. The majority are at an early stage of evaluation with conflicting reports associated with some. The most studied cytokine in the context of ovarian cancer is serum M-CSF (or CSF-1). It appears to be a marker with high specificity for ovarian malignancy with elevation being related to stage (210,211). When combined with other markers, it may have a role in ovarian cancer screening (210,212). Combination of CA-125II, CA 72-4, and M-CSF significantly increased sensitivity for detecting early-stage disease compared to CA-125II alone (70%, versus 45%) while maintaining 98% specificity (213). M-CSF may be highly sensitive and specific for malignant germ-cell tumors of the ovary, especially dysgerminoma (214). It has been shown that elevated serum levels are associated with poor outcome after adjusting for stage, grade, and degree of surgical clearance (88). In patients with advanced disease, low ascitic fluid M-CSF was associated with longer OS and was a better indicator in comparison to other prognostic factors except for zero residual disease (215). Serum M-CSF does not seem to be useful in follow-up of women with advanced disease (216).

Interleukins have also been studied in ovarian cancer. Preliminary reports demonstrated IL-6 elevation in 50% of ovarian cancer (217,218). However, combination of IL-6 and CA-125 did not improve the sensitivity of CA-125 alone (218). A further report investigating the role of CA-125, IL-6, IL-7, and IL-10 in 187 ovarian cancer patients, 45 patients with benign ovarian tumors, and 50 healthy controls found that a combination of IL-7 and CA-125 could accurately predict 69% of the ovarian cancer patients, without falsely classifying patients with benign pelvic mass (219).

Cytokeratins

Cytokeratins are intermediate filaments that are part of the cytoskeleton of all epithelial cells. They are specific markers of epithelial differentiation and continue to be expressed by epithelial cells following malignant transformation. Fragments of cytokeratins, in contrast to cytokeratins themselves, are soluble in serum and can be detected and measured using monoclonal antibodies. Their role as tumor markers in various malignancies is currently being investigated.

Tissue Polypeptide-Specific Antigen

Tissue polypeptide-specific antigen (TPS) is a proliferation marker closely related to the tumor marker TPA. It is recognized by a monoclonal antibody raised against the M3 epitope on cytokeratin 18. TPS is elevated in 50% to 77% of ovarian cancers studied, with a specificity of 84% to 85% (220–223). Preoperatively, serum levels of TPS and CA-125 were significantly higher in patients with cancer rather than benign disease and in those with advanced disease compared to early-stage disease. Similarly, levels of TPS and CA-125 were higher in malignant and benign tumor cysts and ascitic fluids than in corresponding sera with levels in cyst fluid from cancer patients being the highest (224). However, no correlation between TPS levels and survival has been shown (221). Its serial measurement may be of value in the follow-up of patients (220,221). When combined with CA-125, sensitivity for predicting recurrence of 81% was achieved with a specificity of 82% and PPV of 58% (222,223).

CYFRA 21-1

CYFRA 21-1 is a fragment of cytokeratin 19. The assay was first developed in 1993 by Stieber et al. (225). It was initially found to be elevated in cervical and endometrial cancers (226). It does not seem to be very useful in the differential diagnosis of adnexal masses, with most studies reporting sensitivities of 40% to 45% (227,228). It may have a role as a prognostic factor, but there are conflicting reports. Elevated CYFRA 21-1 levels prior to therapy were reported to be associated with poor overall and disease-free survival in ovarian cancer (228). Preoperative levels of CYFRA 21-1 were, however, higher in patients with advanced disease, but Cox regression analysis failed to detect a significant association between preoperative CYFRA 21-1 values and survival. For patients with advanced ovarian cancer, preoperative CYFRA 21-1 levels appear to be predictive of response to chemotherapy but not of survival (229). In a case report, elevated levels of CYFRA 21-1 together with neuron-specific enolase, oestradiol, and CA-125 were described in a patient with Sertoli-Leydig cell tumor of the ovary and it was suggested that it may be useful to investigate further the role of these tumor markers in individualized monitoring (230). In a study looking at a variety of other cancers, CYFRA 21-1 was found to be elevated in 19.6% of OC patients (231). There have been no further studies looking at the utility of CYFRA 21-1 measurements in OC.

Proteomics

Proteomics is the study of the expression, structure, and function of all proteins as a function of state, time, age, and environment (232–234). It complements the genomics-based approaches and has become very popular in the past decade. Surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF) analysis and matrix-associated laser desorption/ionization time-of-flight (MALDI-TOF) technologies have been employed over the past few years to identify patterns or changes in protein profile between those with and without cancer. There were numerous issues with

the study design (195,235–237) of the first OC case-control study undertaken (238). Since then a multi-center case control study has identified 3 potential serum OC biomarkers (lower levels of apolipoprotein A1, a truncated form of transthyretin, and elevated levels of a cleavage fragment of inter- α -trypsin inhibitor heavy chain H4 [ITIH4]) (239) which have been independently validated (240). More recently, various algorithms have been developed to analyze the preprocessed mass-spectrometry data and identify the most informative “common” peaks, sample handling has been fine-tuned to deliver the most promising markers (240), novel indices have been proposed (241) and the reproducibility of SELDI-derived spectra has been shown to be reasonably good as long as the data is properly processed (242). A proteomics study using preclinical as opposed to clinical samples, has shown CTAPIII and putative platelet factor 4 (PF4) to discriminate cases from controls up to 15 and 11 months, respectively, before diagnosis, but more importantly earlier than CA-125 alone (243). The technology still holds promise and is likely to deliver insightful biomarker data in the next 5 years.

Combination with Other Markers

In mucinous ovarian cancer, TATI, CA-19-9, CA 72-4, and CEA in addition to CA-125 may be of use (244). Combining CA-125 with CA 72-4, CA-15-3, and M-CSF can increase preoperative sensitivity for early-stage disease (213). The majority of studies however report limited ability to improve diagnostic sensitivity by addition of other serum markers for patients with nonmucinous tumors (112,245–248). CASA may be useful in the follow-up of patients with advanced disease in the clinic when CA-125 is inconclusive or negative (249). In CA-125-negative ovarian cancers, an immunohistochemistry profile of human kallikrein 10, human kallikrein 6, osteopontin, and claudin 3 with a smaller proportion expressing DF3 (95%), vascular endothelial growth factor (VEGF) (81%), MUC1 (62%), mesothelin (MES) (34%), HE4 (32%), and CA-19-9 (29%) may be useful but important to note that MES and HE4 exhibited greatest specificity (59). Further investigation of these markers in serum is underway.

In a study of 92 OC patients, 40 with benign disease, and 99 healthy individuals, the sensitivity of CA-125 was shown to be improved from 68% to 88% by addition of apolipoprotein A1, truncated transthyretin, and connective tissue activating protein III (250).

Combination of CA-125 and RECAF, the alpha-fetoprotein receptor, was evaluated in normal individuals and those with early (I/II) and late (III/IV) stage OC. RECAF was better at discriminating cancer and healthy individuals when compared to CA-125, especially in early stage disease (AUC = 0.96 and 0.805, respectively), with its sensitivity being high for all stages combined (251).

Other Serum Markers

Other serum markers have been assessed in isolation or as part of biomarker panels in women with OC, both in the context of screening and differential diagnosis, as well as in assessing prognosis, monitoring response to treatment and detecting recurrence. Table 5.12 details their current role in ovarian cancer. It is important to note that in women with ovarian cancer, no single marker or combination of markers has emerged with a clear clinical advantage over CA-125, except in specific tumor subtypes such as germ cell tumors with yolk sac and chorionic elements and granulosa cell tumors. The results of the proteomic and genomics studies are therefore eagerly awaited. The consensus is that these new approaches are most likely to identify novel markers or markers panels that in combination with CA-125 will improve biomarker accuracy in ovarian cancer.

ENDOMETRIAL CANCERS

There are no serum markers with an established role in the clinical management of endometrial cancer. Serum CA-125 is elevated in 10% to 31% of patients (252–255), with elevated levels detected in 63% to 67% of patients with advanced stage and 10% to 19% of those with early-stage disease (256). Preoperative assessment of serum CA-125 may be of use in predicting presence of extrauterine and metastatic disease and to a lesser extent myometrial invasion (257). It was suggested that serum CA-125 may be useful in follow-up of patients with early-stage endometrial cancer, but has not been shown to add to clinical examination and imaging (258). While distant metastases may raise CA-125 levels, isolated recurrences in the vagina do not. Levels can be falsely elevated in the presence of severe radiation injury (253). In an analysis of 97 patients with endometrial cancer, elevations of CA-125 and CA-15-3 were significantly associated with poor prognostic clinical factors. On multivariate analysis, CA-15-3 was highly significant and had a higher hazard ratio than CA-125 (255). More recent retrospective analysis of preoperative CA-125 levels in 120 patients with endometrial cancer has shown that elevated CA-125 of more than 40 U/mL was significantly correlated with higher stage, higher grade, increased depth of myometrial invasion, lymph node metastases, and the presence of lymphovascular space involvement. Women with CA-125 of less than 40 U/mL had a significantly improved 5-year OS and recurrence-free survival (RFS) rates ($p < 0.001$). The OS and RFS were highest for those with CA-125 less than 40 U/mL and without lymph node metastases, and lowest for those with lymph node metastases and CA-125 more than 40 U/mL ($p < 0.001$), suggesting that a preoperative evaluation of CA-125 may be advisable in endometrial cancer patients (259). Serial levels of CA-125 are useful in predicting recurrence in patients with high CA-125 levels at diagnosis (260).

In the 1990s, the role of a number of serum markers were explored in endometrial cancer- CYFRA 21-1 (226), urinary β -core or UGF levels (261,262), SCC and CA-15-3 (263), CA-19-9 (259), amino-terminal propeptide of type III procollagen (264), Placental protein 4 (265), CA-72-4 (266), OVX1 antigen (267), soluble interleukin-2 receptor (268), and M-CSF (252,269). However, none proved to be very useful and this is confirmed by the lack of further publications.

Higher levels of serum and plasma human kallikrein 6 in women with uterine serous papillary endometrial cancer compared to those with endometrioid carcinoma and controls without cancer (270); increased expression of inhibin β B in Grade 3 compared to Grade 2 endometrial cancer (271) and an association of matrix metalloproteinase 2 (MMP-2) expression with CA-125 and clinical course in endometrial carcinoma have been demonstrated. Positive expression of the MMP-2 and MMP-9 proteins was found in 88% and 70% of the primary endometrial cancers with positive MMP-2 immunostaining associated with a shortened recurrence-free and cancer-specific survival. MMP-2 negativity seemed linked to favorable prognosis. Preoperative serum levels of CA-125 were higher in the patients presenting with tumors positive for MMP-2 than in those with negative immunostaining (272). However, the value of such observations still remains to be determined.

More recently, a molecular biomarker study of tissue removed at curettage from Stage I and II endometrioid endometrial cancer demonstrated that combined tissue expression of survivin, p53 and p21 had a better prognostic value than classical prognostic factors (273). OC biomarkers apolipoprotein A1, prealbumin, and transferrin have been evaluated in endometrioid and serous papillary endometrial cancer and have shown a sensitivity of 71% and specificity of 88% for normal versus early stage endometrial cancer, which improved to 82% sensitivity and 86%

Table 5.12 Status of Current Tumor Markers in Ovarian Cancer

Screening		Differential Diagnosis of an Adnexal Mass		Prognostic Indicator	Monitoring Response to Therapy	Monitoring Disease and Recurrence
Epithelial cancers	Clinical practice		CA-125 is the main marker—when combined with menopausal status and ultrasound features in the risk of malignancy index (RMI), a sensitivity of 71%–85% and specificity of 96%–97% is achieved. CEA	CA-125 levels after surgery and during chemotherapy are independent prognostic indicators. Various criteria are used based on CA-125 half-life.	Serial CA-125 levels reflect clinical course in 90% of positive tumors and are used routinely for monitoring patients. HE4	CA-125 detects recurrence with a sensitivity of 84%–94% and a false-positive rate of <2%. Median lead-time compared with clinical diagnosis of recurrence is 60–99 days. HE4
	Research	Serum CA-125 being assessed in screening trials in the general (UKCTOCS) and high-risk (UKFOCSS) and trials by GOG and CGN in the USA populations. Results from PLCO reported in 2012, results from the other trials expected in 2013/14. Main emphasis on algorithms to interpret serial CA-125 and transvaginal ultrasound as a second-line test.	Inhibin pro- α C/total inhibin, kallikreins, mesothelin, prostasin, osteopontin, M-CSF, TPS, proteomic markers (profile, transthyretin, apolipoprotein A)	Kallikrein 8, mesothelin, CYFRA 21-1, M-CSF, TATI, VEGF, CASA, tetranectin HE4	CASA	Osteopontin, TPS CASA
Germ-cell tumors	Clinical practice		CA-15-3, CA-72-4, CA-19-9, TATI, GAT, free serum DNA methylation, free glycans, IL-7, TNF α receptors HE4 microRNAs metabolite profiling			
	Research		Serum AFP in tumors with endodermal sinus/yoik sac elements, serum β -hCG in tumors with chorionic elements M-CSF especially in dysgerminomas			
Sex cord stromal tumors	Clinical practice		Inhibin in granulosa-cell tumors		Inhibin in granulosa-cell tumors	

specificity when the normal endometrium samples were compared to late-stage disease (274).

Cathepsin-B and serum amyloid A have been proposed as useful markers for endometrial cancer. While increased Cathepsin-B expression was found to be predictive of more aggressive tumor behavior over time and can be regarded as an unfavorable and independent tumor marker for endometrial cancer patients with a long follow-up (275), serum amyloid A may be useful in monitoring disease recurrence and response to therapy (280).

MicroRNAs have emerged as novel cancer biomarkers and/or potential novel therapeutic targets. Their expression has been associated with tumorigenesis and tumor progression. Endometrial cancer has recently been shown to have a distinct miRNA profile with certain miRNAs demonstrating a sensitivity of 92%. In advanced disease, an miRNA pattern distinct from early-stage disease was seen, and an overexpression of miR-199c predicted improved cancer survival in this population (277). In endometrial tumors, expression of miR-26a, let-7g, miR-21, miR-181b, miR-200c, miR-192, miR-215, miR-200c, and miR-205 was evaluated and levels of miR-200c ($p < 0.0001$) and miR-205 ($p < 0.0001$) were shown to be significantly increased in endometrial tumors compared to normal tissues. The prognostic value of miRNAs was shown by a poor overall survival (hazard ratio, 0.377; Logrank test, $p = 0.028$) in patients with high levels of miR-205 expression (278). Although these findings look promising, further work on miRNA profile in serum of endometrial cancers cases is warranted.

A number of biomarkers associated with adiposity have been investigated in endometrial cancer, androgens and estrogens, insulin, glucose, IGF-1, SHBG, adiponectin, leptin, prolactin, and TSH (279).

HE4 has also been shown to be elevated in endometrial cancer. HE4, included as one of a panel of biomarkers, may be of use in risk stratification in endometrial cancer at an early stage in patients at high risk (280). In a study of 75 patients surgically treated for endometrial cancer, Kalogera et al. showed that preoperative serum HE4 levels (cut-off 8mfi) was much better at detecting advanced-stage disease than CA-125. Median HE4 was significantly elevated in both types I and II endometrial cancer compared to controls ($p < 0.001$ and $p = 0.019$, respectively). Elevated levels of HE4 were observed in type I endometrial cancer with deep myometrial invasion ($>50\%$, $p < 0.001$) and primary tumor diameter of greater than 2 cm ($p = 0.002$); however, the median HE4 was lower in lower-risk patients (type I, MI $\leq 50\%$ and PTD ≤ 2 cm) ($p < 0.01$). This new data can be of value in preoperative prediction of high-risk disease and therefore guide the need for definitive surgical staging (281).

Recent 5 years have seen a promise in identification of novel biomarkers for endometrial cancer for risk stratification and early detection. With the rising obesity across the world combined with prolonged life expectancy, it is very likely that endometrial cancer incidence will increase within the next decade. It is therefore of importance to find novel biomarkers and the novel approaches/markers shown above may demonstrate a clinical utility for risk stratification/early detection.

CERVICAL CANCERS

Screening for cervical cancer is one of the most prevalent and successful public health measures for prevention of cancer. The screening strategy is based on exfoliative cytology, liquid-based cytology, and high-risk HPV DNA detection in cervical specimens. Currently no serologic markers have been identified to be sensitive or specific enough for screening purposes. However, a variety of serum markers have been investigated in assessing prognosis, monitoring response to treatment, and detecting recurrence.

Squamous-Cell Carcinoma Antigen

In 1977, Kato and Torigoe (282) isolated the tumor antigen TA-4 from a cervical squamous-cell carcinoma (SCC). SCC is one of 14 subfractions of tumor antigen TA-4. Elevated levels of SCC are found in 57% to 70% of women with primary squamous-cell carcinoma of the cervix (283–285). The release of SCC into the circulation is independent of local tissue content, as high antigen concentrations are found in the cytosol of normal cervical squamous epithelia, but in these cases serum levels are always in the normal range (286). The antigen is not specific for cervical squamous-cell carcinoma with elevated levels found in other squamous-cell carcinomas of the head and neck, esophagus, and lung and in adenocarcinoma of the uterus, ovary, and lung. SCC levels can also be raised in skin diseases such as psoriasis and eczema (287). SCC is probably a marker of cellular differentiation of squamous cells, as the incidence of elevated serum levels is higher in women with well-differentiated (78%) and moderately differentiated carcinoma (67%) that in those with poorly differentiated tumors (38%) (286). Its levels before treatment correlate with stage, tumor volume, lymph node status, and blood vessel invasion (288–292).

In the past, there has been conflicting reports on the prognostic significance of pretreatment SCC levels (284,288,289,293–295), but increasingly it seems that a combination of pre- and posttreatment values maybe useful both for predicting prognosis and for estimating clinical response in women especially those undergoing neoadjuvant chemotherapy (295–298). On multivariate analysis of 352 patients with stage IIB-IVA squamous cell carcinoma of the cervix managed with both external irradiation and high-dose rate intracavitary brachytherapy, pretreatment SCC antigen level and lymph node metastases were found to have a significant independent effect on absolute survival and disease-free survival (299). Elevated posttreatment serum SCC levels have been shown to be indicators of treatment failure (294,298,300) and associated with poor survival rates (295). Nonetheless, the evidence is preliminary and whether pretreatment SCC level is really useful in clinical practice remains uncertain. It might be useful for individualizing treatment but no randomized trials have yet been conducted to confirm this hypothesis. There is no evidence that more aggressive treatment improves pelvic control and survival in patients with elevated SCC levels (301).

In serum SCC-positive patients, serial measurements correlate with clinical course of the disease (302,303). Raised SCC levels were found in 50% to 71% of patients with recurrent carcinoma, with a lead-time ranging from 0 to 12 months (283,304). This suggests it may be useful for monitoring disease after primary treatment. However, there is as yet no evidence that earlier detection of recurrent disease influences treatment outcome or prognosis after primary treatment.

Preliminary studies suggest that SCC antigen (SCCA) isoforms may provide additional clinical information when compared to total SCCA. Roijer et al. developed and evaluated specific serum immunoassays for the different forms of SCC antigen (free SCCA2, total SCCA2, total SCCA1, and total SCCA). Patients with recurrence or progressive disease had rising levels of SCCA1 and SCCA2, with elevations in SCCA2 being more prominent than that in SCCA1 (305).

In conclusion, SCC may prove useful in the pretreatment identification of squamous cervical cancer patients at high risk of lymph node metastasis, pretreatment prediction of prognosis, monitoring response to treatment and detecting recurrence. However, further studies are needed before clinical recommendations can be made.

CYFRA 21-1

Following detection of elevated levels of CYFRA 21-1 in patients with squamous-cell carcinoma of the lung, various groups started

investigating its role in cervical carcinoma. Tsai et al. detected elevated CYFRA 21-1 levels in 14% of controls, 35% of patients with stage IB-IIA squamous-cell carcinoma of the cervix, and 64% of patients with stage IIB-IV disease (306). Although CYFRA 21-1 was related to tumor stage and size in patients with cervical cancer (307) and there was a positive correlation with SCC, its sensitivity and specificity for detection of squamous-cell carcinoma of the cervix were lower than SCC (306,308,309). In cervical adenocarcinoma, it was elevated in 63% of patients (309). CYFRA 21-1 may have a role in follow-up of women with cervical cancer (310). In the study by Pras et al. (298) elevated CYFRA 21-1 levels after chemoradiation for cervical cancer indicated residual tumor in 70% of patients. Nonetheless, the evidence available so far does not justify the routine measurements of these markers.

CA-125/CEA

Serum CA-125 is only elevated in 13% to 21% of women with squamous-cell carcinoma (302,311). It is a better marker than SCC for cervical adenocarcinoma (302,311,312). In combination with CA-19-9, a sensitivity of 60% for cervical adenocarcinoma was reported with the addition of CEA to this combination increasing sensitivity to 70% (313). Elevated CA-125 levels have been found to contribute to prognosis (314,315), with levels falling in women who respond to chemotherapy (316). In adenosquamous cervical cancer, serum CA-125, SCC, and CEA were found to be elevated in patients with progressive disease, whereas only CA-125 was elevated in women with adenocarcinoma (312). Serum CEA alone is less useful in cervical cancers, with an overall sensitivity of 15% and specificity of 90%. Patients with cervical adenocarcinoma have significantly higher levels of CEA than those with squamous cell cancers (317).

More recently, methylation markers have been evaluated in cervical cancer. A study by Gokul et al. showed that the DNA methyltransferase (DNMT3L) promoter had lost DNA methylation to varying levels in 14 out of 15 cancer cervix samples. This not only shows a promising role of DNMT3L as biomarker in cervical cancer but also provides insight into its possible role in cancer development (318).

In screening context, a number of biomarkers have been evaluated—Ki-67, p16INK4A, BD ProEx C (containing antibodies to the nuclear proteins minichromosome maintenance protein 2 [MCM 2] and topoisomerase II alpha [TOP2A] and Cytoreactiv HPV L1) (319)—which may not only be able to triage mildly abnormal and indeterminate cytology cases but also identify those with high-grade disease. One of the panel, p16(INK4a), is one of the better studied markers that has been shown to be substantially overexpressed in virtually all HPV-transformed cells, thus improving the accuracy of cytology-based cancer early-detection programs (320).

It is anticipated that the introduction of prophylactic HPV vaccines will reduce the incidence of cervical cancer and its malignant precursors, therefore focusing effort on identifying the women most at high risk who would then require treatment, as well as improving the triage of the HPV-positive tests. It is believed that biomarkers will also serve an important role in the optimization of this alternative screening algorithm; therefore, efforts continue to identify the best-suited biomarkers for this purpose.

More recently, circulating cell-free nucleic acids have emerged as a novel class of markers for cancer detection. Circulating Bmi-1 mRNA was put forward as a potential noninvasive molecular

marker for diagnosis and prognosis of cervical cancer. Zhang et al., in plasma samples of 109 patients with cervical cancer, 138 patients with cervical intraepithelial neoplasia (CIN), and 80 healthy volunteers, found a correlation between increased circulating Bmi-1 mRNA level and reduced disease-free survival (DFS) ($p = 0.001$) and OS ($p = 0.015$). Circulating Bmi-1 mRNA was an independent prognostic factor for DFS and OS (321).

DNA methylation markers may be useful in detecting cervical cancer metastasis. Methylation of the protein tyrosine phosphatase receptor type R (PTPRR) promoter has an important role in metastasis and may be a biomarker of invasive cervical cancer (322).

VULVAR AND VAGINAL CANCERS

Tumors of the vulva and the vagina are rare, and there are relatively few studies on circulating markers in these conditions. TPS has been shown to be elevated in 80% of patients with vulvar or vaginal cancer (220), whereas SCC levels were elevated in 43% (323). Carter et al. (324) studied urinary core fragment of the β -subunit of hCG in these cancers. Although the sensitivity of β -core was only 38%, a highly significant difference was observed in the survival curve between those with elevated β -core levels compared to those with normal levels. Ninety percent of patients with elevated levels died within 24 months in contrast to 32% of those with normal levels. It might also be useful in detecting recurrence, as rising UGF levels at an earlier clinic visit predicted recurrence in four of seven patients. These data, albeit limited, suggest that for lower genital tract malignancies, the measurement of urinary β -core may be valuable as prognostic indicator, allowing a more informed approach to treatment and in follow-up.

CONCLUSIONS

The potential role of serum tumor markers is hampered by the fact that these markers are neither confined to the malignant tumor cell nor limited to the malignant phenotype. Of all the markers available in gynecologic malignancies, serum hCG in gestational trophoblastic disease remains closest to the ideal tumor marker. Serum CA-125 continues to be the most useful clinical marker in OC with an established role in diagnosis and monitoring whilst HE4 shows promise as a complementary marker. Progress in understanding the origin of ovarian cancer may lead to identification of more promising markers that would distinguish Type II from Type I OCs, with implications for screening and differential diagnosis, as well as prognosis and monitoring treatment response. The results of the UKCTOCS trial of screening involving CA-125 and ultrasonography are awaited to clarify the role of OC screening.

Novel biomarkers, identified through proteomics and genomics, are undergoing validation studies and along with developments in metabolomics, DNA methylation, and novel transcriptome and microRNA markers may lead to further candidates that can be used either alone or in combination with existing tumor markers.

REFERENCES

- Sturgeon C. Practice guidelines for tumor marker use in the clinic. *Clin Chem.* 2002; 48(8):1151–1159.
- Sturgeon CM, Lai LC, Duffy MJ. Serum tumour markers: how to order and interpret them. *Br Med J.* 2009;339:b3527.
- Cancer Research UK. CancerStats: Ovarian cancer incidence statistics; <http://info.cancerresearchuk.org/cancerstats/types/ovary/incidence>. [Accessed 25 August 2012.]
- Seidman JD, Horkayne-Szakaly I, Haiba M, et al. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. *Int J Gynecol Pathol.* 2004;23(1):41–44.
- Bast RC Jr, Feeney M, Lazarus H, et al. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest.* 1981;68(5):1331–1337.
- Nustad K, Bast RC Jr, Brien TJ, et al. Specificity and affinity of 26 monoclonal antibodies against the CA 125 antigen: first report from the ISOBM TD-1 workshop. International Society for Oncodevelopmental Biology and Medicine. *Tumour Biol.* 1996;17(4):196–219.
- Davelaar EM, van Kamp GJ, Verstraeten RA, et al. Comparison of seven immunoassays for the quantification of CA 125 antigen in serum. *Clin Chem.* 1998;44(7):1417–1422.
- Mongia SK, Rawlins ML, Owen WE, et al. Performance characteristics of seven automated CA 125 assays. *Am J Clin Pathol.* 2006; 125(6):921–927.
- Kabawat SE, Bast RC Jr, Bhan AK, et al. Tissue distribution of a coelomic-epithelium-related antigen recognized by the monoclonal antibody OC125. *Int J Gynecol Pathol.* 1983;2(3):275–285.
- Bast RC Jr, Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med.* 1983;309(15):883–887.
- Alagoz T, Buller RE, Berman M, et al. What is a normal CA125 level? *Gynecol Oncol.* 1994; 53(1):93–97.
- Bon GG, Kenemans P, Verstraeten R, et al. Serum tumor marker immunoassays in gynecologic oncology: establishment of reference values. *Am J Obstet Gynecol.* 1996;174(1 Pt 1):107–114.
- Zurawski VR Jr, Orjasetter H, Andersen A, et al. Elevated serum CA 125 levels prior to diagnosis of ovarian neoplasia: relevance for early detection of ovarian cancer. *Int J Cancer.* 1988;42(5):677–680.
- Canney PA, Moore M, Wilkinson PM, et al. Ovarian cancer antigen CA125: a prospective clinical assessment of its role as a tumour marker. *Br J Cancer.* 1984;50(6):765–769.
- Jacobs I, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. *Hum Reprod.* 1989;4(1):1–12.
- Tamakoshi K, Kikkawa F, Shibata K, et al. Clinical value of CA125, CA19-9, CEA, CA72-4, and TPA in borderline ovarian tumor. *Gynecol Oncol.* 1996;62(1):67–72.
- Vergote IB, Bormer OP, Abeler VM. Evaluation of serum CA 125 levels in the monitoring of ovarian cancer. *Am J Obstet Gynecol.* 1987; 157(1):88–92.
- Wilson JA, Jungner G. *WHO principles and practice of screening for disease*. Geneva: World Health Organization, 1968. 66–67 (5).
- Shapiro SV, Strax WP, Venet L. *Periodic Screening for Breast Cancer: The Health Insurance Plan Project and its Sequelae*. Baltimore, MD: Johns Hopkins University Press; 1988.
- Mandel JS, Smith R, DeVita VT Jr, Lawrence TS, Rosenberg SA, DePinto RA, Weinberg RA. (Eds.), *Cancer Screening in Cancer: Principles and Practice of Oncology*. Wolters Kluwer Health: Lippincott, Williams & Wilkins; 2011: 582–586.
- Bonfrer JM, Korse CM, Verstraeten RA, et al. Clinical evaluation of the Byk LIA-mat CA125 II assay: discussion of a reference value. *Clin Chem.* 1997;43(3):491–497.
- Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet.* 1999;353(9160):1207–1210.
- Jacobs I, Davies AP, Bridges J, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. *Br Med J.* 1993;306(6884):1030–1034.
- Menon U, Talaat A, Jeyarajah AR, et al. Ultrasound assessment of ovarian cancer risk in postmenopausal women with CA125 elevation. *Br J Cancer.* 1999;80(10):1644–1647.
- Menon U, Talaat A, Rosenthal AN, et al. Performance of ultrasound as a second line test to serum CA125 in ovarian cancer screening. *Bjog.* 2000;107(2):165–169.
- Menon U, Skates SJ, Lewis S, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. *J Clin Oncol.* 2005;23(31):7919–7926.
- Skates SJ, Menon U, MacDonald N, et al. Calculation of the risk of ovarian cancer from serial CA-125 values for preclinical detection in postmenopausal women. *J Clin Oncol.* 2003; 21(suppl. 10):206–210.
- Skates SJ, Xu FJ, Yu YH, et al. Toward an optimal algorithm for ovarian cancer screening with longitudinal tumor markers. *Cancer.* 1995;76 (suppl. 10):2004–2010.
- van Nagell JR Jr, DePriest PD, Ueland FR, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. *Cancer.* 2007;109(9):1887–1896.
- van Nagell JR Jr, Miller RW, DeSimone CP, et al. Long-term survival of women with epithelial ovarian cancer detected by ultrasonographic screening. *Obstet Gynecol.* 2011; 118(6):1212–1221.
- Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. *Int J Gynecol Cancer.* 2008;18(3):414–420.
- Buyss SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized controlled trial. *JAMA.* 2011;305(22):2295–2303.
- Buyss SS, Partridge E, Greene MH, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. *Am J Obstet Gynecol.* 2005;193(5):1630–1639.
- Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol.* 2009;113(4):775–782.
- Menon U, Gentry-Maharaj A, Ryan A, et al. Recruitment to multicentre trials—lessons from UKCTOCS: descriptive study. *Br Med J.* 2008;337:a2079.
- Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol.* 2009;10(4):327–340.
- Menon U, Gentry-Maharaj A, Jacobs I. Ovarian cancer screening and mortality. *JAMA.* 2011; 306(14):1544; author reply 1544–1545.
- Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol.* 2009;10(4):327–340.
- Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007; 25(11):1329–1333.
- Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer.* 1999;81(2):214–218.
- Jacobs I. Screening for familial ovarian cancer: the need for well-designed prospective studies. *J Clin Oncol.* 2005;23(24):5443–5445.
- Manchanda R, Rosenthal A, Burnell M, et al. Change in stage distribution observed with annual screening for ovarian cancer in BRCA carriers. *J Med Genet.* 2009;46(6):423–424.
- Rosenthal AN, Fraser L, Manchanda R, et al. The UK Familial Ovarian Cancer Screening Study (UK FOCSS) Phase 1 - Results Of Annual Screening, in British Gynaecological Cancer Society. 2009. Dublin, Ireland.
- Greene MH, Piedmonte M, Alberts D, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev.* 2008;17(3):594–604.
- [www.clinicaltrials.gov](http://clinicaltrials.gov/ct/gui/show/NCT00039559?order=5). <http://clinicaltrials.gov/ct/gui/show/NCT00039559?order=5>. 2007 25/05/2007; Available from: <http://clinicaltrials.gov/ct/gui/show/NCT00039559?order=5>.
- Skates SJ, D.C.W. Isaacs C, et al. *A Prospective Multi-Center Ovarian Cancer Screening Study in Women at Increased Risk*. American Society of Clinical Oncology. 2007. Chicago, IL: Journal of Clinical Oncology.
- Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol.* 2010;34(3):433–443.
- Menon U, Jacobs I. Screening for ovarian cancer. *Best Pract Res Clin Obstet Gynaecol.* 2002;16(4):469–482.
- Gentry-Maharaj A, Menon U. Screening for ovarian cancer in the general population. Best practice and research. *Clin Obstet Gynaecol.* 2012;26(2):243–256.
- Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol.* 2007;19(1):3–9.
- Kobayashi H, Ooi H, Yamada Y, et al. Serum CA125 level before the development of ovarian cancer. *Int J Gynaecol Obstet.* 2007;99(2):95–99.
- Brown PO, Palmer C. The preclinical natural history of serous ovarian cancer: defining the target for early detection. *PLoS Med.* 2009;6(7):e1000114.
- Hori SS, Gambhir SS. Mathematical model identifies blood biomarker-based early cancer detection strategies and limitations. *Sci Transl Med.* 2011; 3(109):109ra116.
- Urban N, Thorpe JD, Bergan LA, et al. Potential role of HE4 in multimodal screening for epithelial ovarian cancer. *J Natl Cancer Inst.* 2011; 103(21):1630–1634.

55. Jeyarajah AR, Ind TE, Skates S, et al. Serum CA125 elevation and risk of clinical detection of cancer in asymptomatic postmenopausal women. *Cancer*. 1999;85(9):2068–2072.
56. Jeyarajah AR, Ind TE, MacDonald N, et al. Increased mortality in postmenopausal women with serum CA125 elevation. *Gynecol Oncol*. 1999;73(2):242–246.
57. Sjøvall K, Nilsson B, Einhorn N. The significance of serum CA 125 elevation in malignant and nonmalignant diseases. *Gynecol Oncol*. 2002;85(1):175–178.
58. Cramer DW, O'Rourke DJ, Vitonis AF, et al. CA125 immune complexes in ovarian cancer patients with low CA125 concentrations. *Clin Chem*. 2010;56(12):1889–1892.
59. Rosen DG, Wang L, Atkinson JN, et al. Potential markers that complement expression of CA125 in epithelial ovarian cancer. *Gynecol Oncol*. 2005;99(2):267–277.
60. Song H, Ramus SJ, Tyrer J, et al. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. *Nat Genet*. 2009;41(9):996–1000.
61. Goode EL, Chenevix-Trench G, Song H, et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. *Nat Genet*. 2010;42(10):874–879.
62. Bolton KL, Tyrer J, Song H, et al. Common variants at 19p13 are associated with susceptibility to ovarian cancer. *Nat Genet*. 2010;42(10):880–884.
63. Beesley J, Pickett HA, Johnatty SE, et al. Functional polymorphisms in the TERT promoter are associated with risk of serous epithelial ovarian and breast cancers. *PLoS One*. 2011;6(9):e24987.
64. Engelen MJ, Kos HE, Willems PH, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer*. 2006;106(3):589–598.
65. Giede KC, Kieser K, Dodge J, et al. Who should operate on patients with ovarian cancer? An evidence-based review. *Gynecol Oncol*. 2005;99(2):447–461.
66. Paulsen T, Kjaerheim K, Kaern J, et al. Improved short-term survival for advanced ovarian, tubal, and peritoneal cancer patients operated at teaching hospitals. *Int J Gynecol Cancer*. 2006;16(suppl. 1):11–17.
67. van Trappen PO, Rufford BD, Mills TD, et al. Differential diagnosis of adnexal masses: risk of malignancy index, ultrasonography, magnetic resonance imaging, and radioimmunosciintigraphy. *Int J Gynecol Cancer*. 2007;17(1):61–67.
68. Pepe MS, Feng Z, Janes H, et al. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. *J Natl Cancer Inst*. 2008;100(20):1432–1438.
69. Jacobs I, Menon U. The sine qua non of discovering novel biomarkers for early detection of ovarian cancer: carefully selected preclinical samples. *Cancer Prev Res*. 2011;4(3):299–302.
70. Cramer DW, Bast RC Jr, Berg CD, et al. Ovarian cancer biomarker performance in prostate, lung, colorectal, and ovarian cancer screening trial specimens. *Cancer Prev Res*. 2011;4(3):365–374.
71. Anderson GL, McIntosh M, Wu L, et al. Assessing lead time of selected ovarian cancer biomarkers: a nested case-control study. *J Natl Cancer Inst*. 2012(1):26–38.
72. Zhu CS, Pinsky PF, Cramer DW, et al. A framework for evaluating biomarkers for early detection: validation of biomarker panels for ovarian cancer. *Cancer Prev Res(Phila)*. 2011;4(3):375–383.
73. Moore LE, Pfeiffer RM, Zhang Z, et al. Proteomic biomarkers in combination with CA 125 for detection of epithelial ovarian cancer using prediagnostic serum samples from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *Cancer*. 2012;118(1):91–100.
74. Yurkovetsky Z, Skates S, Lomakin A, et al. Development of a multimarker assay for early detection of ovarian cancer. *J Clin Oncol*. 2010;28(13):2159–2166.
75. Einhorn N, Bast RC Jr, Knapp RC, et al. Preoperative evaluation of serum CA 125 levels in patients with primary epithelial ovarian cancer. *Obstet Gynecol*. 1986;67(3):414–416.
76. Curtin JP. Management of the adnexal mass. *Gynecol Oncol*. 1994;55(3 Pt 2):S42–S46.
77. Maggino T, Gadducci A, D'Addario V, et al. Prospective multicenter study on CA 125 in postmenopausal pelvic masses. *Gynecol Oncol*. 1994;54(2):117–123.
78. Parker WH, Levine RL, Howard FM, et al. A multicenter study of laparoscopic management of selected cystic adnexal masses in postmenopausal women. *J Am Coll Surg*. 1994;179(6):733–737.
79. Zhang Z, Barnhill SD, Zhang H, et al. Combination of multiple serum markers using an artificial neural network to improve specificity in discriminating malignant from benign pelvic masses. *Gynecol Oncol*. 1999;73(1):56–61.
80. Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol*. 1990;97(10):922–929.
81. Geomini P, Kruitwagen R, Bremer GL, et al. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. *Obstet Gynecol*. 2009;113(2 Pt 1):384–394.
82. Hakansson F, Hogdall EV, Nedergaard L, et al. Risk of malignancy index used as a diagnostic tool in a tertiary centre for patients with a pelvic mass. *Acta Obst Gynecol Scand*. 2012;91(4):496–502.
83. Moolthiya W, Yuenyao P. The risk of malignancy index (RMI) in diagnosis of ovarian malignancy. *Asian Pac J Cancer Prev*. 2009;10(5):865–868.
84. Alanbay I, Akturk E, Coksuer H, et al. Comparison of risk of malignancy index (RMI), CA125, CA 19-9, ultrasound score, and menopausal status in borderline ovarian tumor. *Gynecol Endocrinol*. 2012;28(6):478–482.
85. Van Gorp T, Veldman J, van Calster B, et al. Subjective assessment by ultrasound is superior to the risk of malignancy index (RMI) or the risk of ovarian malignancy algorithm (ROMA) in discriminating benign from malignant adnexal masses. *Eur J Cancer*. 2012;48(11):1649–1656.
86. Andersen ES, Knudsen A, Rix P, et al. Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. *Gynecol Oncol*. 2003;90(1):109–112.
87. Makar AP, Kristensen GB, Kaern J, et al. Prognostic value of pre- and postoperative serum CA 125 levels in ovarian cancer: new aspects and multivariate analysis. *Obstet Gynecol*. 1992;79(6):1002–1010.
88. Scholl SM, Bascou CH, Mosseri V, et al. Circulating levels of colony-stimulating factor 1 as a prognostic indicator in 82 patients with epithelial ovarian cancer. *Br J Cancer*. 1994;69(2):342–346.
89. Venesmaa P, Lehtovirta P, Stenman UH, et al. Tumour-associated trypsin inhibitor (TATI): comparison with CA125 as a preoperative prognostic indicator in advanced ovarian cancer. *Br J Cancer*. 1994;70(6):1188–1190.
90. Hogdall CK, Norgaard-Pedersen B, Mogensen O. The prognostic value of pre-operative serum tetranectin, CA-125 and a combined index in women with primary ovarian cancer. *Anticancer Res*. 2002;22(3):1765–1768.
91. Petri AL, Hogdall E, Christensen IJ, et al. Preoperative CA125 as a prognostic factor in stage I epithelial ovarian cancer. *APMIS*. 2006;114(5):359–363.
92. Obermair A, Fuller A, Lopez-Varela E, et al. A new prognostic model for FIGO stage 1 epithelial ovarian cancer. *Gynecol Oncol*. 2007;104(3):607–611.
93. Raspollini MR, Amunni G, Villanucci A, et al. COX-2 and preoperative CA-125 level are strongly correlated with survival and clinical responsiveness to chemotherapy in ovarian cancer. *Acta Obstet Gynecol Scand*. 2006;85(4):493–498.
94. Rosen A, Sevela P, Klein M, et al. A CA125 score as a prognostic index in patients with ovarian cancer. *Arch Gynecol Obstet*. 1990;247(3):125–129.
95. Yedema CA, Kenemans P, Thomas CM, et al. CA 125 serum levels in the early post-operative period do not reflect tumour reduction obtained by cytoreductive surgery. *Eur J Cancer*. 1993;29A(7):966–971.
96. Gadducci A, Zola P, Landoni F, et al. Serum half-life of CA 125 during early chemotherapy as an independent prognostic variable for patients with advanced epithelial ovarian cancer: results of a multicentric Italian study. *Gynecol Oncol*. 1995;58(1):42–47.
97. Rosman M, Hayden CL, Thiel RP, et al. Prognostic indicators for poor risk epithelial ovarian carcinoma. *Cancer*. 1994;74(4):1323–1328.
98. Yedema CA, Kenemans P, Voorhorst F, et al. CA 125 half-life in ovarian cancer: a multivariate survival analysis. *Br J Cancer*. 1993;67(6):1361–1367.
99. van der Burg ME, Lammes FB, van Putten WL, et al. Ovarian cancer: the prognostic value of the serum half-life of CA125 during induction chemotherapy. *Gynecol Oncol*. 1988;30(3):307–312.
100. Hawkins RE, Roberts K, Wiltshaw E, et al. The prognostic significance of the half-life of serum CA 125 in patients responding to chemotherapy for epithelial ovarian carcinoma. *Br J Obstet Gynaecol*. 1989;96(12):1395–1399.
101. Makar AP, Kristensen GB, Borner OP, et al. Serum CA 125 level allows early identification of nonresponders during induction chemotherapy. *Gynecol Oncol*. 1993;49(1):73–79.
102. Redman CW, Blackledge GR, Kelly K, et al. Early serum CA125 response and outcome in epithelial ovarian cancer. *Eur J Cancer*. 1990;26(5):593–596.
103. Markman M, Liu PY, Rothenberg ML, et al. Pre-treatment CA-125 and risk of relapse in advanced ovarian cancer. *J Clin Oncol*. 2006;24(9):1454–1458.
104. Makar AP, Liu PY, Rothenberg ML, et al. Is serum CA 125 at the time of relapse a prognostic indicator for further survival prognosis in patients with ovarian cancer? *Gynecol Oncol*. 1993;49(1):3–7.
105. Budiu RA, et al. Soluble MUC1 and serum MUC1-specific antibodies are potential prognostic biomarkers for platinum-resistant ovarian cancer. *Cancer Immunol Immunother*. 2011;60(7):975–984.
106. No JH, et al. Quantitative detection of serum survivin and its relationship with prognostic factors in ovarian cancer. *Gynecol Obstet Invest*. 2011;71(2):136–140.
107. Hawkins RE, et al. The clinical correlates of serum CA125 in 169 patients with epithelial ovarian carcinoma. *Br J Cancer*. 1989;60(4):634–637.
108. Hempling RE, et al. Predictive value of serum CA125 following optimal cytoreductive surgery during weekly cisplatin induction therapy for advanced ovarian cancer. *J Surg Oncol*. 1993;54(1):38–44.
109. Morgan RJ Jr, et al. Modulation of 5-fluorouracil with high-dose leucovorin calcium: activity in ovarian cancer and correlation with CA-125 levels. *Gynecol Oncol*. 1995;58(1):79–85.

110. Gallion HH, et al. The prognostic implications of low serum CA 125 levels prior to the second-look operation for stage III and IV epithelial ovarian cancer. *Gynecol Oncol.* 1992;46(1):29–32.
111. Buller RE, et al. Serum CA125 regression in epithelial ovarian cancer: correlation with reassessment findings and survival. *Gynecol Oncol.* 1992;47(1):87–92.
112. de Bruijn HW, van der Zee AG, Aalders JG. The value of cancer antigen 125 (CA 125) during treatment and follow-up of patients with ovarian cancer. *Curr Opin Obstet Gynecol.* 1997; 9(1):8–13.
113. Rustin GJ, et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. *J Clin Oncol.* 1996;14(5):1545–1551.
114. Rustin GJ, et al. Phase II trial of oral altretamine for relapsed ovarian carcinoma: evaluation of defining response by serum CA125. *J Clin Oncol.* 1997;15(1):172–176.
115. Riedinger JM, et al. CA 125 half-life and CA 125 nadir during induction chemotherapy are independent predictors of epithelial ovarian cancer outcome: results of a French multicentric study. *Ann Oncol.* 2006;17(8):1234–1238.
116. Rustin GJ, et al. Defining progression of ovarian carcinoma during follow-up according to CA 125: a North Thames Ovary Group Study. *Ann Oncol.* 1996;7(4):361–364.
117. Cruickshank DJ, Terry PB, Fullerton WT. The potential value of CA125 as a tumour marker in small volume, non-evaluable epithelial ovarian cancer. *Int J Biol Markers.* 1991;6(4):247–252.
118. Duffy MJ, et al. CA125 in ovarian cancer: European Group on Tumor Markers guidelines for clinical use. *Int J Gynecol Cancer.* 2005; 15(5):679–691.
119. Santillan A, et al. Risk of epithelial ovarian cancer recurrence in patients with rising serum CA-125 levels within the normal range. *J Clin Oncol.* 2005;23(36):9338–9343.
120. Ferrozzi F, et al. Thin-section CT follow-up of metastatic ovarian carcinoma correlation with levels of CA-125 marker and clinical history. *Clin Imaging.* 1998;22(5):364–370.
121. Fehm T, et al. Evaluation of CA125, physical and radiological findings in follow-up of ovarian cancer patients. *Anticancer Res.* 2005; 25(3A):1551–1554.
122. van Altena AM, et al. CA125 nadir concentration is an independent predictor of tumor recurrence in patients with ovarian cancer: a population-based study. *Gynecol Oncol.* 2010;119(2):265–269.
123. Rustin GJ. What surveillance plan should be advised for patients in remission after completion of first-line therapy for advanced ovarian cancer? *Int J Gynecol Cancer.* 2010;20(11 suppl. 2): S27–S28.
124. Hellstrom I, et al. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. *Cancer Res.* 2003;63(13):3695–3700.
125. Molina R, et al. HE4 a novel tumour marker for ovarian cancer: comparison with CA 125 and ROMA algorithm in patients with gynaecological diseases. Tumour biology: *J Int Soc Oncodev Biol Med.* 2011;32(6):1087–1095.
126. Moore RG, et al. Serum HE4 levels are less frequently elevated than CA125 in women with benign gynecologic disorders. *Am J Obstet Gynecol.* 2012;206(4):351.e1–8.
127. Moore RG, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecol Oncol.* 2008;108(2):402–408.
128. Jacob F, et al. No benefit from combining HE4 and CA125 as ovarian tumor markers in a clinical setting. *Gynecol Oncol.* 2011;121(3):487–491.
129. Hogdall EK, MA, Christensen IJ, Lundvall, L, Engelholm SA, Nedergaard L, Pedersen AT, Hartwell D, Hogdall CK. Diagnostic value of HE4, CA125 and the ROMA index in ovarian cancer patients from a tertiary center. *IGCS.* 2012.
130. Partheen K, Kristjansdottir B, Sundfeldt K. Evaluation of ovarian cancer biomarkers HE4 and CA-125 in women presenting with a suspicious cystic ovarian mass. *J Gynecol Oncol.* 2011;22(4):244–252.
131. Schummer M, et al. Evaluation of ovarian cancer remission markers HE4, MMP7 and Mesothelin by comparison to the established marker CA125. *Gynecol Oncol.* 2012;125(1):65–69.
132. Fujirebio Diagnostics, I. CA125, HE4 and ROMA. 2008; Available from: http://www.he4test.com/us/about/about_roma.html.
133. Moore RG, et al. Serum levels of the ovarian cancer biomarker HE4 are decreased in pregnancy and increase with age. *Am J Obstet Gynecol.* 2012; 206(4):349.e1–7.
134. Park Y, et al. Reference ranges for HE4 and CA125 in a large Asian population by automated assays and diagnostic performances for ovarian cancer. *Int J Cancer.* 2012;130(5): 1136–1144.
135. Horowitz IR, et al. Increased glycodelin levels in gynecological malignancies. *Int J Gynecol Cancer.* 2001;11(3):173–179.
136. Mandelin E, et al. Glycodelin in ovarian serous carcinoma: association with differentiation and survival. *Cancer Res.* 2003;63(19):6258–6264.
137. Jeschke U, et al. Development of monoclonal and polyclonal antibodies and an ELISA for the determination of glycodein in human serum, amniotic fluid and cystic fluid of benign and malignant ovarian tumors. *Anticancer Res.* 2005; 25(3A):1581–1589.
138. Havrilesky LJ, et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. *Gynecol Oncol.* 2008;110(3):374–382.
139. Widschwendter M, Menon U. Circulating methylated DNA: a new generation of tumor markers. *Clin Cancer Res.* 2006;12(24):7205–7208.
140. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. *Nat Rev Genet.* 2002;3(6):415–428.
141. Jen J, Wu L, Sidransky D. An overview on the isolation and analysis of circulating tumor DNA in plasma and serum. *Ann N Y Acad Sci.* 2000;906:8–12.
142. Laird PW. The power and the promise of DNA methylation markers. *Nat Rev Cancer.* 2003;3(4):253–266.
143. Wallner M, et al. Methylation of serum DNA is an independent prognostic marker in colorectal cancer. *Clin Cancer Res.* 2006;12(24):7347–7352.
144. Teschendorff AE, et al. An epigenetic signature in peripheral blood predicts active ovarian cancer. *PLoS One.* 2009;4(12):e8274.
145. Dai W, et al. Systematic CpG islands methylation profiling of genes in the wnt pathway in epithelial ovarian cancer identifies biomarkers of progression-free survival. *Clin Cancer Res.* 2011;17(12):4052–4062.
146. Ho CM, et al. Promoter methylation of sFRP5 in patients with ovarian clear cell adenocarcinoma. *Eur J Clin Invest.* 2010;40(4):310–318.
147. Lee YH, et al. Salivary transcriptomic biomarkers for detection of ovarian cancer: for serous papillary adenocarcinoma. *J Mol Med.* 2012;90(4):427–434.
148. Kamat AA, et al. Plasma cell-free DNA in ovarian cancer: an independent prognostic biomarker. *Cancer.* 2010;116(8):1918–1925.
149. Denkert C, et al. The Mass spectrometry-based metabolic profiling reveals different metabolite patterns in invasive ovarian carcinomas and ovarian borderline tumors. *Cancer Res.* 2006;66(22):10795–10804.
150. Iorio MV, et al. MicroRNA signatures in human ovarian cancer. *Cancer Res.* 2007;67(18): 8699–8707.
151. Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. *Gynecol Oncol.* 2008;110(1):13–21.
152. Resnick KE, et al. The detection of differentially expressed microRNAs from the serum of ovarian cancer patients using a novel real-time PCR platform. *Gynecol Oncol.* 2009;112(1):55–59.
153. Gold P, Freedman SO. Specific carcinoembryonic antigens of the human digestive system. *J Exp Med.* 1965;122(3):467–481.
154. Onsrud M. Tumour markers in gynaecologic oncology. *Scand J Clin Lab Invest Suppl.* 1991;206:60–70.
155. Roman LD, et al. Carcinoembryonic antigen in women with isolated pelvic masses. Clinical utility? *J Reprod Med.* 1998;43(5):403–407.
156. Nomellini RS, et al. Parameters of blood count and tumor markers in patients with borderline ovarian tumors: a retrospective analysis and relation to staging. *ISRN Oncol.* 2012;2012:947831.
157. Sorensen SS, Mosgaard BJ. Combination of cancer antigen 125 and carcinoembryonic antigen can improve ovarian cancer diagnosis. *Danish Med Bull.* 2011;58(11):A4331.
158. Hogdall EV, et al. Protein expression levels of carcinoembryonic antigen (CEA) in Danish ovarian cancer patients: from the Danish 'MALOVA' ovarian cancer study. *Pathology.* 2008;40(5): 487–492.
159. Kawai M, et al. Seven tumor markers in benign and malignant germ cell tumors of the ovary. *Gynecol Oncol.* 1992;45(3):248–253.
160. Olt G, Berchuck A, Bast RC Jr. The role of tumor markers in gynecologic oncology. *Obstet Gynecol Surv.* 1990;45(9):570–577.
161. Maida Y, et al. Ovarian endometrioid adenocarcinoma with ectopic production of alpha-fetoprotein. *Gynecol Oncol.* 1998;71(1):133–136.
162. Chow SN, et al. Malignant ovarian germ cell tumors. *Int J Gynaecol Obstet.* 1996;53(2): 151–158.
163. Zalel Y, et al. Diagnosis and management of malignant germ cell ovarian tumors in young females. *Int J Gynaecol Obstet.* 1996;55(1):1–10.
164. Mayordomo JI, et al. Ovarian and extragonadal malignant germ-cell tumors in females: a single-institution experience with 43 patients. *Ann Oncol.* 1994;5(3):225–231.
165. Zong C, et al. Chemiluminescence imaging immunoassay of multiple tumor markers for cancer screening. *Anal Chem.* 2012;84(5):2410–2415.
166. Mann K, Saller B, Hoermann R. Clinical use of HCG and hCG beta determinations. *Scand J Clin Lab Invest Suppl.* 1993;216:97–104.
167. Murugaesu N, et al. Malignant ovarian germ cell tumors: identification of novel prognostic markers and long-term outcome after multimodal treatment. *J Clin Oncol.* 2006;24(30): 4862–4866.
168. Oltmann SC, et al. Can we preoperatively risk stratify ovarian masses for malignancy? *J Pediatr Surg.* 2010;45(1):130–134.
169. Lenhard M, et al. Human chorionic gonadotropin and its relation to grade, stage and patient survival in ovarian cancer. *BMC Cancer.* 2012;12:2.
170. Muller CY, Cole LA. The quagmire of hCG and hCG testing in gynecologic oncology. *Gynecol Oncol.* 2009;112(3):663–672.

171. Lappohn RE, et al. Inhibin as a marker for granulosa-cell tumors. *N Engl J Med.* 1989; 321(12):790–793.
172. Boggett JF, et al. Serum inhibin and disease status in women with ovarian granulosa cell tumors. *Gynecol Oncol.* 1997;64(1):64–69.
173. Cooke I, et al. Inhibin as a marker for ovarian cancer. *Br J Cancer.* 1995;71(5):1046–1050.
174. Jobling T, et al. A prospective study of inhibin in granulosa cell tumors of the ovary. *Gynecol Oncol.* 1994;55(2):285–289.
175. Petraglia F, et al. Inhibin B is the major form of inhibin/activin family secreted by granulosa cell tumors. *J Clin Endocrinol Metab.* 1998; 83(3):1029–1032.
176. Yamashita K, et al. Production of inhibin A and inhibin B in human ovarian sex cord stromal tumors. *Am J Obstet Gynecol.* 1997;177(6): 1450–1457.
177. Rey RA, et al. Antimüllerian hormone as a serum marker of granulosa cell tumors of the ovary: comparative study with serum alpha-inhibin and estradiol. *Am J Obstet Gynecol.* 1996; 174(3):958–965.
178. Silverman LA, Gitelman SE. Immunoreactive inhibin, müllerian inhibitory substance, and activin as biochemical markers for juvenile granulosa cell tumors. *J Pediatr.* 1996;129(6):918–921.
179. Blaakaer J, et al. Immunoreactive inhibin-production in post-menopausal women with malignant epithelial ovarian tumors. *Eur J Obstet Gynecol Reprod Biol.* 1993;52(2):105–110.
180. Healy DL, et al. Elevated serum inhibin concentrations in postmenopausal women with ovarian tumors. *N Engl J Med.* 1993;329(21):1539–1542.
181. Phocas I, et al. A comparative study of serum alpha-beta A immunoreactive inhibin and tumor-associated antigens CA125 and CEA in ovarian cancer. *Anticancer Res.* 1996;16(6B): 3827–3831.
182. Khosravi J, et al. Enzyme-linked immunosorbent assay of total inhibin: direct determination based on inhibin alpha subunit-specific monoclonal antibodies. *Clin Biochem.* 2004;37(5): 370–376.
183. Tsigkou A, et al. Total inhibin is a potential serum marker for epithelial ovarian cancer. *J Clin Endocrinol Metab.* 2007;92(7):2526–2531.
184. Burger HG, et al. Characterization of inhibin immunoreactivity in post-menopausal women with ovarian tumours. *Clin Endocrinol (Oxf).* 1996;44(4):413–418.
185. Lambert-Messerlian GM, et al. Multiple immunoreactive inhibin proteins in serum from post-menopausal women with epithelial ovarian cancer. *Gynecol Oncol.* 1997;65(3):512–516.
186. Burger HG, et al. Inhibin and ovarian cancer. *J Reprod Immunol.* 1998;39(1–2):77–87.
187. Menon U, et al. Serum inhibin, activin and follistatin in postmenopausal women with epithelial ovarian carcinoma. *BJOG.* 2000;107(9): 1069–1074.
188. Geerts I, et al. The role of inhibins B and anti-müllerian hormone for diagnosis and follow-up of granulosa cell tumors. *Int J Gynecol Cancer.* 2009;19(5):847–855.
189. Welt CK, et al. Presence of activin, inhibin, and follistatin in epithelial ovarian carcinoma. *J Clin Endocrinol Metab.* 1997;82(11):3720–3727.
190. Michiel DF, Oppenheim JJ. Cytokines as positive and negative regulators of tumor promotion and progression. *Semin Cancer Biol.* 1992;3(1):3–15.
191. Cobellis L, et al. High concentrations of activin A in the peritoneal fluid of women with epithelial ovarian cancer. *J Soc Gynecol Invest.* 2004; 11(4):203–206.
192. Ludlow H, et al. A new ‘total’ activin B enzyme-linked immunosorbent assay (ELISA): development and validation for human samples. *Clin Endocrinol.* 2009;71(6):867–873.
193. Prezas P, et al. Overexpression of the human tissue kallikrein genes KLK4, 5, 6, and 7 increases the malignant phenotype of ovarian cancer cells. *Biol Chem.* 2006;387(6):807–811.
194. Diamandis EP, et al. Human kallikrein 6 (zyme/protease M/neurosin): a new serum biomarker of ovarian carcinoma. *Clin Biochem.* 2000;33(7):579–583.
195. Diamandis EP. Proteomic patterns in serum and identification of ovarian cancer. *Lancet.* 2002;360(9327):170; author reply 170–171.
196. Davidson B, et al. Kallikrein 4 expression is up-regulated in epithelial ovarian carcinoma cells in effusions. *Am J Clin Pathol.* 2005;123(3):360–368.
197. Paliouras M, Borgono C, Diamandis EP. Human tissue kallikreins: the cancer biomarker family. *Cancer Lett.* 2007;249(1):61–79.
198. Oikonomopoulou K, et al. Kallikreins as markers of disseminated tumour cells in ovarian cancer—a pilot study. *Tumour Biol.* 2006;27(2):104–114.
199. Borgono CA, et al. Human kallikrein 8 protein is a favorable prognostic marker in ovarian cancer. *Clin Cancer Res.* 2006;12(5):1487–1493.
200. Shan SJ, et al. Unfavorable prognostic value of human kallikrein 7 quantified by ELISA in ovarian cancer cytosols. *Clin Chem.* 2006;52(10): 1879–1886.
201. Dorn J, et al. Circulating biomarker tissue kallikrein-related peptidase KLK5 impacts ovarian cancer patients’ survival. *Ann Oncol.* 2011;22(8):1783–1790.
202. Tiniakos DG, Yu H, Liapis H. Osteopontin expression in ovarian carcinomas and tumors of low malignant potential (LMP). *Hum Pathol.* 1998;29(11):1250–1254.
203. Kim JH, et al. Osteopontin as a potential diagnostic biomarker for ovarian cancer. *JAMA.* 2002;287(13):1671–1679.
204. Nakae M, et al. Preoperative plasma osteopontin level as a biomarker complementary to carbohydrate antigen 125 in predicting ovarian cancer. *J Obstet Gynaecol Res.* 2006;32(3):309–314.
205. Brakora KA, et al. Utility of osteopontin as a biomarker in recurrent epithelial ovarian cancer. *Gynecol Oncol.* 2004;93(2):361–365.
206. Schorge JO, et al. Osteopontin as an adjunct to CA125 in detecting recurrent ovarian cancer. *Clin Cancer Res.* 2004;10(10):3474–3478.
207. Matsuura M, et al. Statin-mediated reduction of osteopontin expression induces apoptosis and cell growth arrest in ovarian clear cell carcinoma. *Oncol Rep.* 2011;25(1):41–47.
208. Chang K, Pastan I. Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas, and ovarian cancers. *Proc Natl Acad Sci USA.* 1996;93(1):136–140.
209. Huang CY, et al. Serum mesothelin in epithelial ovarian carcinoma: a new screening marker and prognostic factor. *Anticancer Res.* 2006; 26(6C):4721–4728.
210. Suzuki M, et al. Macrophage colony-stimulating factor as a tumor marker for epithelial ovarian cancer. *Obstet Gynecol.* 1993;82(6):946–950.
211. Suzuki M, et al. Serum level of macrophage colony-stimulating factor as a marker for gynecologic malignancies. *Oncology.* 1995;52(2):128–133.
212. Woolas RP, et al. Elevation of multiple serum markers in patients with stage I ovarian cancer. *J Natl Cancer Inst.* 1993;85(21):1748–1751.
213. Skates SJ, et al. Preoperative sensitivity and specificity for early-stage ovarian cancer when combining cancer antigen CA-125II, CA 15-3, CA 72-4, and macrophage colony-stimulating factor using mixtures of multivariate normal distributions. *J Clin Oncol.* 2004;22(20):4059–4066.
214. Suzuki M, et al. Macrophage colony-stimulating factor as a marker for malignant germ cell tumors of the ovary. *Gynecol Oncol.* 1998;68(1):35–37.
215. Price FV, et al. Colony-stimulating factor-1 in primary ascites of ovarian cancer is a significant predictor of survival. *Am J Obstet Gynecol.* 1993;168(2):520–527.
216. Gadducci A, et al. Serum macrophage colony-stimulating factor (M-CSF) levels in patients with epithelial ovarian cancer. *Gynecol Oncol.* 1998;70(1):111–114.
217. Scambia G, et al. Interleukin-6 serum levels in patients with gynecological tumors. *Int J Cancer.* 1994;57(3):318–323.
218. Scambia G, et al. Prognostic significance of interleukin 6 serum levels in patients with ovarian cancer. *Br J Cancer.* 1995;71(2):354–356.
219. Lambeck AJ, et al. Serum cytokine profiling as a diagnostic and prognostic tool in ovarian cancer: a potential role for interleukin 7. *Clin Cancer Res.* 2007;13(8):2385–2391.
220. Salman T, et al. The clinical value of serum TPS in gynecological malignancies. *Int J Biol Markers.* 1995;10(2):81–86.
221. Shabana A, Onsrud M. Tissue polypeptide-specific antigen and CA 125 as serum tumor markers in ovarian carcinoma. *Tumour Biol.* 1994;15(6):361–367.
222. Sliutz G, et al. Tissue polypeptide specific antigen and cancer associated serum antigen in the follow-up of ovarian cancer. *Anticancer Res.* 1995;15(3):1127–1129.
223. Tempfer C, et al. Tissue polypeptide specific antigen in the follow-up of ovarian and cervical cancer patients. *Int J Cancer.* 1998;79(3):241–244.
224. Harlozinska A, et al. TPS and CA 125 levels in serum, cyst fluid and ascites of patients with epithelial ovarian neoplasms. *Anticancer Res.* 1997;17(6D):4473–4478.
225. Stieber P, et al. Cytokeratin 19 fragments: a new marker for non-small-cell lung cancer. *Clin Biochem.* 1993;26(4):301–304.
226. Inaba N, et al. Cytokeratin fragment 21-1 in gynecologic malignancy: comparison with cancer antigen 125 and squamous cell carcinoma-related antigen. *Tumour Biol.* 1995;16(6):345–352.
227. Hasholzner U, et al. Significance of the tumour markers CA 125 II, CA 72-4, CASA and CYFRA 21-1 in ovarian carcinoma. *Anticancer Res.* 1994; 14(6B):2743–2746.
228. Tempfer C, et al. CYFRA 21-1 serum levels in women with adnexal masses and inflammatory diseases. *Br J Cancer.* 1998;78(8):1108–1112.
229. Gadducci A, et al. The clinical relevance of serum CYFRA 21-1 assay in patients with ovarian cancer. *Int J Gynecol Cancer.* 2001;11(4):277–282.
230. Lenhard M, et al. Use of novel serum markers in clinical follow-up of Sertoli-Leydig cell tumours. *Clin Chem Lab Med.* 2007;45(5):657–661.
231. Wojcik E, et al. Utility of ProGRP determinations in cancer patients. *Clin Lab.* 2010; 56(11–12):527–534.
232. Wilkins MR, et al. Progress with proteome projects: why all proteins expressed by a genome should be identified and how to do it. *Biotechnol Genet Eng Rev.* 1996;13:19–50.
233. Reynolds T. For proteomics research, a new race has begun. *J Natl Cancer Inst.* 2002;94(8): 552–554.
234. Wilkins MR, et al. Current challenges and future applications for protein maps and post-translational vector maps in proteome projects. *Electrophoresis.* 1996;17(5):830–838.

235. Rockhill B. Proteomic patterns in serum and identification of ovarian cancer. *Lancet*. 2002;360(9327):169; author reply 170–171.
236. Pearl DC. Proteomic patterns in serum and identification of ovarian cancer. *Lancet*. 2002; 360(9327):169–170; author reply 170–171.
237. Elwood M. Proteomic patterns in serum and identification of ovarian cancer. *Lancet*. 2002; 360(9327):170; author reply 170–171.
238. Petricoin EF, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet*. 2002; 359(9306):572–577.
239. Zhang Z, et al. Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. *Cancer Res*. 2004; 64(16):5882–5890.
240. Timms JF, et al. Preanalytic influence of sample handling on SELDI-TOF serum protein profiles. *Clin Chem*. 2007;53(4):645–656.
241. Hogdall E, et al. Proteomic biomarkers for overall and progression-free survival in ovarian cancer patients. *Proteomics. Clin Appl*. 2010; 4(12):940–952.
242. Diao L, et al. Reproducibility of SELDI spectra across time and laboratories. *Cancer Inform*. 2011;10:45–64.
243. Timms JF, et al. Early detection of ovarian cancer in samples pre-diagnosis using CA125 and MALDI-MS peaks. *Cancer Gnomics Proteomics*. 2011;8(6):289–305.
244. Stenman UH, et al. Markers supplementing CA 125 in ovarian cancer. *Ann Med*. 1995; 27(1):115–120.
245. Padungst P, et al. Accuracy of tissue polypeptide specific antigen (TPS) in the diagnosis of ovarian malignancy. *Anticancer Res*. 2000; 20(2B):1291–1295.
246. Sehoul J, et al. Preoperative determination of CASA (Cancer Associated Serum Antigen) and CA-125 for the discrimination between benign and malignant pelvic tumor mass: a prospective study. *Anticancer Res*. 2003;23(2A): 1115–1118.
247. Senapad S, et al. Predictive value of the combined serum CA 125 and TPS during chemotherapy and before second-look laparotomy in epithelial ovarian cancer. *Anticancer Res*. 2000; 20(2B):1297–1300.
248. Hogdall EV, et al. OVX1 radioimmunoassay results are dependent on the method of sample collection and storage. *Clin Chem*. 1999;45(5): 692–694.
249. Oehler MK, Sutterlin M, Caffier H. CASA and Ca 125 in diagnosis and follow-up of advanced ovarian cancer. *Anticancer Res*. 1999;19(4A):2513–2518.
250. Clarke CH, et al. Proteomic biomarkers apolipoprotein A1, truncated transthyretin and connective tissue activating protein III enhance the sensitivity of CA125 for detecting early stage epithelial ovarian cancer. *Gynecol Oncol*. 2011;122(3):548–553.
251. Tcherkassova J, et al. Combination of CA125 and RECAF biomarkers for early detection of ovarian cancer. *Tumour Biol*. 2011;32(4):831–838.
252. Hakala A, et al. Macrophage colony-stimulating factor 1, a clinically useful tumor marker in endometrial adenocarcinoma: comparison with CA 125 and the aminoterminal propeptide of type III procollagen. *Am J Obstet Gynecol*. 1995;173(1):112–119.
253. Patsner B, Orr JW Jr, Mann WJ Jr. Use of serum CA 125 measurement in posttreatment surveillance of early-stage endometrial carcinoma. *Am J Obstet Gynecol*. 1990;162(2):427–429.
254. Takeshima N, et al. Combined assay of serum levels of CA125 and CA19-9 in endometrial carcinoma. *Gynecol Oncol*. 1994;54(3):321–326.
255. Lo SS, et al. Prognostic significance of tumour markers in endometrial cancer. *Tumour Biol*. 1997;18(4):241–249.
256. Gadducci A, et al. A comparison of pretreatment serum levels of four tumor markers in patients with endometrial and cervical carcinoma. *Eur J Gynaecol Oncol*. 1990;11(4):283–288.
257. Kurihara T, et al. Determination of a normal level of serum CA125 in postmenopausal women as a tool for preoperative evaluation and postoperative surveillance of endometrial carcinoma. *Gynecol Oncol*. 1998;69(3):192–196.
258. Price FV, et al. CA 125 may not reflect disease status in patients with uterine serous carcinoma. *Cancer*. 1998;82(9):1720–1725.
259. Chen YL, et al. Value of pre-operative serum CA125 level for prediction of prognosis in patients with endometrial cancer. *Aust N Z J Obstet Gynaecol*. 2011;51(5):397–402.
260. Rose PG, et al. Serial serum CA 125 measurements for evaluation of recurrence in patients with endometrial carcinoma. *Obstet Gynecol*. 1994;84(1):12–16.
261. Cole LA, et al. Beta-core fragment (beta-core/UGF/UGP), a tumor marker: a 7-year report. *Gynecol Oncol*. 1996;60(2):264–270.
262. Kinugasa M, et al. Combination assay of urinary beta-core fragment of human chorionic gonadotropin with serum tumor markers in gynecologic cancers. *Jpn J Cancer Res*. 1995;86(8): 783–789.
263. Matorras R, et al. Monitoring endometrial adenocarcinoma with a four tumor marker combination. CA 125, squamous cell carcinoma antigen, CA 19.9 and CA 15.3. *Acta Obstet Gynecol Scand*. 1992;71(6):458–464.
264. Tomas C, et al. Serum concentrations of CA 125 and aminoterminal propeptide of type III procollagen (PIIINP) in patients with endometrial carcinoma. *Cancer*. 1990;66(11):2399–2406.
265. Ota Y, et al. Enzyme immunoassay for placental protein 4 (PP4) and its possible diagnostic significance in patients with genital tract cancer. *Arch Gynecol Obstet*. 1990;247(3):139–147.
266. Hareyama H, et al. Serum and tissue measurements of CA72-4 in patients with endometrial carcinoma. *J Clin Pathol*. 1996;49(12):967–970.
267. Xu Y, et al. OVX1 as a marker for early stage endometrial carcinoma. *Cancer*. 1994;73(7): 1855–1858.
268. Ferdeghini M, et al. Serum soluble interleukin-2 receptor (sIL-2R) assay in cervical and endometrial cancer. Preliminary data. *Anticancer Res*. 1993;13(3):709–713.
269. Olt G, et al. Preoperative evaluation of macrophage colony-stimulating factor levels in patients with endometrial cancer. *Am J Obstet Gynecol*. 1996;174(4):1316–1319.
270. Santin AD, et al. Human kallikrein 6: a new potential serum biomarker for uterine serous papillary cancer. *Clin Cancer Res*. 2005;11(9):3320–3325.
271. Worbs S, et al. Expression of the inhibin/activin subunits (-alpha, -betaA and -betaB) in normal and carcinogenic endometrial tissue: possible immunohistochemical differentiation markers. *Oncol Rep*. 2007;17(1):97–104.
272. Honkavuori M, et al. MMP-2 expression associates with CA 125 and clinical course in endometrial carcinoma. *Gynecol Oncol*. 2007; 104(1):217–221.
273. Steinbakk A, et al. The prognostic value of molecular biomarkers in tissue removed by curettage from FIGO stage 1 and 2 endometrioid type endometrial cancer. *Am J Obstet Gynecol*. 2009;200(1):78 e1-8.
274. Farias-Eisner G, et al. Validation of serum biomarkers for detection of early- and late-stage endometrial cancer. *Am J Obstet Gynecol*. 2010; 202(1):73 e1-5.
275. Devetzi M, et al. Cathepsin B protein levels in endometrial cancer: potential value as a tumour biomarker. *Gynecol Oncol*. 2009;112(3):531–536.
276. Cocco E, et al. Serum amyloid A: a novel biomarker for endometrial cancer. *Cancer*. 2010;116(4):843–851.
277. Cohn DE, et al. Comprehensive miRNA profiling of surgically staged endometrial cancer. *Am J Obstet Gynecol*. 2010;202(6):656 e1-8.
278. Karaayvaz M, et al. Prognostic significance of miR-205 in endometrial cancer. *PLoS One*. 2012; 7(4):e35158.
279. Fader AN, et al. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. *Gynecol Oncol*. 2009;114(1):121–127.
280. Li J, et al. HE4 as a biomarker for ovarian and endometrial cancer management. *Expert Rev Mol Diagn*. 2009;9(6):555–566.
281. Kalogera E, et al. Correlation of serum HE4 with tumor size and myometrial invasion in endometrial cancer. *Gynecol Oncol*. 2012;124(2):270–275.
282. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. *Cancer*. 1977;40(4):1621–1628.
283. Lozza L, et al. Cancer of the uterine cervix: clinical value of squamous cell carcinoma antigen (SCC) measurements. *Anticancer Res*. 1997;17(1B):525–529.
284. Ngan HY, et al. Prognostic significance of serum tumour markers in carcinoma of the cervix. *Eur J Gynaecol Oncol*. 1996;17(6):512–517.
285. Yoon SM, et al. The clinical values of squamous cell carcinoma antigen and carcinoembryonic antigen in patients with cervical cancer treated with concurrent chemoradiotherapy. *Int J Gynecol Cancer*. 2007;17(4):872–878.
286. Crombach G, et al. Detection of squamous cell carcinoma antigen in normal squamous epithelia and in squamous cell carcinomas of the uterine cervix. *Cancer*. 1989;63(7):1337–1342.
287. Duk JM, et al. Elevated levels of squamous cell carcinoma antigen in patients with a benign disease of the skin. *Cancer*. 1989;64(8):1652–1656.
288. Bolger BS, et al. Prognostic value of preoperative squamous cell carcinoma antigen level in patients surgically treated for cervical carcinoma. *Gynecol Oncol*. 1997;65(2):309–313.
289. Duk JM, et al. Pretreatment serum squamous cell carcinoma antigen: a newly identified prognostic factor in early-stage cervical carcinoma. *J Clin Oncol*. 1996;14(1):111–118.
290. Massuger LF, et al. Improvement of clinical staging in cervical cancer with serum squamous cell carcinoma antigen and CA 125 determinations. *Gynecol Oncol*. 1997;64(3):473–476.
291. Scambia G, et al. Squamous cell carcinoma antigen: prognostic significance and role in the monitoring of neoadjuvant chemotherapy response in cervical cancer. *J Clin Oncol*. 1994;12(11): 2309–2316.
292. Takeshima N, et al. The value of squamous cell carcinoma antigen as a predictor of nodal metastasis in cervical cancer. *Gynecol Oncol*. 1998;68(3):263–266.
293. Gaarenstroom KN, et al. Clinical value of pre-treatment serum Cyfra 21-1, tissue polypeptide antigen, and squamous cell carcinoma antigen levels in patients with cervical cancer. *Cancer*. 1995;76(5):807–813.
294. Hong JH, et al. The prognostic significance of pre- and posttreatment SCC levels in patients with squamous cell carcinoma of the cervix

- treated by radiotherapy. *Int J Radiat Oncol Biol Phys*. 1998;41(4):823–830.
295. Bonfrer JM, et al. Cyfra 21-1 in monitoring cervical cancer: a comparison with tissue polypeptide antigen and squamous cell carcinoma antigen. *Anticancer Res*. 1997;17(3C):2329–2334.
 296. Scambia G, et al. Multiple tumour marker assays in advanced cervical cancer: relationship to chemotherapy response and clinical outcome. *Eur J Cancer*. 1996;32A(2):259–263.
 297. Bae SN, et al. Prognostic significance of pretreatment squamous cell carcinoma antigen and carcinoembryonic antigen in squamous cell carcinoma of the uterine cervix. *Gynecol Oncol*. 1997;64(3):418–424.
 298. Pras E, et al. Serum squamous cell carcinoma antigen and CYFRA 21-1 in cervical cancer treatment. *Int J Radiat Oncol Biol Phys*. 2002;52(1):23–32.
 299. Ogino I, et al. The role of pretreatment squamous cell carcinoma antigen level in locally advanced squamous cell carcinoma of the uterine cervix treated by radiotherapy. *Int J Gynecol Cancer*. 2006;16(3):1094–1100.
 300. Hung YC, et al. Early predicting recurrent cervical cancer with combination of tissue polypeptide specific antigen (TPS) and squamous cell carcinoma antigen (SCC). *Neoplasma*. 2002;49(6):415–417.
 301. Sturgeon CM, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers. *Clin Chem*. 2010;56(6):e1–48.
 302. Gocze PM, Vahrson HW, Freeman DA. Serum levels of squamous cell carcinoma antigen and ovarian carcinoma antigen (CA 125) in patients with benign and malignant diseases of the uterine cervix. *Oncology*. 1994;51(5):430–434.
 303. Yoon SM, et al. Use of serum squamous cell carcinoma antigen for follow-up monitoring of cervical cancer patients who were treated by concurrent chemoradiotherapy. *Radiat Oncol*. 2010;5:78.
 304. Rose PG, et al. Serum squamous cell carcinoma antigen levels in invasive cervical cancer: prediction of response and recurrence. *Am J Obstet Gynecol*. 1993;168(3 Pt 1):942–946.
 305. Roijer E, et al. Squamous cell carcinoma antigen isoforms in serum from cervical cancer patients. *Tumour Biol*. 2006;27(3):142–152.
 306. Tsai SC, Kao CH, Wang SJ. Study of a new tumor marker, CYFRA 21-1, in squamous cell carcinoma of the cervix, and comparison with squamous cell carcinoma antigen. *Neoplasma*. 1996;43(1):27–29.
 307. Bonfrer JM, et al. Prognostic significance of serum fragments of cytokeratin 19 measured by Cyfra 21-1 in cervical cancer. *Gynecol Oncol*. 1994;55(3 Pt 1):371–375.
 308. Ferdeghini M, et al. Determination of serum levels of different cytokeratins in patients with uterine malignancies. *Anticancer Res*. 1994;14(3B):1393–1397.
 309. Ferdeghini M, et al. Serum CYFRA 21-1 assay in squamous cell carcinoma of the cervix. *Anticancer Res*. 1993;13(5C):1841–1844.
 310. Callet N, et al. Cancer of the uterine cervix: sensitivity and specificity of serum Cyfra 21.1 determinations. *Eur J Gynaecol Oncol*. 1998;19(1):505–506.
 311. Tomas C, et al. Use of various epithelial tumor markers and a stromal marker in the assessment of cervical carcinoma. *Obstet Gynecol*. 1991;77(4):566–572.
 312. Duk JM, et al. Tumor markers CA 125, squamous cell carcinoma antigen, and carcinoembryonic antigen in patients with adenocarcinoma of the uterine cervix. *Obstet Gynecol*. 1989;73(4):661–668.
 313. Borrás G, et al. Tumor antigens CA 19.9, CA 125, and CEA in carcinoma of the uterine cervix. *Gynecol Oncol*. 1995;57(2):205–211.
 314. Avall-Lundqvist EH, et al. Prognostic significance of pretreatment serum levels of squamous cell carcinoma antigen and CA 125 in cervical carcinoma. *Eur J Cancer*. 1992;28A(10):1695–1702.
 315. Duk JM, et al. Adenocarcinoma of the uterine cervix. Prognostic significance of pretreatment serum CA 125, squamous cell carcinoma antigen, and carcinoembryonic antigen levels in relation to clinical and histopathologic tumor characteristics. *Cancer*. 1990;65(8):1830–1837.
 316. Leminen A, et al. Chemotherapy as initial treatment for cervical carcinoma: clinical and tumor marker response. *Acta Obstet Gynecol Scand*. 1992;71(4):293–297.
 317. Lam CP, et al. Evaluation of carcinoembryonic antigen, tissue polypeptide antigen, and squamous cell carcinoma antigen in the detection of cervical cancers. *Zhonghua Yi Xue Za Zhi (Taipei)*. 1992;50(1):7–13.
 318. Gokul G, et al. DNA methylation profile at the DNMT3L promoter: a potential biomarker for cervical cancer. *Epigenetics*. 2007;2(2):80–85.
 319. Brown CA, et al. Role of protein biomarkers in the detection of high-grade disease in cervical cancer screening programs. *J Oncol*. 2012;289–315.
 320. von Knebel Doeberitz M, et al. Biomarkers for cervical cancer screening: the role of p16(INK4a) to highlight transforming HPV infections. *Expert Rev Proteomics*. 2012;9(2):149–163.
 321. Zhang X, et al. Detection of circulating Bmi-1 mRNA in plasma and its potential diagnostic and prognostic value for uterine cervical cancer. *Int J Cancer*. 2012;131(1):165–172.
 322. Su PH, et al. Epigenetic silencing of PTPRR activates MAPK signaling, promotes metastasis and serves as a biomarker of invasive cervical cancer. *Oncogene*. 2012.
 323. Nam JH, et al. Urinary gonadotropin fragment, a new tumor marker. III. Use in cervical and vulvar cancers. *Gynecol Oncol*. 1990;38(1):66–70.
 324. Carter PG, et al. Measurement of urinary beta core fragment of human chorionic gonadotropin in women with vulvovaginal malignancy and its prognostic significance. *Br J Cancer*. 1995;71(2):350–353.

Cancer Prevention Strategies

MARY B. DALY

INTRODUCTION

As our knowledge of the genetic, physiologic, environmental, and lifestyle factors associated with the carcinogenic process grows, the prevention of cancer is increasingly becoming a reality and being incorporated into oncology practice. Options for the primary prevention of cancer are expanding and include avoidance of carcinogens (e.g., smoking cessation, sun avoidance, removal of asbestos), diet modification, exercise, and weight loss, use of cancer vaccines, prophylactic surgery, and chemoprevention. It is estimated that avoidance of tobacco, sun exposure, and elimination of obesity could have a major public health impact on cancer incidence, as well as other chronic conditions. Options for secondary prevention through screening for occult disease when treatment may be more effective are also becoming more sophisticated. Great strides have been made in the prevention of many of the most common cancers.

The most common risk factor for lung cancer, which is the largest cause of death from cancer for both men and women, is tobacco use. Primary prevention strategies, including tax increases on tobacco products, restrictions on smoking in public places, and the physiologic and psychologic treatment of nicotine addiction have all contributed to the reduction in smoking prevalence rates and the decrease in the incidence of lung cancer (1,2). Recently, low-dose spiral CT scans have been shown to detect early-stage lung cancer and result in a reduction in lung cancer mortality (3,4).

Nonsteroidal anti-inflammatory drugs reduce the risk of adenomatous polyps and invasive cancer among individuals with very high risks of colon cancer due to hereditary syndromes (5). Their use for primary prevention among individuals at average risk, however, is not recommended due to potential side effects. Perhaps the greatest contribution to the prevention of colorectal cancer is the increasing adoption of screening colonoscopy to identify and remove premalignant polyps (6).

Large randomized trials have established the efficacy of both tamoxifen and raloxifene to prevent estrogen receptor positive breast cancer (7,8). With the demonstration of the increased risk in breast cancer associated with combined estrogen and progesterone hormone replacement therapy by the Women's Health Initiative, the use of these products has declined significantly, and the decline is thought to be associated with a subsequent decrease in breast cancer incidence (9,10). Both prophylactic mastectomy and prophylactic oophorectomy reduce the risk of breast cancer and are considered options for women with hereditary syndromes that convey high rates of breast and ovarian cancer (11). Advances in screening modalities for breast cancer, including the increasing adoption of digital mammography and the use of screening breast MRI in selected high-risk individuals

has improved the detection of early-stage occult cancers, and has led to a down staging of disease (12,13).

A large randomized trial of finasteride, which reduces the androgenic stimulation of the prostate, produced a 25% reduction in prostate cancer incidence (14). Several other agents have been proposed as chemopreventive agents for prostate cancer, but so far none have proven efficacy. The role of prostate cancer screening with digital rectal exam and serum PSA levels among average risk men has recently been challenged (15). The role of screening high-risk men, African American men and those with a family history of this cancer, is the subject of ongoing studies.

The prevention of gynecologic cancer is becoming a reality due to the recognition that the initiation and progression of gynecologic cancers is a multistep process characterized by distinct molecular genetic events that provide opportunities to intervene in the carcinogenic process at several steps and reverse its early stages. The concept of preventing gynecologic cancer is based on an understanding of causally related risk factors, their role in carcinogenesis, and opportunities for their avoidance and/or reversal of their effect. There are 3 distinct models that can be applied to gynecologic cancer prevention: (a) *risk avoidance and adoption of protective practices* includes the identification of key risk factors and the development of strategies for their avoidance. Included in risk avoidance are the avoidance of exogenous and endogenous exposures (chemical, hormonal, infectious, etc.) and the avoidance of risky health behaviors. The adoption of protective practices, such as vaccination with the human papillomavirus (HPV) vaccine, a healthy diet, and exercise, may forestall early premalignant events; (b) the use of *chemopreventive agents*, both natural and synthetic, to reverse early, premalignant changes; and (c) *surgical prophylaxis* to remove either healthy at-risk organs or tissues with premalignant changes.

In addition to establishing valid interventions for cancer prevention, it is important to identify optimal target populations for their application, and to tailor the interventions to the level of risk. Interventions for use in the general population at average risk must be highly effective, safe, inexpensive, and socially acceptable. Population groups with high risks may tolerate interventions that confer more risk and higher costs. All prevention efforts are greatly enhanced by public and professional education about their use and by a health care system that values, promotes, and invests in prevention activities.

The avoidance of environmental, occupational, and lifestyle risk factors through public education and social policies has the potential to prevent a large proportion of human cancer. The epidemiological literature has provided a wealth of information about the risks associated with cancers of the cervix, uterus, and ovary, which allows us to devise risk avoidance and risk reduction strategies. This chapter focuses on the opportunities for primary prevention of these three cancers and directions for the future.

CERVIX CANCER

Risk Factors

There are approximately 13,000 new cases of cervical cancer per year in the United States, and over 4,000 women die of the disease. The disease burden is not distributed equally but is overrepresented in the United States among African American, Hispanic/Latina, and American Indian women (16). The greatest burden of cervical cancer is in the developing countries (Fig. 6.1), which account for 86% of the cases and 88% of deaths (17). Traditionally, the most significant factor associated with the risk of cervical cancer has been number of sexual partners and the early onset of sexual activity. This observation has led to the discovery that the primary cause of cervical cancer, and its precursor, intraepithelial lesions, is persistent infection with HPV, which is sexually transmitted. The HPVs are a large (over 100 types) family of viruses that infect skin and mucosa (Fig. 6.2). Of the approximately 40 HPV types that infect the genital tract, about one-half are associated with anogenital warts and are considered low risk for malignancy, or nononcogenic. The other half may give rise to a range of anogenital cancers, including cervix, vulva, and anus in women, and penis and anus in men, and are referred to as high-risk or oncogenic (18). HPV types 16 and 18 alone account for >70% (Fig. 6.3) of all cervical cancers. Similarly, HPV types 6 and 11 account for >90% of all anogenital warts. In the United States, where the median age of sexual debut is 17 years, close to 20% of girls are sexually active by age 15 years, and close to 60% are sexually active at age 18 years. As a result, the infection rate of HPV among the general population is high, peaking in the second and third decades of life when infection rates range from

27% to 46% (19). The median length of infection is 8 to 12 months, and most individuals have cleared the virus by 2 years. A small proportion, 10% to 13%, however, develop chronic persistent HPV infection, which can lead to genital warts, cervical dysplasia, carcinoma *in situ*, and invasive cancer (Fig. 6.4). Persistence of HPV infection is likely to be related to modifying factors, including immune status, the use of oral contraceptives (OCP), smoking, and infection with other sexually transmitted diseases (20). Prolonged duration of OCP use is thought to function as a promoter of HPV-related carcinogenesis, not as a facilitator of HPV infection, although the mechanisms are uncertain (21). Tobacco carcinogens have been found in cervical secretions, and it is postulated that smoking constituents may interact with HPV to induce immunologic changes leading to cervical dysplasia, or may produce genomic damage via genotoxins (22,23).

The HPVs are nonenveloped, double-stranded DNA viruses whose circular DNA encodes eight genes, six early genes, which encode nonstructural proteins (E1, E2, E3, E4, E5, and E6) responsible for viral replication and transcription, and two late genes (L1 and L2), which encode the structural components of the viral capsid. HPV can infect the basal cells of the cervical epithelium and replicate in an extrachromosomal form. In HPV-related malignancy, the virus can integrate into cellular DNA and interact with p53 and RB (retinoblastoma), which prolongs the cell cycle, inhibits apoptosis, and can result in malignant transformation (24). Another potential mechanism for carcinogenesis that has been observed in HPV-16-infected cells is aberrant mitotic spindle pole formation resulting in genetic instability (25). The recent production of prophylactic vaccines that induce the generation of neutralizing antibodies to certain oncogenic types of HPV, therefore, represents a major breakthrough in the prevention of cervical cancer.

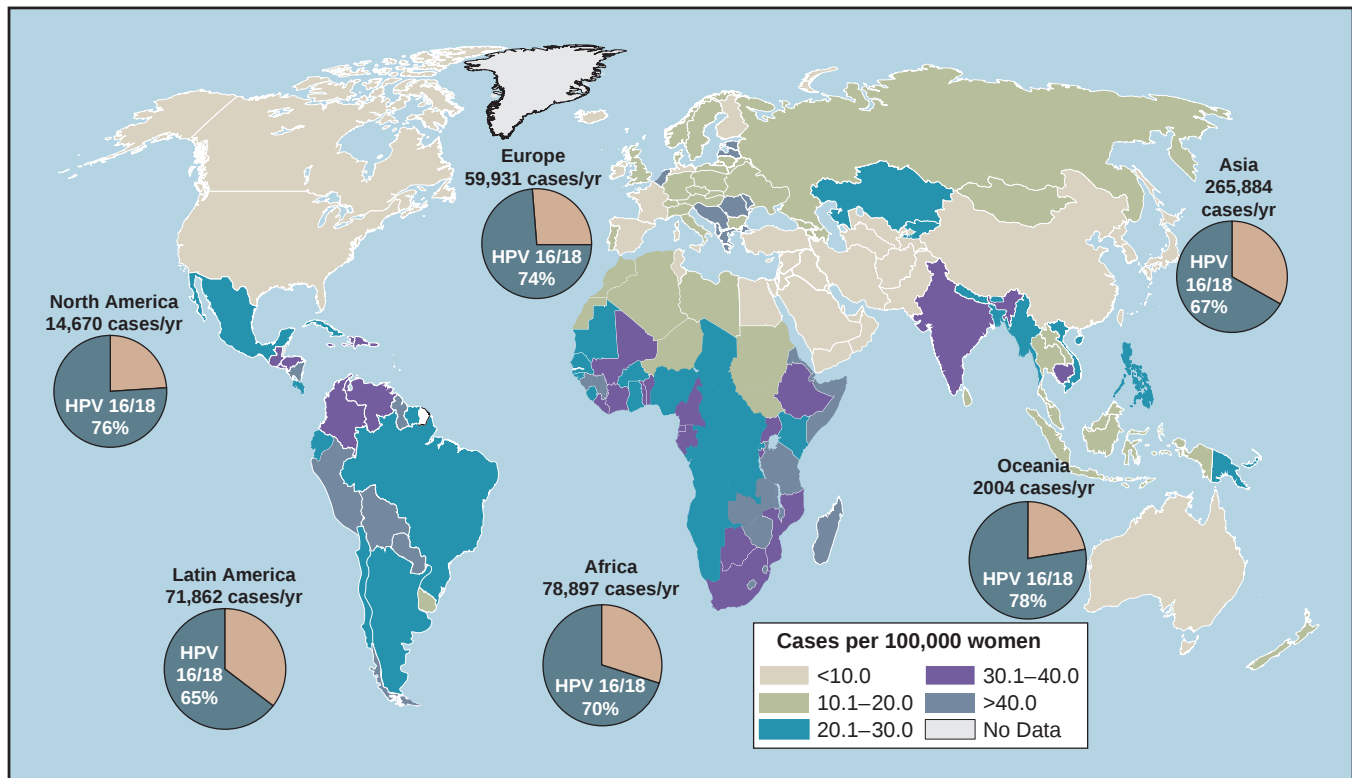


FIGURE 6.1. Age-standardized rates of new cases of cervical cancer per 100,000 women, 2002.



FIGURE 6.2. Human papillomavirus.

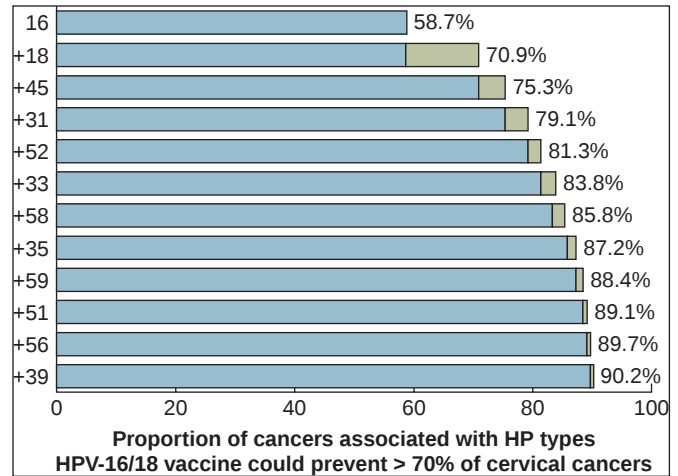


FIGURE 6.3. HPV types in cervical cancer.

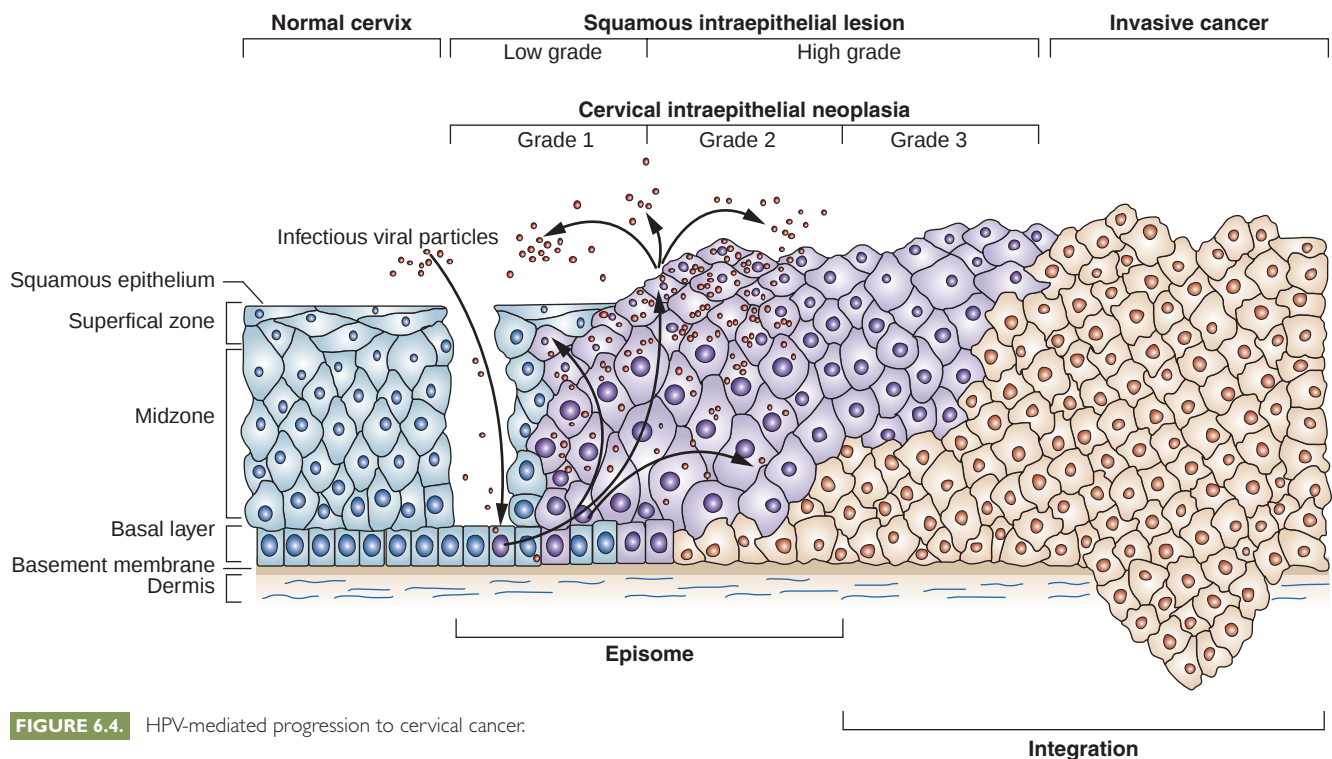


FIGURE 6.4. HPV-mediated progression to cervical cancer.

Prevention

Risk Reduction and/or Adoption of Healthy Practices

Cervical cancer prevention requires decreasing the risk of infection with oncogenic strains of HPV. Having few sexual partners and the use of condoms have been associated with a reduced risk for cervical cancer (26). Avoidance of those factors that enhance the persistence of HPV infection, viz. smoking and OCP use, has the potential to reduce the rate of malignant change. OCPs, however, are the most effective means of contraception, and their avoidance overall is not a wise public health strategy. Safe and effective vaccines now offer the best option for cervical cancer prevention. Early studies in animal models provided

the proof of principle that neutralizing antibodies, directed to determinants on the major viral capsid protein, were generated by infection with HPV and could be detected in the serum. In the early 1990s it was found that the L1 protein, when expressed in recombinant vectors, self-assembled into virus-like particles (VLPs), which closely resemble the antigenic characteristics of the wild-type virions. VLPs formulated on aluminum adjuvants were shown to induce a strong virus-neutralizing antibody response in nonhuman primates (27,28), leading to their development for human populations. A series of phase 1 trials in humans tested the immunogenicity and safety of monovalent VLP-based vaccines and found that they generated levels of neutralizing antibodies that far exceeded those seen in natural infections, and were sustained at long-term follow-up. The predominant antibody responses are of the immunoglobulin G1

(IgG1) subclass (18). In these early trials, vaccine efficacy against infection with HPV-16/18 and against CIN 2+ at 6.4 years of follow-up was 100% (29).

Subsequently, 2 vaccines have been developed for use in humans, Gardasil (Merck), a quadrivalent vaccine that includes HPV-16, -18, -6, and -11 and is formulated with aluminum adjuvant, and a bivalent vaccine Cervarix (GlaxoSmithKline), which includes HPV-16 and -18 and is formulated with a proprietary adjuvant, AS04, which contains aluminum and a bacterial lipid. Gardasil has undergone several randomized, placebo-controlled trials among over 21,000 women. In a U.S. multicenter proof of principle study, 2,391 young women aged 16 to 25 were assigned to a monovalent yeast-derived HPV-16L1 VLP, formulated on aluminum adjuvant, by intramuscular injection at day 0, month 2, and month 6 or placebo. The primary outcomes were persistent HPV-16 infection and HPV-16-related carcinoma *in situ* CIN 2 and 3. At a follow-up of 48 months, administration of the three-dose regimen of HPV-16 vaccine resulted in a 94% reduction in persistent HPV infection in those treated according to protocol. The vaccine was 100% effective in protecting against HPV-16-related CIN 2 and 3 (30).

A phase 2 dose-ranging assessment of immunogenicity and efficacy was conducted in the United States, Brazil, and Europe among 552 women aged 16 to 23 years. Women were randomized to 1 of 3 vaccine doses versus placebo given at day 1, month 2, and month 6. At close to 3 years of follow-up, vaccine efficacy for reduction of persistent HPV infection was 90% and for clinical disease (cytologic abnormalities, CIN, cervical cancer, or external genital lesions) was 100%. Vaccine efficacy was similar for each of the three doses. All women who received the vaccine developed high antibody titers by month 7 (31). Early data on vaccine efficacy found similar results with 2 versus 3 doses, which if borne out, is likely to improve compliance (32).

The two pivotal phase 3 trials enrolled more than 18,000 women and included both precancerous lesions, CIN 2, CIN 3, adenocarcinoma *in situ* (AIS), or invasive cervical cancer with documented HPV-16 or -18 in DNA from the involved tissue, vulvar and vaginal lesions, and genital warts as outcomes. Women with evidence of previous infection with HPV, or with cytologic abnormalities, were not excluded. At 3 years, vaccine efficacy in those women treated according to protocol was 99%, with only one case of CIN 3 occurring among the vaccine recipients. In the intent to treat population, which included women with prevalent HPV-16/18 infection and women who did not complete the vaccination schedule, CIN 2/3 and AIS were reduced by 44% (33,34). The vaccine was also efficacious against high-grade vulvar and vaginal lesions (35). To

investigate the efficacy of Gardasil among older women, 3,891 women aged 24 to 45 years were randomized to vaccine or placebo. Efficacy against persistent infection and cervical lesions was 89% (36). Side effects in all of the studies were minimal and included discomfort at the injection site and occasional mild fever. Anti-HPV antibody titers remain high 5 years after administration. In June 2006, Gardasil received FDA approval for the vaccination of women aged 9 to 26, followed closely by approval for its use in children and adults aged 9 to 26 years by the European Commission.

The initial trial of Cervarix randomized 1,113 women aged 15 to 25 years to receive a bivalent HPV-16, -18 vaccine versus placebo. No cases of persistent HPV-16 or HPV-18 were seen in the women vaccinated according to protocol, whereas there were seven cases of infection in the control group. The vaccine was 95% effective against persistent infection and 93% effective against cytologic abnormalities even when including those women who did not complete the vaccine regimen. In an extended follow-up of 776 women, the vaccine continued to demonstrate 98% efficacy at close to 4 years (37,38). The Papilloma TRIal against Cancer In young Adults (PATRICIA) randomized 18,644 women to 3 doses of Cervarix versus hepatitis A vaccine. At a mean of 34.9 months follow-up, HPV vaccine efficacy, assessed in women who were seronegative DNA for HPV-16/18 at baseline, against CIN 2+ lesions was 92% (39).

There was also efficacy against CIN 3+, especially in the 15- to 17-year age group (40). Furthermore, the vaccine provided cross-protective efficacy against 4 oncogenic nonvaccine types: HPV-33, HPV-31, HPV-45, and HPV-51 (41).

Overall, achieving close to 100% effective vaccination of a cohort of 12-year-old girls is estimated to result in a 76% reduction in the incidence of cervical cancer (42). Mathematical modeling has been used to estimate the clinical benefits and cost-effectiveness of a population-based HPV-16/18 vaccination program in Africa (Fig. 6.5). Parameters considered were the natural history of HPV and cervical cancer, age at vaccination, vaccine cost, vaccine efficacy, waning immunity, the risk of replacement with other oncogenic strains of HPV, age at onset of screening, and screening intervals. A review of 27 studies of cost-effectiveness models found considerable variability in the incremental cost-effectiveness ratios (ICER) due to the different assumptions made. Overall, however, the implementation of routine vaccination programs for adolescent girls is consistently shown to be cost-effective compared to screening alone (43). The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends routine vaccination for HPV of girls age 11 to 12 (range, 9 to

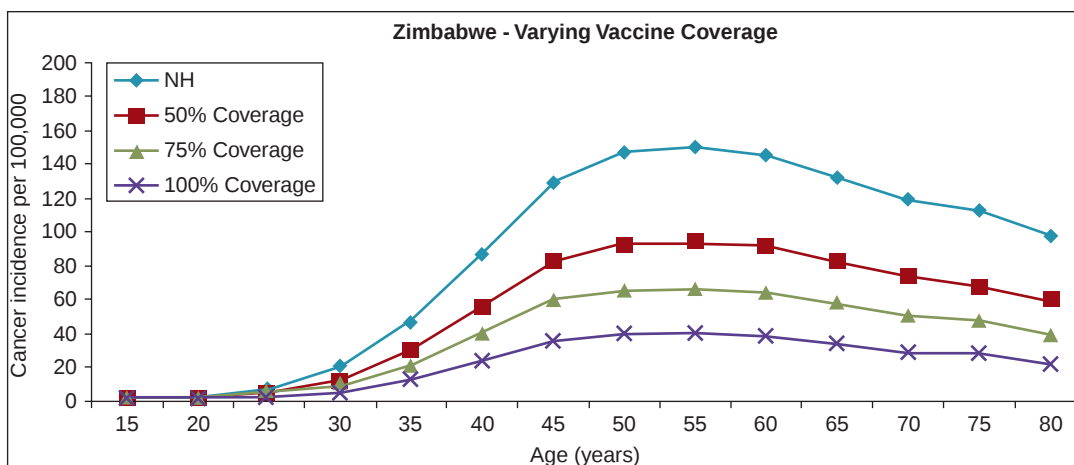


FIGURE 6.5. Impact of HPV-16/18 vaccines on incidence of cervical cancer.

26 years) and has added Gardasil to its Vaccines for Children program (44,45). Similarly, the American Academy of Pediatrics recommends that all girls should be vaccinated against HPV at age 11 to 12 years (46).

Both Gardasil and Cevaxix are licensed for use in the United States for girls aged 11 to 12 years, with catch up vaccination up to age 26 years. Immunogenicity of both vaccines is close to 100% (47).

There are several questions remaining regarding the use of HPV vaccines. The duration of protection afforded by HPV vaccines is not known, although data from animal models report long-lasting protection even with low levels of circulating antibody. Evidence from recent clinical trials in humans suggests persistence of immunity beyond 4 years. The need for a booster dose is at this time unknown. Because the neutralizing antibodies generated by the current vaccines appear to be type specific, it is not clear if there is cross-reactivity with other HPV types. It is also unclear whether vaccinating an adolescent population will be socially acceptable in all cultures. Most of the randomized trials performed to date focused on young women in their late teens and early 20s, an age when sexual activity has likely already begun. Because HPV vaccines are ineffective after infection with HPV, vaccination should occur prior to the onset of sexual activity, or at a younger age. The majority of females will become infected with HPV within 2 to 3 years of the onset of sexual activity. Depending on socio-cultural variations in sexual debut, the target age for vaccination would ideally be girls aged 9 to 12 years. There is currently no systematic vaccination program beyond infancy and preschool in the United States. Although vaccinating older women who are uninfected with HPV has been shown to induce an effective immune response (36), studies have shown that antibody response is higher among younger age groups (30,48).

Another unanswered question is the added benefit of vaccinating males. Although the majority of morbidity associated with HPV is seen in females, males remain the major vector for the disease. Furthermore, both males and females would need to be vaccinated to achieve herd immunity. Information on the natural history of HPV in males is lacking, and vaccination studies to date have focused predominantly on females. One Phase III study of Gardasil in men reported a 90% reduction in HPV-associated external genital lesions (32). Among women, the impact of effective vaccination on subsequent screening practices is not known. There is concern that women who receive the HPV vaccine might be less likely to adhere to screening guidelines because they feel protected from cervical cancer. Women who have been vaccinated will, however, need to continue cytologic screening since the current vaccines do not protect against all oncogenic types, and since some women will have already been infected at the time of vaccination. It is likely, however, that the onset of screening could safely be delayed. Concerns about the impact of HPV vaccination on the subsequent accuracy of cytologic screening have also been raised.

Much work remains to be done to educate the public about HPV and cervical cancer. Recent studies have shown that the majority of women are unaware of the link between HPV and cervical cancer. Awareness of HPV is increased among young women, more educated women, and those with more access to the health care system (49,50). Public health efforts to introduce the vaccine will clearly need to be accompanied by vigorous educational programs directed at both young women and their parents to increase acceptability and the success of the HPV vaccine program. Since the introduction of Gardasil into clinical care, there has been vigorous debate about the issue of compulsory HPV vaccination. Concerns raised include the lack of long-term safety data, the expense of the vaccine, and resistance to governmental coercion (51). Another concern that parent and other groups have expressed is the fear that vaccination against HPV may lead to a sense of invulnerability, would undermine

abstinence-based messages, and may increase high-risk sexual behavior. There is no data, however, to suggest that fear of HPV is an important deterrent from sexual activity in young men or women. Several states have considered legislation to mandate HPV vaccination, although few have actually enacted such laws. All of the proposed laws have opt-out provisions for parents who object. However, they do not address the potential financial burdens imposed by the mandate. Mandating HPV vaccination would certainly boost vaccine coverage rates, but at a price of loss of parental autonomy.

These and other vaccine-related concerns will need to be addressed by primary care providers as well as public health officials. Vaccine delivery by primary care practitioners in the United States is approximately 32% among 13- to 17-year-old girls. In contrast, rates of vaccination completion in the UK and Australia, where vaccine programs are school-based, are much higher ($\geq 84\%$ and $\geq 72\%$, respectively) (52).

The most significant unresolved issue pertains to the application of HPV vaccines to underdeveloped nations, where the greatest burden of disease attributable to HPV is found (Fig. 6.5). Contributing to this burden is a lack of understanding of the dimensions of the disease, weak infrastructures and insufficient funds for population-wide vaccination programs, and a lack of the political will to address a sexually transmitted disease. The delivery of a new vaccine to a nonpediatric population is particularly problematic in countries with limited public health resources. Yet it is precisely in these countries that the potential benefit for a widespread vaccination program is greatest. Administering the vaccine in infancy along with other basic childhood vaccines may be the best choice, even though the duration of protection is at this time unknown. Clearly, the contribution of the international community will be required to make HPV vaccination a reality in the third world.

Chemoprevention

Several promising targets for the chemoprevention of cervical cancer have been identified, including topical retinoids, carotenoids, prostaglandins, indole-3-carbinol, green tea, and immune modulators (53,54). In phase 1 and 2 trials, topical retinoids applied directly to the cervix resulted in significant complete histologic regression of CIN 2 lesions compared to placebo (55). None of the proposed agents, however, have been subject to definitive phase 3 randomized trials.

Surgical Prophylaxis

The introduction of widespread cervical cancer screening using the Papanicolaou (Pap) smear has dramatically reduced the incidence of invasive cervical cancer through the detection of treatable, premalignant lesions, referred to as cervical intraepithelial neoplasia (CIN). Recently, the detection and quantification of oncogenic HPV DNA in cervical epithelial cells has been added to routine Pap screening in selected situations, with demonstrated improvement in sensitivity. Cotesting with HPV DNA detects high-grade lesions earlier, thus providing a subsequent longer low-risk period (56). HPV screening is recommended in women with atypical squamous cells of undetermined significance (ASCUS) on cytology, cotesting with cytology in asymptomatic women aged 30 and older, among whom a positive HPV screen is thought to represent persistent infection, and in follow-up of treated individuals for more aggressive detection and management of persistent HPV infection (19,57). Its use in asymptomatic women under the age of 30 leads to overdiagnosis because of the transient nature of infection in this age group. Studies of cost-effectiveness of cotesting with HPV DNA and cytology offer a cost saving by allowing for a reduction in the frequency of screening (58).

Transient HPV infections are associated with low-grade lesions (CIN 1). When oncogenic HPV infections persist, the

Table 6.1 Cervix Cancer—Major Points

Virtually all cervix cancer is related to persistent infection with HPV

HPV infection is common, affects up to 50% of women, and peaks in the second and third decades of life

Altered immune status, smoking, and the use of OCPs affect the rate of persistent HPV infection

Cervical cancer is a leading cause of cancer morbidity and mortality among women in the underdeveloped world

Two HPV vaccines have shown high efficacy in eliminating persistent HPV infection and cervical lesions in previously uninfected women

HPV, human papillomavirus; OCPs, oral contraceptives.

viral genome is integrated into the host genome and cervical lesions progress to more advanced lesions (CIN 2 and VIN 3) (57). Because of the high rate of spontaneous regression, management of women with CIN 1 and satisfactory colposcopy (visualization of the entire squamocolumnar junction) is repeat cytology at 6 and 12 months or DNA testing for oncogenic types of HPV at 12 months. Alternatively, ablative (cryotherapy, electrocoagulation, or laser vaporization) or excisional (cold-knife conization or loop electrosurgical excision procedure [LEEP]) treatment may be offered. If the entire squamocolumnar junction cannot be visualized, an excisional procedure is the preferred approach. Treatment of CIN 2-3 lesions with satisfactory colposcopy involves excision or ablation of the entire transformation zone rather than just the colposcopically identified lesion (59). Cryotherapy, laser vaporization, and LEEP all appear to be effective modalities, although over time LEEP has become the procedure most widely chosen. When colposcopy is not satisfactory, a diagnostic excisional procedure is recommended. A variety of posttreatment surveillance protocols utilizing cervical cytology with or without colposcopy and HPV testing at frequent intervals have been proposed. Hysterectomy is reserved for recurrent or persistent biopsy-confirmed CIN 2-3, for positive margins when repeat diagnostic excision is not possible, or for women with persistent CIS who have been previously treated and who no longer desire fertility (60). This approach to cervical cancer prevention based on large-scale cytologic screening programs is not feasible, however, in countries in the developing world, due to lack of infrastructure, funding, and public health education (Tables 6.1 and 6.2).

Table 6.2 Cervix Cancer—Remaining Questions

What is the duration of protection of HPV vaccines?

What is the extent of cross-vaccination with the current HPV vaccines?

What is the socio-cultural acceptability of vaccinating adolescent girls?

What is the added benefit of vaccinating males?

What is the impact of effective vaccination on subsequent screening practices and screening performance?

Which methods will best educate the public about HPV vaccines?

How should HPV vaccines be made available to underdeveloped nations?

What are the best cervical cancer screening approaches for use in the underdeveloped countries?

HPV, human papillomavirus.

OVARIAN CANCER

Risk Factors

Ovarian cancer is the most common cause of death from a gynecologic cancer in the United States and accounts for approximately 15,500 deaths per year (16). Worldwide there are 192,000 new cases per year. Ovarian cancers are categorized as serous, endometrioid, clear cell, and mucinous. These categories are further divided into high-grade and low-grade. High-grade serous cancer represents the majority of epithelial ovarian cancer (70%) (61). Due to a lack of effective screening tools to identify ovarian cancer at early, highly curable stages, the majority of ovarian cancers are diagnosed at advanced stages when survival is poor. Historically, the origin of epithelial ovarian cancer was believed to be from the invagination of ovarian surface epithelium (OSE) into the ovarian stroma forming inclusion cysts, which had the potential to undergo malignant transformation (62). The recent adoption of prophylactic salpingo-oophorectomy for women with deleterious mutations in *BRCA1* and *BRCA2*, however, has challenged that theory. Careful examination of the fallopian tubes obtained at the time of prophylactic surgery has identified a high prevalence of occult primary serous carcinomas and serous tubal intraepithelial carcinomas (STIC) in the fimbrial end of the fallopian tube. Both lesions are often accompanied by p53 mutations, suggesting that STIC is the precursor lesion for invasive ovarian carcinoma. While these changes were originally thought to be present only in women with *BRCA1* or *BRCA2* mutations, there is growing evidence pointing to the existence of these precursor lesions among women who develop sporadic serous ovarian cancer (63). The distal fallopian tube, therefore, is increasingly being seen as the origin of tubal, ovarian, and peritoneal serous ovarian cancer. The fallopian tube is also implicated in the presentation of endometrioid and clear cell ovarian cancers, which are attributed to the passage of endometriosis tissue from the uterus through the fallopian tube to implant on the surface of the ovary or the peritoneum where it can undergo malignant transformation (64).

While our understanding of the biology of epithelial ovarian cancer is rapidly advancing, most of our current knowledge regarding risks for ovarian cancer has emerged from the epidemiologic literature. Advancing age, reproductive factors (specifically, nulliparity), and heredity are established risk factors for the disease. The majority of ovarian cancers are diagnosed after menopause. Rates are higher in nulliparous women, while parity has been found to offer protection. The risk of ovarian cancer is increased twofold in women who are infertile, and the risk appears to be independent of fertility drug treatment (65). Chronic inflammation, with its attendant increase in cell proliferation and potential for DNA disruption, has been proposed as a precursor for many cancers, including ovarian cancer. Endometriosis and pelvic inflammatory disease, both of which induce chronic inflammatory states, are associated with ovarian cancer (64).

Although the majority of cases of ovarian cancer are sporadic, approximately 5% to 10% are thought to fit a hereditary pattern of autosomal dominant inheritance. Epidemiologic studies have estimated a two- to fourfold increase in risk among first-degree relatives of women with ovarian cancer. Recently, a number of genes have been identified that account for a large percentage of hereditary ovarian cancer and that allow more precise estimates of risk. Since the identification of *BRCA1* on chromosome 17q in 1994, and *BRCA2* on chromosome 13q in 1995, several hundred mutations in these genes have been characterized, many of which lead to premature truncation of protein transcription and, therefore, presumably defective gene products. Ovarian cancer in these families is characterized by multiple cases of ovarian and breast cancer in successive generations, earlier age of onset, and evidence of both maternal and paternal transmission (Fig. 6.6). The penetrance of *BRCA1/2*,

of ovarian cancer provides new opportunities to understand the biology of the disease and to devise novel preventive strategies.

Prevention

Risk Avoidance and/or Adoption of Protective Practices

The available evidence regarding factors that lower ovarian cancer risk has been based primarily on the results of case-control studies retrospectively comparing the reproductive, hormonal, or behavioral characteristics of ovarian cancer cases with matched controls, not on prospective randomized trials. These studies have consistently shown an inverse association of ovarian cancer with increasing parity, with the first birth conferring significantly more protection (35%) than subsequent births (15%). The protective effect of pregnancy occurs regardless of fertility history and is not age dependent (68). Pregnancy is characterized by a prolonged period of anovulation as well as high levels of circulating progesterone, which may cause terminal differentiation of premalignant cells (69,70).

The evidence supporting a protective effect of breast-feeding against epithelial ovarian cancer risk is weak and inconsistent. Some studies suggest a 10% to 20% decrease in ovarian cancer risk associated with breast-feeding. In those studies that are positive, the impact of breast-feeding on ovarian cancer risk appears to be greatest for the first 6 months of lactation with no apparent increase in ovarian cancer protection with longer-term lactation (71,72).

Several studies have examined the association of hormone replacement therapy (HRT) with ovarian cancer risk. While the majority find a modest increase in risk, most lack statistical significance. The strongest association is seen in endometrioid histologies, where relative risks range from 1.2 to 5.5 (73).

Several retrospective and prospective studies have examined associations between dietary factors and ovarian cancer risk. Modest levels of protection have been reported for fruits and vegetables in general, and for vitamin A and β -carotene in particular, although findings are inconsistent (74,75). While there is some case-control data that invasive ovarian cancer is reduced among women who report frequent high-intensity exercise, the relationship between physical activity and ovarian cancer risk is inconsistent, and may differ by histologic type (65,76,77).

Chemoprevention

The majority of theoretical models of ovarian cancer chemoprevention have been based on the assumption that the origin of ovarian cancer is the OSE. As the paradigm has shifted to identifying the epithelial surface of the fallopian tube as the site of origin, it is not clear how to interpret the previous theories. Prior research has explored the presence of receptors for most members of the steroid hormone superfamily, including receptors for progestins, retinoids, androgens, and vitamin D. Progestins, retinoids, and vitamin D have been shown to exert a broad range of common biologic effects in epithelial cells, including induction of apoptosis, upregulation of transforming growth factor- β (TGF- β), cellular differentiation, and inhibition of proliferation. In addition to hormonal agents, there is growing evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) may have ovarian cancer preventive effects (78). *It is yet to be demonstrated that these agents are active in the fallopian tube epithelium.*

To date, only OCP use has been consistently shown to be protective against ovarian cancer. OCPs were first introduced in the United States in the 1960s. Most formulations include estrogen, progesterone, or a combination of the 2. In addition to suppressing ovulation, OCPs also reduce pituitary secretion of

gonadotropins and protect against chronic inflammation associated with pelvic inflammatory disease (79). In addition to these potential mechanisms, a 3-year study on primates demonstrated that the progestin component of an OCP had a potent effect on apoptotic and TGF- β signaling pathways in the ovarian epithelium, raising the possibility that progestin-mediated biologic effects may underlie the protective effects of OCPs (80). The use of OCPs appears to decrease a woman's risk for ovarian cancer by 30% to 60%. Risk reduction is apparent with as little as 3 months of use, increases in magnitude with increased duration of use, and persists for as long as 10 years after discontinuation of use. The risk reduction applies to nulliparous as well as parous women, to all histologic subtypes, including tumors of low malignant potential, to women with a hereditary risk for ovarian cancer, is consistent across races, and is independent of age at use or menopausal status (70,81,82). Although there has never been a randomized clinical trial to demonstrate the protective effect of OCPs on ovarian cancer risk, it is often recommended empirically to women with a family history of ovarian cancer to reduce their risk.

Epidemiologic and laboratory evidence suggest a potential role for retinoids as preventive agents for ovarian cancer (83). Retinoids are natural and synthetic derivatives of vitamin A. They have great potential for cancer prevention, due to a broad range of important biologic effects on epithelial cells, including inhibition of cellular proliferation, induction of cellular differentiation, induction of apoptosis, cytostatic activity, and induction of TGF- β . The most significant evidence supporting a rationale for retinoids as chemopreventive agents for ovarian cancer is that of a chemoprevention study in Italy, which suggested an ovarian cancer preventive effect from the retinoid 4-HPR. Among women randomized to receive either 4-HPR or placebo in a trial designed to evaluate 4-HPR as a chemopreventive for breast carcinoma, significantly fewer ovarian cancer cases were noted in the 4-HPR group as compared to controls (84).

Vitamin D is a fat-soluble vitamin that is essential as a positive regulator of calcium homeostasis. The vitamin D receptor and the retinoic acid receptors share strong homology and readily dimerize, making it likely that vitamin D and retinoids have common signaling pathways in the cell (85). Vitamin D has been shown to have diverse biologic effects in epithelial cells relevant to cancer prevention, including retardation of growth, induction of cellular differentiation, induction of apoptosis and upregulation of TGF- β (86). With regard to ovarian cancer, a recent study has correlated population-based data regarding ovarian cancer mortality in large cities across the United States with geographically based long-term sunlight data reported by the National Oceanic and Atmospheric Administration. The study demonstrated a statistically significant inverse correlation between regional sunlight exposure and ovarian mortality risk suggesting that sunlight induces production of native vitamin D in the skin (87). However, a systematic review of 20 ecologic and case-control studies failed to find consistent evidence for a relationship between vitamin D exposure and ovarian cancer incidence or mortality (88).

Epidemiologic studies have suggested that use of NSAIDs may lower ovarian cancer risk (89). Several biologic mechanisms have been proposed to account for the chemopreventive effects of NSAIDs, including inhibition of ovulation, inhibition of COX, and downregulation of prostaglandins, enhancement of the immune response, and induction of apoptosis (70,90,91). Similarly, dietary antioxidants have shown an inverse association with ovarian cancer (92). Despite a growing body of preclinical data indicating chemopreventive effects of several agents, clinical research exploring their efficacy to reduce rates of ovarian cancer is hindered by the relatively low incidence of the disease, insufficient understanding of the preclinical course of ovarian cancer, the lack of validated preclinical biomarkers, and inadequate screening strategies.

Surgical Prophylaxis

For women with a family history of ovarian cancer, or a hereditary pattern of breast cancer, bilateral salpingo-oophorectomy (BSO) has been shown to lower the risk of subsequent epithelial ovarian cancer by 80% to 95% (66,93). Prospective follow-up of a large international cohort of 2,482 *BRCA* carriers found not only a lower risk of ovarian cancer, but also a significantly lower all-cause mortality (HR 0.40; 95% CI, 0.26–0.61) and ovarian cancer specific mortality (HR 0.21; 95% CI, 0.06–0.76). There is also a 50% reduction in rates of breast cancer in women who undergo prophylactic BSO (94). Occult invasive and *in situ* tumors have been found at the time of BSO in 2% to 10% of *BRCA1/2* mutation carriers (95), a large proportion of which occur in the fimbrial end of the fallopian tube (79,96), emphasizing the need for both deliberate removal of the fallopian tubes at the time of prophylactic surgery, and of careful pathologic examination of the surgical specimen (97). The incidence of primary peritoneal cancer following BSO is reported to be approximately 2% to 5% (98). Because the median age of diagnosis of ovarian cancer among women with a hereditary risk is 50 years, the recommended age for prophylactic surgery is at the completion of childbearing, or at age 35 to 40 years. Although the incidence of premenopausal ovarian cancer is higher in *BRCA1* carriers than *BRCA2* carriers, removal of the ovaries before menopause is recommended for both groups given the added benefit of breast cancer risk reduction, which is highest for women who undergo the surgery before natural menopause (17). In addition, because there is an approximate 15% risk of ovarian cancer after age 60 years among *BRCA* carriers, BSO is also justified at older ages for women who still have intact ovaries (99).

Women undergoing prophylactic hysterectomy for a deleterious mutation related to Lynch syndrome are also counseled to remove their ovaries because of the approximate 10% to 12% incidence of ovarian cancer (100).

In addition to the significant reduction in ovarian cancer incidence associated with BSO, several studies have found a significant decline in ovarian cancer worry and anxiety following the procedure (101). These potential benefits of prophylactic oophorectomy must, however, be weighed against its adverse consequences, including the short- and long-term surgical risks, the physical and psychological impact of early menopause, and the potential subsequent risks of cardiovascular disease and osteoporosis related to early estrogen/progesterone depletion (102). Although the use of combined estrogen/progesterone HRT has been associated with an increased risk for breast cancer among postmenopausal women in the general population, one study with short follow-up found no increased risk of breast cancer among *BRCA1/2* mutation carriers who took HRT following BSO (11). Also, data from the Mayo Clinic showed that there was no increase in breast cancer among women under the age of 50 years undergoing BSO (103). Women seeking information regarding prophylactic oophorectomy should be counseled about the practical short- and long-term sequelae of the surgery, the risks and benefits of postoperative HRT, and the small potential for primary peritoneal cancer.

Given the recent evidence that a majority of ovarian cancers arise in the fimbrial end of the fallopian tube, an alternative surgical procedure, radical fimbriectomy, has been introduced. The principle is that complete removal of both fallopian tubes will remove the source of the premalignant changes in the fallopian tube, which give rise to serous ovarian cancer. In addition, removing the tubes will prevent any endometrial tissue from reaching the ovary or peritoneal cavity. Because prospective data to establish the efficacy of this approach are lacking, and because there is still a proportion of ovarian cancer that may arise out of inclusion cysts in the ovary, radical fimbriectomy is currently proposed as a temporary solution which will prolong the production of ovarian hormone for *BRCA1/2* carriers, thus postponing the onset of premature menopause (104,105).

Table 6.3 Ovarian Cancer—Major Points

Several risk factors, including age, nulliparity, and family history, have been identified for ovarian cancer

Germ-line mutations in the *BRCA1/2* genes and the DNA mismatch repair genes associated with Lynch syndrome significantly increase the risk of ovarian cancer

Primary cancer of the fallopian tube is considered a component of the hereditary ovarian cancer syndromes

The fimbrial end of the fallopian tube, not the ovarian surface epithelium, has been identified as the source of most serous ovarian cancers

OCPs confer significant protection from ovarian cancer and the level of protection is related to the duration of use

Tubal ligation also confers significant protection from ovarian cancer, although the physiologic mechanism is unknown

Prophylactic bilateral salpingo-oophorectomy is the most effective method of preventing ovarian cancer in women with a hereditary pattern of ovarian cancer

Radical fimbriectomy has been proposed as a temporary alternative to bilateral salpingo-oophorectomy to forestall surgical menopause

No effective method of screening for ovarian cancer has been identified

OCPs, oral contraceptives.

Tubal ligation has been associated with lower ovarian cancer risk in both case-control and cohort studies. A strong inverse association was observed between tubal ligation and ovarian cancer risk in the Nurses Health Study, with a relative risk (RR) of 0.33 (CI, 0.16–0.64) after controlling for age, OCP use, and parity (106). A recent meta-analysis of 13 case-control, retrospective, and prospective studies found that tubal ligation reduced the risk of invasive epithelial ovarian cancer by 34% (RR 0.66; 95% CI, 0.60–0.73) (107). The International *BRCA1/2* Carrier Cohort Study found a 52% reduction in ovarian cancer among *BRCA1* carriers who had undergone tubal ligation (82). Proposed mechanisms include changes in local or circulating hormones, reduced access of carcinogens to the ovary, or a reduction in inflammatory processes. As it appears that a significant proportion of ovarian cancers arise in the fallopian tube, tubal ligation may reduce the risk by compromising the blood supply to the fimbrial end of the fallopian tube. Although the protective effect of tubal ligation appears to be substantial, the ability to perform BSO using a laparoscopic approach would seem to make this procedure a preferable choice among women with an increased risk of ovarian cancer (Tables 6.3 and 6.4).

Because of the risk reduction associated with BSO among high-risk women, some have advocated the routine removal

Table 6.4 Ovarian Cancer—Remaining Questions

What is the duration of latent, preclinical ovarian cancer?

What is the percentage of high-grade serous ovarian cancers that arise in the fallopian tube?

Can effective screening strategies, using biomarkers and/or imaging studies, be identified?

Are there effective chemopreventive agents that will reduce the risk of ovarian cancer?

What degree of protection from ovarian cancer does radical fimbriectomy confer?

of the ovaries among all women undergoing hysterectomy for benign conditions. However, data do not support the removal of the ovaries at the time of hysterectomy for benign disease in women at average risk of ovarian cancer, among whom the negative cardiovascular and metabolic impact of early surgical menopause outweighs any potential benefit (108,109).

ENDOMETRIAL CANCER

Risk Factors

Endometrial cancer is the most common gynecologic cancer in the United States. Over 45,000 new cases are diagnosed each year, and there are 8,100 deaths annually (16). Unlike many other tumors, the incidence and mortality from endometrial cancer is increasing, with a lifetime risk of 3% and a 16% risk of death (110,111). The increasing incidence of endometrial cancer is thought by some to be related to the increased prevalence of obesity (112). Worldwide, there are 287,900 estimated new cases per year (113). The relatively low case fatality rate is due to early detection and treatment of early-stage disease. The majority of risk factors associated with type 1 (endometrioid) endometrial cancer, viz. increased age, nulliparity, early age at menarche, late age at menopause, obesity, long-term use of unopposed estrogen replacement therapy, polycystic ovary syndrome (PCOS), and the use of tamoxifen, are all thought to exert their effect through estrogen-induced endometrial proliferation leading to hyperplasia and malignant transformation. The increased risk associated with diabetes, hypertension, and thyroid disease also suggests a role for altered growth hormone pathways in addition to the steroid hormone pathways (Fig. 6.8). There are also genetic syndromes associated with endometrial cancer. Women with germ-line mutations in the DNA repair genes associated with the HNPCC or Lynch syndrome

have a 40% to 60% risk of endometrial cancer. The mean age at diagnosis in this group is approximately 50 years (67). Epigenetic silencing of the Lynch syndrome genes by hypermethylation is also thought to contribute to endometrial cancer risk (114). Endometrial cancer is also a component of Cowden syndrome, in which it is estimated that mutations in the PTEN gene confer a lifetime risk for endometrial cancer of approximately 6%, with most cases occurring between the ages of 38 and 59 years (115). Type 2 serous endometrial cancer is uncommon and is not related to unopposed estrogen exposure.

Prevention

Risk Avoidance and Uptake of Protective Behaviors

It has been estimated that approximately 40% of endometrial cancers are attributable to excess body weight in developed countries (112) (Fig. 6.9). Maintenance of ideal body weight, regular physical activity, and control of diseases associated with endometrial cancer (diabetes, hypertension, and thyroid disease) are prudent approaches to reduce disease risk. Vigorous physical activity helps to control, prevent, or reverse weight gain, improve insulin sensitivity and reduce circulating estrogen levels, thus leading to a 22% reduction in endometrial cancer (116). Tamoxifen is a proven chemotherapeutic strategy to reduce the incidence of breast cancer in women at increased risk. While acting as an estrogen antagonist in the glandular epithelium of the breast, tamoxifen acts as an agonist in the endometrium, increasing the risk of postmenopausal bleeding, endometrial hyperplasia, endometrial polyps, and endometrial cancer. Although the absolute numbers were small, the relative risks for endometrial cancer in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) for women on the tamoxifen arm compared to placebo were

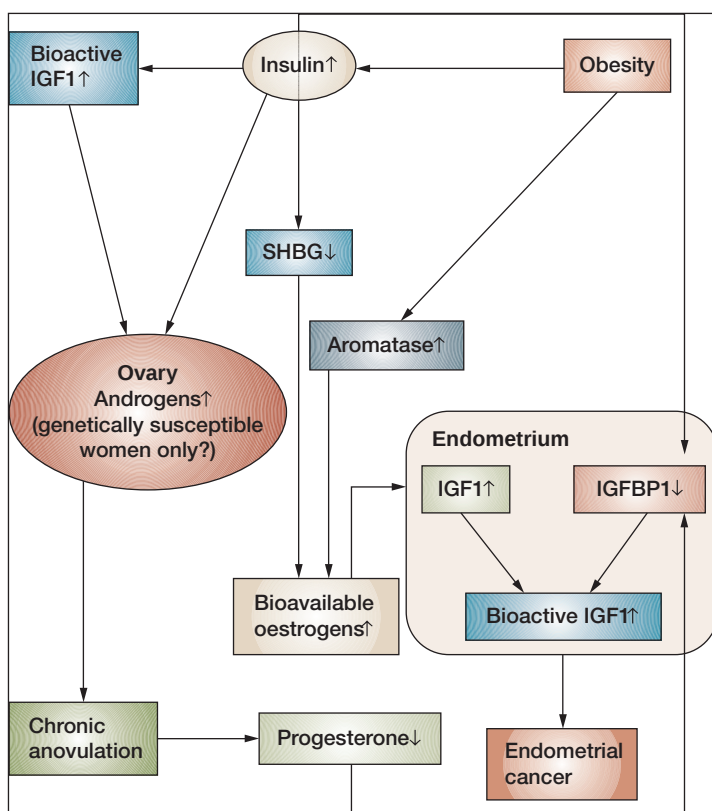


FIGURE 6.8. Molecular pathways involved in obesity and endometrial cancer.

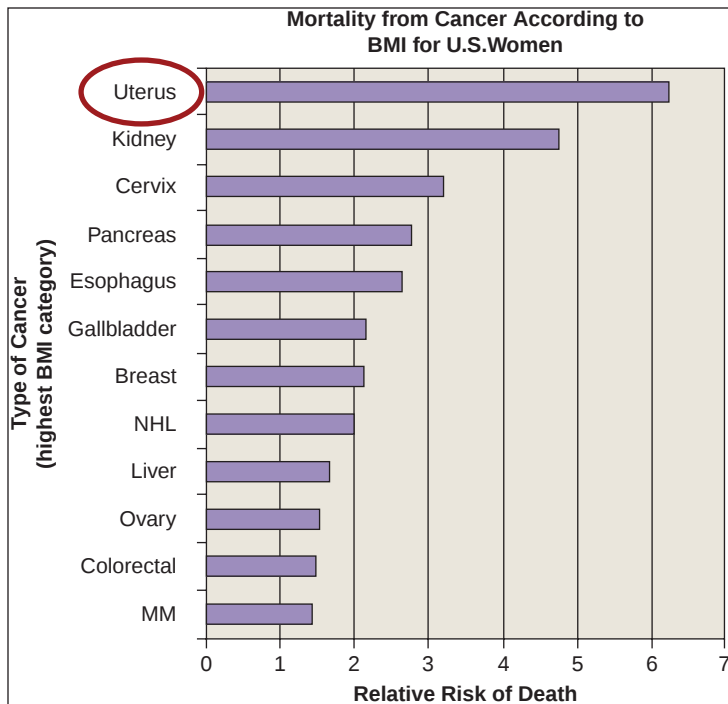


FIGURE 6.9. Relative risk of death among US women by BMI.

2.53 (95% CI, 1.35–4.97) for all women, and 4.01 (95% CI, 1.70–10.90) for women aged 50 years and older (117). Women considering the use of tamoxifen for breast cancer risk reduction should carefully weigh the greater than two-fold risk of endometrial cancer with the benefits as they make their decision (118).

Chemoprevention

The addition of a progestin to the estrogen component of HRT has been shown to eliminate the increased risk of endometrial cancer. Progesterone controls many pathways resulting in growth inhibition and tissue homeostasis, and reverses the estrogen effect on the endometrium, thus preventing the development of hyperplasia. The use of combined estrogen and progesterone OCP decreases the risk of endometrial cancer by 50%, although their effectiveness in obese women is not clear (119). Oral progestins have long been used to reverse premalignant hyperplasia and to prevent the development of endometrial carcinoma (111). More recently, progestin-releasing intrauterine devices (IUDs), which deliver local therapy to the endometrium and spare some of the systemic effects, have been studied as an alternative to oral progestins both for women with early-stage endometrial cancer who desire to preserve fertility, and among those taking adjuvant tamoxifen following breast cancer treatment (115,120).

Surgical Prophylaxis

It is thought that the majority of invasive endometrial cancers progress through a series of premalignant stages, simple hyperplasia, complex hyperplasia, simple atypical hyperplasia, and complex atypical hyperplasia, all of which may present with abnormal vaginal bleeding (121). Conservative management of these conditions involves the use of progestational agents, which results in a complete regression of atypical hyperplasia in 50% to 94% of cases. Even in complete responders, however, there is a high rate of recurrence, and definitive therapy of atypical hyperplasia is hysterectomy (53). Among women with documented germ-line mutations associated with the Lynch syndrome, a retrospective study found that prophylactic hysterectomy conferred 100% protection from subsequent endometrial cancer (122). Because of the high success rate for endometrial cancer treatment,

Table 6.5 Endometrial Cancer—Major Points

The major risk factors for type 1 endometrial cancer exert their effect through estrogen stimulation of the endometrial surface epithelium.

Altered growth hormone pathways may also be involved in endometrial carcinogenesis.

Hereditary forms of endometrial cancer have been associated with the Lynch syndrome and with Cowden syndrome.

The majority of endometrial cancers present at an early stage with abnormal uterine bleeding.

Endometrial cancer screening is not recommended for the general population, although women with a hereditary risk are recommended to undergo annual endometrial biopsy.

Prophylactic hysterectomy in high-risk women has been shown to protect women from subsequent endometrial cancer.

however, it is not clear if this protection would translate into a significant survival benefit. This study also found 100% protection from ovarian cancer, which may warrant the consideration of prophylactic total abdominal hysterectomy–bilateral salpingo-oophorectomy (TAH-BSO) in this population. Alternatively, routine endometrial biopsies starting at age 30 to 35 years may be suggested in women with Lynch syndrome to detect early, premalignant endometrial lesions (123) (Tables 6.5 and 6.6).

Table 6.6 Endometrial Cancer—Remaining Questions

Can interventions targeting weight control and physical activity impact the incidence of endometrial cancer?

What are the most effective forms of progesterone-containing contraceptive preparations for reducing the incidence of endometrial cancer?

Does prophylactic hysterectomy translate into a survival benefit?

FUTURE DIRECTIONS

The prevention of gynecologic malignancies involves many disciplines and requires the collaboration of basic scientists, clinicians, behavioral scientists, and policy makers. The successful development of the HPV vaccines is a major breakthrough in the prevention of cervical cancer and will likely

undergo further improvements and refinements. Advances in molecular genetics, molecular pathology, and molecular imaging will contribute to the early identification of specific markers of premalignant change associated with gynecologic malignancies. The identification of safe and effective chemopreventive agents will provide additional strategies for prevention. Accompanying this progress will be the need to address the psychosocial and cultural barriers to the adoption of preventive strategies.

REFERENCES

- Bala MM, Lesniak W, Strzeszynski L. Efficacy of pharmacological methods used for treating tobacco dependence: meta-analysis. *Pol Arch Med Wewn.* 2008;118(1)–(2):20–28.
- Bala MM, Lesniak W. Efficacy of non-pharmacological methods used for treating tobacco dependence: meta-analysis. *Pol Arch Med Wewn.* 2007;117(11)–(12):504–511.
- Bach PB, Mirkkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer. *JAMA.* 2012;307(22):2418–2429.
- Tanner NT, Mehta H, Silvestri GA. New testing for lung cancer screening. *Oncology.* 2012;26(2):176–182.
- Burn J, Gerdes A, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet.* 2011;378:2081–2087.
- Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin.* 2008;58:130–160.
- Fisher B, Costantino J, Wickerham D, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 2005;97(22):1652–1662.
- Vogel V, Costantino J, Wickerham D, et al. Update of the national surgical adjuvant breast and bowel project study of tamoxifen and raloxifene (STAR) P-2 trial: preventing breast cancer. *Cancer Prev Res.* 2010;3(6):696–706.
- Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA.* 2010;304(15):1684–1692.
- Majumdar SR, Almasi EA, Stafford RS. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *JAMA.* 2004;292:1983–1988.
- Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol.* 2005;23(31):7804–7810.
- Boetes C. Update on screening breast MRI in high-risk women. *Obstet Gynecol Clin N Am.* 2011;38:149–158.
- Berg WA, Zhang Z, Lehrer D. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA.* 2012;307(13):1394–1404.
- Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003;349:215–224.
- Moyer VA on behalf of the U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157(2):120–134.
- Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2012;62(1):10–29.
- Sahasrabudhe VV, Parham GP, Mwanahamuntu MH, et al. Cervical cancer prevention in low-and middle-income countries: feasible, affordable, essential. *Cancer Prev Res.* 2011;5(1):11–17.
- Stanley M. HPV vaccines. *Best Pract Res Clin Obstet Gynaecol.* 2006;20(2): 279–293.
- Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guideline for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012;62(3):147–172.
- Garland SM, Quin MA. How to manage and communicate with patients about HPV? *Int J Gynecol Obstet.* 2001;94(suppl. 1):S106–S112.
- Moreno V, Bosch FX, Munoz N, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet.* 2002;359(9312):1085–1092.
- McCann ME, Irwin DE, Walton LA, et al. Nicotine and cotinine in the cervical mucus of smokers, passive smokers, and nonsmokers. *Cancer Epidemiol Biomarkers Prev.* 1992;1(2):125–129.
- McIntyre-Seltman K, Castle PE, Guido R, et al. Smoking is a risk factor for cervical intraepithelial neoplasia grade 3 among oncogenic human papillomavirus DNA-positive women with equivocal or mildly abnormal cytology. *Cancer Epidemiol Biomarkers Prev.* 2005;14(5):1165–1170.
- Tomson TT, Roden RB, Wu TC. Human papillomavirus vaccines for the prevention and treatment of cervical cancer. *Curr Opin Investig Drugs.* 2004;5(12):1247–1261.
- Duensing S, Lee LY, Duensing A, et al. The human papillomavirus type 16 E6 and E7 oncoproteins cooperate to induce mitotic defects and genomic instability by uncoupling centrosome duplication from the cell division cycle. *Proc Natl Acad Sci USA.* 2000;97(18):10002–10007.
- Bailey J, Cymet TC. Planning for the HPV vaccine and its impact on cervical cancer prevention. *Compr Ther.* 2006;32(2):102–105.
- Lowe RS, Brown DR, Bryan JT, et al. Human papillomavirus type 11 (HPV-11) neutralizing antibodies in the serum and genital mucosal secretions of African green monkeys immunized with HPV-11 virus-like particles expressed in yeast. *J Infect Dis.* 1997;176(5):1141–1145.
- Palker TJ, Monteiro JM, Martin MM, et al. Antibody, cytokine and cytotoxic T lymphocyte responses in chimpanzees immunized with human papillomavirus virus-like particles. *Vaccine.* 2001;19(27):3733–3743.
- The GlaxoSmithKline Vaccine HPV-007 Study Group. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomized placebo-controlled trial up to 6.4 years. *Lancet.* 2009;374:1975–1985.
- Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstet Gynecol.* 2006;107(1):18–27.
- Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol.* 2005;6(5):271–278.
- ACOG Practice Bulletin. Hereditary breast and ovarian cancer syndrome. *Gynecol Oncol.* 2009;113:6–11.
- Shi L, Sings HL, Bryan JT, et al. Gardasil: prophylactic human papillomavirus vaccine development—from bench top to bed-side. *Clin Pharmacol Ther.* 2007;81(2):259–264.
- FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007;356(19):1915–1927.
- Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet.* 2007;369(9574):1693–1702.
- Castellsagué X, Muñoz N, Pitsuttithum P, et al. End-of study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age. *Br J Cancer.* 2011;105:28–37.
- Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet.* 2004;364(9447):1757–1765.
- Harper DM, Franco EL, Wheeler CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet.* 2006;367(9518):1247–1255.
- Paavonen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet.* 2009;374:301–314.

40. Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomized double-blind PATRICIA trial. *Lancet Oncol*. 2012;13:89–99.
41. Wheeler CM, Castellsague X, Garland S, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomized, double-blind PATRICIA trial. *Lancet Oncol*. 2010;13:100–110.
42. Kohli M, Ferko N, Martin A, et al. Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK. *Br J Cancer*. 2007;96(1):143–150.
43. Seto K, Marra F, Raymakers A, et al. The cost effectiveness of human papillomavirus vaccines: a systematic review. *Drugs*. 2012;72(5):715–743.
44. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-2):1–24.
45. Charo RA. Politics, parents, and prophylaxis—mandating HPV vaccination in the United States. *N Engl J Med*. 2007;356(19):1905–1908.
46. Committee on Infectious Diseases. HPV vaccine recommendations. *Pediatrics*. 2012;129(3):602–605.
47. Grant LA, Dunne EF, Chesson H, Markowitz LE. Considerations for human papillomavirus (HPV) vaccination of mid-adult women in the United States. *Vaccine*. 2011;29:2365–2370.
48. Block SL, Nolan T, Sattler C, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics*. 2006;118(5):2135–2145.
49. Moreira ED Jr, de Oliveira BG, Neves RC, et al. Assessment of knowledge and attitudes of young uninsured women toward human papillomavirus vaccination and clinical trials. *J Pediatr Adolesc Gynecol*. 2006;19(2):81–87.
50. Tiro JA, Meissner HI, Kobrin S, et al. What do women in the U.S. know about human papillomavirus and cervical cancer? *Cancer Epidemiol Biomarkers Prev*. 2007;16(2):288–294.
51. Colgrove J, Abiola S, Mello MM. HPV vaccination mandates – lawmaking amid political and scientific controversy. *NEJM*. 2010;363(8):785–791.
52. Wheeler CM. Less is more: a step in the right direction for Human Papillomavirus (HPV) vaccine implementation. *JNCI*. 2011;103(19):1424–1425.
53. Alberts DS, Barakat RR, Daly M, et al. Prevention of gynecologic malignancies. In: Gershenson DM, McGuire WP, Gore M, et al., eds. *Gynecologic Cancer Controversies in Management*. Philadelphia: Elsevier Ltd.; 2004:883–919.
54. Zou C, Liu H, Feugang JM, et al. Green tea compound in chemoprevention of cervical cancer. *Int J Gynecol Cancer*. 2010;20(4):617–624.
55. Meyskens FL Jr, Surwit E, Moon TE, et al. Enhancement of regression of cervical intraepithelial neoplasia II (moderate dysplasia) with topically applied all-trans-retinoic acid: a randomized trial. *J Natl Cancer Inst*. 1994;86(7):539–543.
56. Ronco G, Giorgi-Rossi P, Carozzi C, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomized controlled trial. *Lancet Oncol*. 2010;11:240–257.
57. Brown AJ, Trimble CL. New technologies for cervical cancer screening. *Best Pract Res Clin Obstet Gynaecol*. 2011; doi:10.1016/j.bpobgyn.2011.11.001.
58. Kulasingam S, Havrilesky L. Health economics of screening for gynaecological cancers. *Best Pract Res Clin Obstet Gynaecol*. 2012;26:163–173.
59. Spitzer M, Apgar BS, Brotzman GL. Management of histologic abnormalities of the cervix. *Am Fam Physician*. 2006;73(1):105–112.
60. Wright TC Jr, Cox JT, Massad LS, et al. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. *J Low Genit Tract Dis*. 2003;7(3):154–167.
61. Tone AA, Salvador S, Finlayson SJ, et al. The role of the fallopian tube in ovarian cancer. *Clin Adv Hematol Oncol*. 2012;10(5):295–306.
62. Mingels MJJM, Roelofsen T, van der Laak JAWM, et al. Tubal epithelial lesions in salpingo-oophorectomy specimens of BRCA mutation carriers and controls. *Gynecol Oncol*. 2012; doi:10.1016/j.ygyno.2012.06.015.
63. Crum CP, McKeon FD, Xian W. BRCA, the oviduct, and the space and time continuum of pelvic serous carcinogenesis. *Int J Gynecol Cancer*. 2012;22:S29–S34.
64. Nezhat F, Datta MS, Hanson V, et al. The relationship of endometriosis and ovarian malignancy: a review. *Fertil Steril*. 2008;90(5):1559–1570.
65. Hanna L, Adams M. Prevention of ovarian cancer. *Best Pract Res Clin Obstet Gynaecol*. 2006;20(2):339–362.
66. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst*. 2009;101:80–87.
67. Celentano V, Luglio G, Antonelli G, et al. Prophylactic surgery in Lynch syndrome. *Tech Coloproctol*. 2011;15:129–134.
68. Whiteman DC, Murphy MF, Cook LS, et al. Multiple births and risk of epithelial ovarian cancer. *J Natl Cancer Inst*. 2000;92(14):1172–1177.
69. Pike MC, Pearce CL, Wu AH. Prevention of cancers of the breast, endometrium and ovary. *Oncogene*. 2004;23(38):6379–6391.
70. Barnes MN, Grizzle WE, Grubbs CJ, et al. Paradigms for primary prevention of ovarian carcinoma. *CA Cancer J Clin*. 2002;52(4):216–225.
71. Risch HA, Marrett LD, Howe GR. Parity, contraception, infertility, and the risk of epithelial ovarian cancer. *Am J Epidemiol*. 1994;140(7):585–597.
72. Rosenblatt KA, Thomas DB. Lactation and the risk of epithelial ovarian cancer. The WHO collaborative study of neoplasia and steroid contraceptives. *Int J Epidemiol*. 1993;22(2):192–197.
73. Auranen A, Hietanen S, Salmi T, et al. Hormonal treatments and epithelial ovarian cancer risk. *Int J Gynecol Cancer*. 2005;15(5):692–700.
74. Tung KH, Wilkens LR, Wu AH, et al. Association of dietary vitamin A, carotenoids, and other antioxidants with the risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(3):669–676.
75. Zhang M, D'Arcy C, Holman J, et al. Intake of specific carotenoids and the risk of epithelial ovarian cancer. *Br J Nutr*. 2007;98:187–193.
76. Weiderpass E, Margolis KL, Sandin S, et al. Prospective study of physical activity in different periods of life and the risk of ovarian cancer. *Int J Cancer*. 2006;118(12):3153–3160.
77. Rossing MA, Cushing-Hauger KL, Wicklund KG, et al. Recreational physical activity and risk of epithelial ovarian cancer. *Cancer Causes Control*. 2010;21:485–491.
78. Rodriguez-Burford C, Barnes MN, Oelschlaeger DK, et al. Effects of nonsteroidal anti-inflammatory agents (NSAIDs) on ovarian carcinoma cell lines: preclinical evaluation of NSAIDs as chemopreventive agents. *Clin Cancer Res*. 2002;8(1):202–209.
79. Salvador S, Gilks B, Köbel M, et al. The fallopian tube: primary site of most pelvic high-grade serous carcinomas. *Int J Gynecol Cancer*. 2009;19(1):58–64.
80. Rodriguez GC, Nagarsheth NP, Lee KL, et al. Progesterin-induced apoptosis in the Macaque ovarian epithelium: differential regulation of transforming growth factor-beta. *J Natl Cancer Inst*. 2002;94(1):50–60.
81. Whittemore AS, Balise RR, Pharoah PD, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer*. 2004;91(11):1911–1915.
82. Antoniou AC, Rookus M, Andrieu N, et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the International BRCA1/2 Carrier Cohort Study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):601–610.
83. Brewer MA, Johnson K, Follen M, et al. Prevention of ovarian cancer: intraepithelial neoplasia. *Clin Cancer Res*. 2003;9(1):20–30.
84. De Palo G, Veronesi U, Camerini T, et al. Can fenretinide protect women against ovarian cancer? *J Natl Cancer Inst*. 1995;87(2):146–147.
85. Campbell MJ, Park S, Uskokovic MR, et al. Expression of retinoic acid receptor-beta sensitizes prostate cancer cells to growth inhibition mediated by combinations of retinoids and a 19-nor hexafluoride vitamin D3 analog. *Endocrinology*. 1998;139(4):1972–1980.
86. Studzinski GP, Moore DC. Sunlight—can it prevent as well as cause cancer? *Cancer Res*. 1995;55(18):4014–4022.
87. Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int J Epidemiol*. 1994;23(6):1133–1136.
88. Cook LS, Neilson HJ, Lorenzetti DL, et al. A systematic literature review of vitamin D and ovarian cancer. *Am J Obstet Gynecol*. 2010;203:70.e1–70.e8.
89. Moysich KB, Mettlin C, Piver MS, et al. Regular use of analgesic drugs and ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2001;10(8):903–906.
90. Rodriguez C, Patel AV, Calle EE, et al. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA*. 2001;285(11):1460–1465.
91. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, et al. Aspirin and epithelial ovarian cancer. *Prev Med*. 2001;33(6):682–687.
92. Gates MA, Tworoger SS, Hecht JL, et al. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. *Int J Cancer*. 2007;121:2225–2232.
93. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol*. 2008;26:1331–1337.
94. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. 2010;304(9):967–975.
95. Rabban JT, Barnes M, Chen LM, et al. Ovarian pathology in risk-reducing salpingo-oophorectomies from women with BRCA mutations from women with BRCA mutations, emphasizing the differential diagnosis of occult primary and metastatic carcinoma. *Am J Surg Pathol*. 2009;33(8):1125–1136.

96. Manchanda R, Abdelraheim A, Johnson M, et al. Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. *BJOG Int J Obstet Gynaecol*. 2011;118(7):814–824.
97. Hirst JE, Gard GB, McIlroy K, et al. High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. *Int J Gynecol Cancer*. 2009;19:826–829.
98. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. *JAMA*. 2006;296(2):185–192.
99. Van der Kolk DM, de Bock GH, Leegre BK, et al. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. *Breast Cancer Res Treat*. 2010;124:643–651.
100. Yang KY, Caughey AB, Little SE, et al. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) families. *Fam Cancer*. 2011;10:535–543.
101. Michelson TM, Dørum A, Dahl AA. A controlled study of mental distress and somatic complaints after risk-reducing salpingo-oophorectomy in women at risk for hereditary breast ovarian cancer. *Gynecol Oncol*. 2009;113:128–133.
102. Finch A, Metcalfe KA, Chiang JK, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. *Gynecol Oncol*. 2011;12:163–168.
103. Olson JE, Sellers TA, Iturria SJ, et al. Bilateral oophorectomy and breast cancer risk reduction among women with a family history. *Cancer Detect Prev*. 2004;28(5):357–360.
104. Leblanc E, Narducci F, Farre I. Radical fimbriectomy: a reasonable temporary risk-reducing surgery for selected women with a germ line mutation of BRCA1 or 2 genes? Rationale and preliminary development. *Gynecol Oncol*. 2011;121:472–476.
105. Green MH, Mai PL, Schwartz PE. Does bilateral salpingectomy with ovarian retention warrant consideration as a temporary bridge to risk-reducing bilateral oophorectomy in BRCA1/2 mutation carriers? *Am J Obstet Gynecol*. 2011;204:19e1–6.
106. Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. *JAMA*. 1993;270(23):2813–2818.
107. Cibula D, Widschwendter M, Májek O, et al. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. *Hum Reprod Update*. 2011;17(1):55–67.
108. Hickey M, Ambekar M, Hammond I. Should the ovaries be removed or retained at the time of hysterectomy for benign disease. *Hum Reprod Update*. 2010;16(2):131–141.
109. Berek JS, Chalas E, Edelson M, et al. Prophylactic and risk-reducing bilateral salpingo-oophorectomy: recommendations based on risk of ovarian cancer. *Obstet Gynecol*. 2010;116(3):733–743.
110. Leslie KK, Thiel KW, Yang S. Endometrial cancer: potential treatment and prevention with progestin-containing intrauterine devices. *Obstet Gynecol*. 2012;118(2):419–420.
111. Yang S, Thiel KW, Leslie KK. Progesterone: the ultimate endometrial tumor suppressor. *Trends Endocrinol Metab*. 2011;22(4):145–152.
112. Rice LW. Hormone prevention strategies for breast, endometrial and ovarian cancers. *Gynecol Oncol*. 2010;118:202–207.
113. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69–90.
114. Backes FJ, Cohn DE. Lynch syndrome. *Clin Obstet Gynecol*. 2011;54(2):199–214.
115. Brown AJ, Westin SN, Broaddus RR, et al. Progestin intrauterine device in an adolescent with grade 2 endometrial cancer. *Obstet Gynecol*. 2012;119(2):423–426.
116. Moore SC, Gierach GL, Schatzkin A, et al. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. *Br J Cancer*. 2010;103:933–938.
117. Freedman AN, Yu B, Gail MH, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *J Clin Oncol*. 2011;29:2327–2333.
118. Gabriel EM, Jatoti I. Breast cancer prevention. *Expert Rev Anticancer Ther*. 2012;12(2):223–228.
119. Schmandt RE, Iglesias DA, Co NN, et al. Understanding obesity and endometrial cancer risk: opportunities for prevention. *Am J Obstet Gynecol*. 2011;518–525.
120. Chin J, Konje JC, Hickey M. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev*. 2009;(4):CD007245.
121. Sherman ME, Sturgeon S, Brinton L, et al. Endometrial cancer chemoprevention: implications of diverse pathways of carcinogenesis. *J Cell Biochem Suppl*. 1995;23:160–164.
122. Schmeler KM, Sun CC, Bodurka DC, et al. Prophylactic bilateral salpingo-oophorectomy compared with surveillance in women with BRCA mutations. *Obstet Gynecol*. 2006;108(3 Pt 1):515–520.
123. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. *Acta Obstet Gynecol Scand*. 2011;90:437–444.

7

Preinvasive Disease of the Lower Genital Tract

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INTRODUCTION

At the forefront of any discussion on preinvasive and invasive lesions of the lower genital tract is the Human Papillomavirus (HPV). Infection with HPV is necessary for the development of almost all preinvasive cervical and vaginal lesions, and it is present in roughly half of preinvasive vulvar disease. Moreover, HPV is the most commonly diagnosed sexually transmitted infection in the United States with an overall lifetime prevalence of nearly 80% and a point prevalence of over 40% (1,2). Our knowledge surrounding HPV biology and epidemiology has increased exponentially in the past three decades, leading to improved screening modalities and recommendations as well as development of prophylactic vaccinations.

In this chapter, we will discuss the biology and epidemiology of HPV infections as they relate to cervical, vaginal, and vulvar carcinogenesis. Additionally, we will review clinical and HPV-associated risk factors for development of disease, the pathology of preinvasive lesions including cytology and histology, and discuss efficacy and impact of prophylactic HPV vaccination.

SECTION 1: HPV

Evidence for Causal Relationship

HPV was first proposed as a causative agent in the development of cervical cancer in the 1970s when Dr. Harald zur Hausen, a German physician and virologist, suggested that the same viral particles noted in genital warts may also be responsible for genital tract malignancies (3). This served to contrast the prevailing medical idea at that time that it was likely a herpes simplex virus that might have been the causative agent in cervical neoplasia. His work evolved and eventually in 1983, he isolated HPV type 16 and implicated its role in the development of cervical cancer (4). One year later, he had isolated HPV 18, thus discovering the two HPV types that today are associated with approximately 70% of all cervical cancers worldwide (5). For this body of important work, zur Hausen was awarded the 2008 Nobel Prize in Medicine.

In 1991, the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) concluded that, beyond a reasonable doubt, there is an association between HPV and cervical cancer (6). Though factors such as tobacco use, parity, contraceptive use, and sexual history may increase one's risk for development of the disease, persistent high-risk HPV infection is indisputably the most important causative factor (7). The association between HPV and cervical cancer is far higher than the association between smoking and lung cancer (8).

In fact, all steps, from HPV infection to cervical precancerous lesions, and from cervical carcinoma *in situ* to cancer, have been demonstrated in prospectively followed cohorts (9–11).

Classification of HPV

Papillomaviruses are double stranded DNA viruses that are members of the Alpha genus of the family Papovaviridae. Papillomaviruses are highly species specific and infect a wide range of vertebrate hosts. All papillomaviruses have regulatory, early (E) and late (L) genomic regions. Within a given host species, many types of papillomaviruses exist and this phylogenetic subdivision is determined by the extent of DNA relatedness. Specifically, the E6, E7, and L1 gene sequences must differ from one another by more than 10% to be classified as a distinct type, 2% to 10% to be a subtype, and 2% to be a variant of a subtype.

HPVs are epitheliotropic- infecting epithelial cells of the skin and mucous membranes and causing epithelial proliferation at the site of infection. HPV is currently divided into 120 distinct genotypes, and this list continues to expand (Fig. 7.1) (12). Over 40 types of HPV infect the anogenital tract (13). Traditionally, specific HPV types have been classified as high-risk types based on their potential to cause preinvasive and invasive disease. The most recent meeting of the IARC described 12 α -1 HPV types as high risk. These include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Additionally, HPV 68, in the group α -2A, is categorized as probably carcinogenic (14).

Biology of HPV

HPV is a nonenveloped virus with a proteinaceous coat, which encases and protects the viral DNA. More specifically, the particle is composed of 72 capsomeres made of the viral proteins L1 and L2, also known as the major and minor capsid proteins, respectively. In addition to providing protection for the viral nucleic acid, the capsomeres also serve as the initial interaction site of the viral particle with the host cell.

The HPV genome is circular, double stranded, and contains nearly 8,000 base pairs (Fig. 7.2). The overall organization of various HPV types is similar. The genome contains eight open reading frames, which are transcribed as a single polycistronic mRNA and through alternative splicing mechanisms and ribosomal scanning, this mRNA is translated into the eight proteins E1, E2, E4, E5, E6, E7, L1, and L2.

The HPV genome can be divided into three regions. The first region is the upstream regulatory region (URR), composed of nearly 1,000 base pairs. The URR does not code for proteins but contains binding sites for different cellular transcriptional activators and repressors, which then regulate the expression of the early viral genes (15). This region also contains binding sites

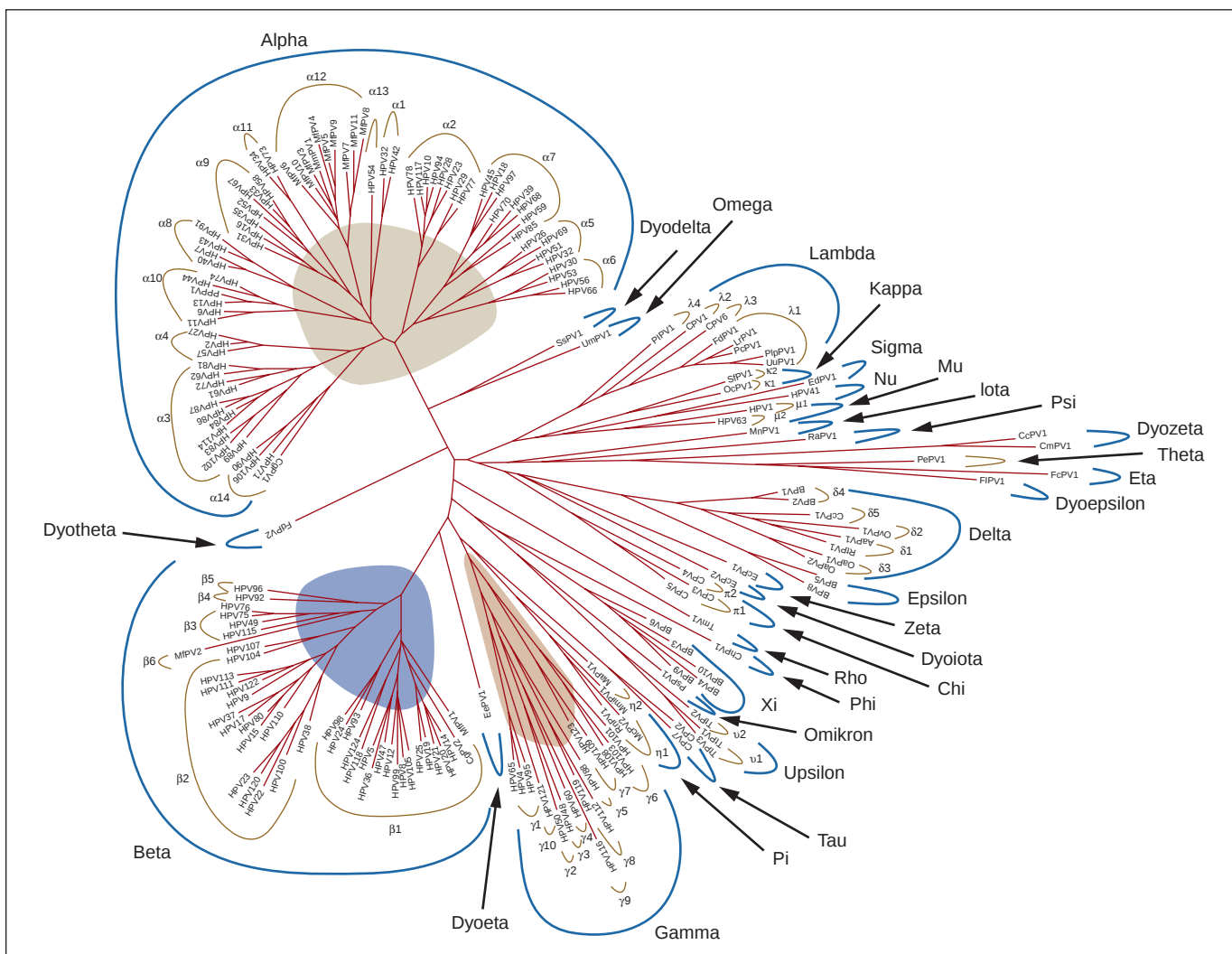


FIGURE 7.1. Papillomavirus phylogenetic tree.

Source: Reprinted with permission from Bernard HU, Burk RD, Chen Z, et al. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* 2010;401:70–79.

for the viral proteins E1 and E2, which initiate viral replication and transcription (16). The URR is necessary for the regulation of gene expression, replication of the genome and packaging of virus particles.

The URR primarily regulates the transcription of proteins in early infection including proteins E6, E7, E1, and E2. The late promoter is activated during the productive phase of the viral life cycle and results in transcription of the capsid proteins (L1 and L2) as well as E1, E2, E4, and E5.

HPV Lifecycle

Like other viruses, HPV must deliver its genome to the host cell and subsequently exploit the cellular machinery for its own purposes. HPV infects the host at sites of epithelial microtrauma, where the HPV particle can gain access to the actively proliferating basal cells of the epithelium (Fig. 7.3). The mechanisms of cell entry are complex and continue to be better elucidated (17). The HPV particle interacts with the cell surface via its major and minor capsid proteins (L1 and L2). α -6-Integrin had initially been suggested as a receptor; however, controversies exist regarding its specific involvement with HPV (18,19). Attachment receptors for HPV particles are likely heparan sulfate proteoglycans

(HSPG), specifically syndecan-1, which is found in the extracellular matrix of epithelial cells (19). Laminin-5 may be another specific extra-cellular matrix receptor involved in binding and cell entry (20,21). Though the main target of HPV are the keratinocytes of the epithelium, HPV virus-like particles have also been shown to attach to cells important in immune function such as dendritic cells and Langerhans cells (22).

The binding of HPV to cell surface receptors in the basal cells over the basement membrane then initiates conformational changes in L2, which exposes additional binding sites (23,24). HPV then enters the cells via endocytosis. Most studies suggest clathrin or caveolin-dependent endocytosis (25), although internalization independent of these proteins has also been described (26).

Once inside the basal epithelial cells, the viral genome begins to replicate and maintains about 50 to 100 copies per cell. The life cycle of HPV is closely linked to the state of differentiation of the squamous epithelium of the natural host tissue. In normal squamous human epithelium, the basal layers (stratum basale) are the areas of active cell division. After division, the daughter cells migrate away from the basal cells (stratum spinosum) and no longer progress through the cell cycle. Instead, these terminally differentiated cells produce high-molecular-weight keratins until eventually the nuclear envelope breaks down and the cells become empty keratin-filled sacs (stratum corneum).

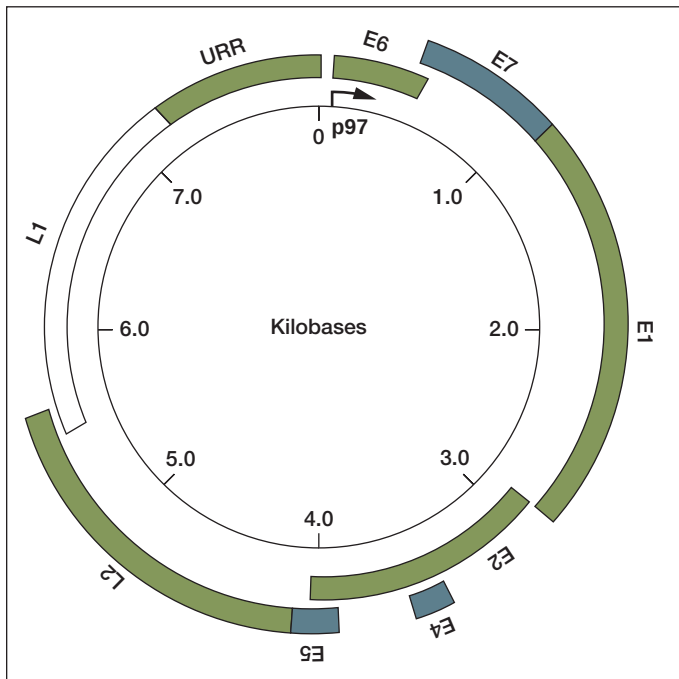


FIGURE 7.2. Schematic of genomic organization of HPV.

Source: Reprinted with permission from Wright TC, Ferency AF, Kurman RJ. Precancerous lesions of the cervix. In: Kurman RJ, ed. *Blaustein's Pathology of the Female Genital Tract*. 4th ed. New York, NY: Springer-Verlag; 1994:229–241.

When the HPV-infected basal cell divides, the viral DNA segregates with the 2 daughter cells, 1 cell remains as part of the basal epithelium while the other migrates to the next layer. Because terminally differentiated cells of the upper epithelial layer contain little or no enzymes, in order to replicate, the virus causes the cell to reenter S phase, causing only partial instead of terminal differentiation. Thus the viral genome replication is synchronous with the cellular DNA replication. HPV infected cells migrate away from the basal layer and as

the cells reach higher epithelial layers the late promoter is activated and late gene transcription and translation occur. There is high-level amplification of the viral genome in these layers and in the uppermost layer, DNA is packaged into capsids and the infectious virions are assembled. Typical HPV-associated cytopathic changes such as koilocytosis, multinucleation, and nuclear enlargement are due to the assembly of the viral particles in the upper epithelial layers. The epithelium is then shed and HPV particles are released, which can then infect a new host.

Oncogenic Proteins

The oncogenic potential of high-risk HPV is primarily attributed to the E6 and E7 proteins. E6 and E7 proteins differ in high-risk and low-risk types. These proteins do not have intrinsic enzymatic activities, but instead interact directly and indirectly with other cellular proteins affecting cell cycle regulation. In addition to their individual effects, their combined effects are likely synergistic. In transgenic mouse models, the combinations of E6 and E7 have resulted in particularly aggressive invasive cancers (27).

HPV E7

The E7 protein is responsible for immortalizing cells infected with HPV, primarily by affecting the cell's transition from G1 into S-phase. E7 has a variety of targets including the retinoblastoma (Rb) protein family, histone deacetylases, cyclins, cyclin-dependent kinases (cdks) and cdk inhibitors (28). E7 is composed of 98 amino acids and is divided into 3 domains. CR1 is the amino terminus consisting of amino acids 1 to 20. The CR2 domain (amino acids 21 to 39) contains a sequence that binds E7 to retinoblastoma tumor-suppressor proteins. The CR3 domain (amino acids 40 to 98) contains zinc finger motifs that are essential for protein folding (29).

Rb proteins regulate the cell cycle by controlling the transition at the G1/S phase. Rb is hypophosphorylated and bound to E2F, a cellular transcription factor. In its bound state, Rb and

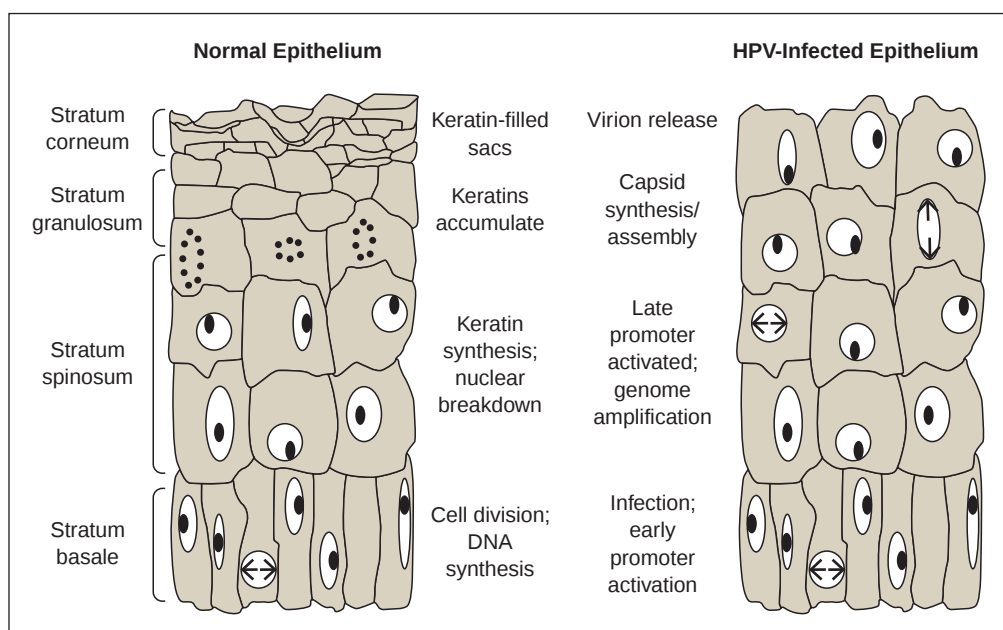


FIGURE 7.3. Diagram of normal epithelium and HPV-infected epithelium.

Source: Reprinted with permission from Hebner CM, Laimins LA. Human papillomaviruses: basic mechanisms of pathogenesis and oncogenicity. *Rev Med Virol* 2006; 16(2):83–97.

E2F inhibit cellular proliferation. In normal cells, when cyclin-kinase complexes phosphorylate Rb, E2F is released and transcription of S phase genes occurs. E7 disrupts this process. The CR1 and CR2 domains of E7 bind to and degrade hypophosphorylated Rb, disrupting the Rb-E2F complex (30,31). E2F is released, which results in the expression of S-phase genes.

The zinc finger region of E7 can interact with the class I histone deacetylases (HDACs). Through deacetylation of histones, HDACs induce chromatin remodeling (32). E7 binding to HDACs causes progression into S-phase thereby lengthening the life of the cell.

Independent of these effects, continuous activity of the E7 protein leads to increasing genomic instability, which leads to more dysregulated cell growth and eventually cancer. It has been observed that cells expressing E7 show irregularities in numerous centrosomes leading to aberrant mitotic spindle poles, thereby affecting chromosome number during replication (33). E7 expression is a late event in malignant transformation.

HPV E6

Like E7, E6 is a small 151 amino acid protein that induces important changes in the host cell. It also lacks endogenous enzymatic activity and binds to cell cycle-regulatory proteins, affecting life cycle and immortalization.

E6's most notable effect is its ability to bind to p53. p53 is a transcriptional activator and is an important tumor-suppressor gene. p53 induces expression of genes involved in apoptosis and cell cycle arrest. p53 levels typically increase in response to stress, DNA damage, or abnormal cellular proliferation (e.g., radiation exposure, hypoxia, and infection). This increase in p53 corresponds to arrest in the G1 phase of the cell cycle, thereby allowing for repair of DNA damage or progression to apoptosis. In HPV infected cells, E6 binds to p53 and causes degradation of the protein through a ubiquitin-dependent pathway. Thus less apoptosis and growth-arrest occurs, leading to cellular proliferation (34).

E6 has also been shown to interact with other proteins that are involved in a variety of cellular functions. E6 binds to transcriptional co-activators CBP/p300, further downregulating p53-mediated transcription (35). E6 also interacts with the PDZ proteins, which are involved in cell signaling and cell-to-cell adhesions, which ultimately affects lifecycle and carcinogenesis (36–38).

In addition to its inhibition of apoptosis through p53 interaction, E6 also upregulates the cellular telomerase complex. By synthesizing new DNA, telomerase maintains the length of the telomeric DNA at each end of a chromosome. Without this, the telomeres shorten with each cell division until they reach a critically short length and can no longer replicate. Therefore, by up-regulating the cellular telomerase complex, E6 further immortalizes the host cell (39,40). E6 expression is a late event in malignant transformation.

HPV E1/E2

Both E1 and E2 are proteins necessary for HPV DNA replication. E1 first initiates viral replication by binding near the start site of transcription. E1 complexes with the E2 protein, then binds to the viral genome, which initiates helicase activity (41). E1 also binds various other nuclear proteins for further replication of the viral DNA (42–44).

E2 is involved with DNA replication as well as genome transcription. In addition to forming a complex with E1 to assist in replication, E2 also works on the upper regulatory region to affect transcription of early genes (45,46). High concentrations of E2 repress transcription and low levels activate transcription.

E2 therefore regulates E6 and E7 and loss of E2 expression can lead to carcinoma due to the unrestricted effects of E6 and E7 (47). Like E1, other interactions have been noted between E2 and various proteins involved with transcription as well as mitosis and cell division. E1 and E2 expressions are early events in the natural history of cervical dysplasia.

Viral Integration and Transformation to Malignancy

HPV genomes infect the cell via circular extra-chromosomal copies; however, over time, its viral genome can become inserted into host cell DNA, a process called integration. In low-grade cervical intraepithelial neoplasia (CIN), the HPV DNA is maintained in its closed, circular, episomal shape. However, in most high-grade CIN and cancers, the HPV DNA becomes integrated in the host chromosomal DNA (47–50). Many believe this is a necessary event to cervical carcinogenesis (51). Integrated HPV has been found to be present in 83% of invasive cervical cancers, as compared to 8% of low-grade CIN, suggesting that integration is highly associated with the transition of low-grade to high-grade lesions (52,53). Integration occurs at random sites in the host DNA; however, breaks in the HPV viral episome seem to occur at regions of genomic instability, such as fragile sites. Often the E2 ORF is disrupted during these breaks (54). As noted previously, E2 concentration affects the transcription of E6 and E7. Thus, once integration has occurred, disruptions in the E2 ORF lead to increased production of E6 and E7, thereby promoting immortalization and the oncogenic potential of the cell.

SECTION 2: EPIDEMIOLOGY OF HPV INFECTIONS

Prevalence

HPV is the most common of all sexually transmitted infections; while age, race, geographic region, and other modifiable risk factors also correlate with new infections, age, and sexual behaviors are most clearly linked to new HPV infections. Early studies likely underestimated the prevalence of HPV infections. As newer molecular technologies have been developed, detection of viral infection improved, even at low levels (55). In addition to variability surrounding detection methods, HPV positivity may be episodic, corresponding to times of viral shedding.

Utilizing polymerase chain reactions (PCR) on self-collected cervicovaginal specimens from over 4,000 US females, ages 14 to 49, the prevalence of HPV infection was recently estimated as part of the 2011 National Health and Nutrition Examination Survey (NHANES) (1) (Fig. 7.4). The overall prevalence of the 37 separate types was 42.5%. Prevalence was lower among females aged 14 to 19 (32.9%) and highest among females 20 to 24 years (53.8%), which is the peak age of new exposures. In that study, prevalence varied by race with non-Hispanic Blacks having the highest prevalence (59.2%) followed by Mexican Americans (44.2%) and non-Hispanic Whites (39.2%). HPV positivity was significantly associated with poverty, sexual activity (including number of partners, age, and first encounter) and history of genital warts.

HPV Prevalence Worldwide

Worldwide age-related trends are similar to US cohorts (56). Women less than 25 years old showed the highest prevalence of HPV infection, and in most regions of the world showed an

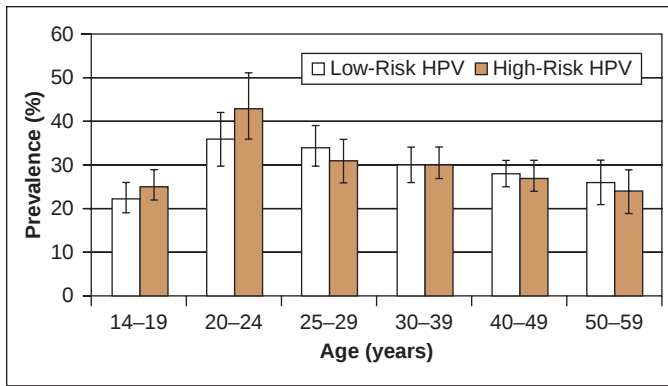


FIGURE 7.4. U.S. Prevalence of HPV infections in Women.

Source: Reprinted with permission from Hariri S, Unger ER, Sternberg M, et al. Prevalence of genital human papillomavirus among females in the United States, the National Health And Nutrition Examination Survey, 2003–2006. *J Infect Dis* 2011;204:566–573.

overall decrease in prevalence with increase in age. In Africa, prevalence ranges from 12% to 55%, though most trials consisted of younger cohorts of women. In Central and South America, prevalence has been reported to be as high as 64%, and interestingly many studies showed an overall decrease in prevalence with age followed by an upward trend in women over 50. Canadian prevalence was lower than in the US, with a peak incidence of 25%. Chinese trials showed a range of 6% to 53% while Japanese trials generally reported lower prevalence of less than 15%. Studies of Indian women show ranges from 0% to 45%. European prevalence was almost consistently lower than in the United States with a peak of approximately 20% in young women (56).

HPV Prevalence in Men

The trends in prevalence and clearance in men are inextricably linked to the epidemiology of HPV infections in women. HPV testing in men has limited yield when compared to HPV testing in women, due to the generally keratinized surfaces where HPV-infection is present in men. The largest US population-based

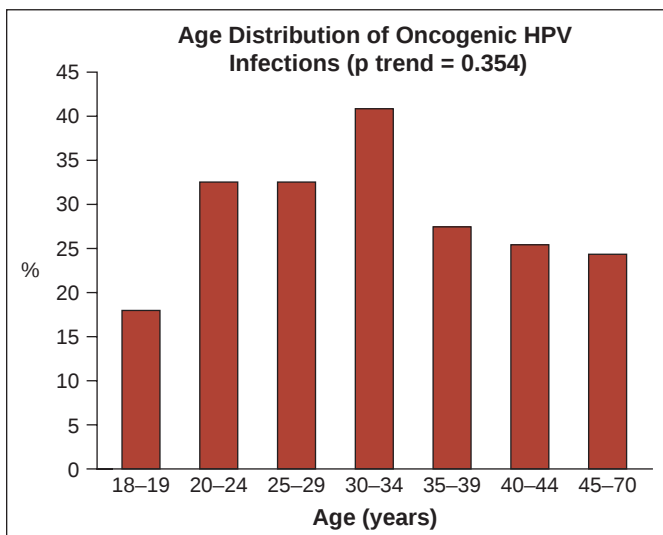


FIGURE 7.5. HPV prevalence in US Men.

Source: Reprinted with permission from Giuliano AR, Lazcano-Ponce E, Villa LL, et al. The human papillomavirus infection in men study: human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States. *Cancer Epidemiol Biomarkers Prev* 2008;17:2036–2043.

trial investigating HPV infection in men, where sampling was thoroughly performed, demonstrated a prevalence of 61% of any type of HPV infection. Specifically, high-risk HPV infections were found in 23%, with HPV 16 (7%) and HPV 51 (6%) being the most common (57). Additional data from the NHANES survey showed that men have a higher incidence of oral HPV infection of 10% versus 4% (58). In contrast to trends in women, prevalence of any HPV infection was not affected by age. Only low-risk HPV infections increased with age. Clearance of HPV infections seems to occur quicker in men, with an average clearance time of any HPV infection of approximately 6 months. In one study, nearly 75% of HPV infections in men were cleared within 1 year (57). Male circumcision significantly reduces genital HPV prevalence in men, which has led some to suggest circumcision as a method to reduce HPV-related disease burden in endemic communities where vaccination and screening is not yet feasible (59). In contrast to squamous cell carcinomas (SCC) of the female genital tract, HPV has only been detected in half of invasive penile SCC (60).

Natural History of HPV Infection (Rates of Abnormal Cytology, CIN, Cancer)

Despite its high prevalence, the majority of HPV infections are cleared by the body's immune system. Only a minority of persistent high-risk HPV infections result in CIN and an even smaller subset progress to invasive cancer.

Determining the exact rate of HPV clearance is complex. Some trials examine existing infections (prevalence trials) while others follow women who develop new infections (incident trials). Even within incidence-based trials, methods vary and any subject may have a combination of low-risk, high-risk, preexisting, or incident HPV infections. It is important to also note that though a negative HPV test likely represents clearance of infection, it may also represent a “latent,” subclinical infection. This concept is derived from a number of sources including data examining HIV positive women who became HPV positive in the absence of new sexual exposures, suggesting a reactivation of viral shedding during periods of immunodeficiency (61). Also, in long-term cohort studies, recurrent infections are often HPV types that the patient has previously had, suggesting reactivation (62). However, once cleared, very few HPV type-specific infections reappear and far fewer lead to clinically relevant disease such as high-grade CIN or cervical cancer (63).

The 1-year clearance rate of incident HPV infection ranges from 40% to 70%. Two- to 5-clearance rates are as high as 70% to 100% in young women (10, 64–67). This rate may be significantly lower in older women; one trial showed no clearance of high-risk HPV infections in women over the age of 70 (67). Young women are more likely to clear infections than older women, and low-risk HPV infections clear more quickly than high-risk HPV infections (64). The longest course of persistent infection was seen with HPV types 16, 31, 54, and 53 (64,68).

The majority of women who acquire HPV infections do not develop CIN or invasive cancer. Of women who have persistent high-risk HPV infections, trials report variable rates of progression to CIN 2/3 from 8% to 28% (69–71). In cross-sectional studies, an estimated 3% to 5% will eventually develop cervical cancer without any intervention (72,73). In a prospective cohort study of New Zealand women with carcinoma *in situ* followed over decades, the cumulative incidence of cancer of the cervix or vaginal vault was over 30% (9).

Transmission

HPV infections are almost exclusively acquired during sexual exposure. Areas of microtrauma within the skin and mucosal surfaces are the likely sites of initial infection. Many natural history

Table 7.1 HPV Persistence

Study	Year	Average Age	Type of Infection	HPV Persistence at 1 year	HPV Persistence at 2 years
Richardson et al.	2003	23	Incident, High Risk	61%	x
Ho et al.	1998	20	Incident, High and Low Risk	30%	9%
Dalstein et al.	2003	32	Prevalent, High Risk	60%	50%
Bae et al.	2009	48	Prevalent, High Risk	x	41%

Sources: Richardson H, Kelsall G, Tellier P, et al. The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiol Biomarkers Prev* 2003;12:485–490. Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338:423–428. Dalstein V, Riethmuller D, Pretet JL, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. *Int J Cancer* 2003;106:396–403. Bae J, Seo SS, Park YS, et al. Natural history of persistent high-risk human papillomavirus infections in Korean women. *Gynecol Oncol* 2009;115:75–80.

studies of HPV negative women at baseline who initiated intercourse confirm precedent sexual activity with new HPV infections (10). Furthermore, the rate of acquisition correlates with increasing number of sexual partners (74). Data regarding concordance and HPV transmission efficacy among couples are conflicting. In trials of young women and their male partners, HPV concordance ranged from 40% to 60%. Specific mechanisms that determine the efficiency of HPV transmission and concordance are poorly understood although it appears that length of sexual activity may increase concordance (75–77). Additionally, viral shedding may occur based on asynchronous replicative cycles of the HPV virus; thus, couples may appear to be less concordant than they really are at any specific time (68). In addition to cervical, vaginal, and penile detection, HPV has been detected on areas of unprotected genital skin such as the vulva and scrotum, providing an explanation as to why condoms offer some but not complete protection against HPV infection (78).

SECTION 3: ADDITIONAL RISK FACTORS FOR DEVELOPMENT OF PREINVASIVE LESIONS OF THE LOWER GENITAL TRACT

Although HPV has been implicated as the most important and necessary risk factor for development of preinvasive lesions of the lower genital tract, other risk factors have been identified that either increase the risk of HPV infection or potentiate the progression of HPV infection to malignant transformation.

Sexual History

Even before data convincingly linked HPV to the development of cervical cancer, it was well recognized that various aspects of a patient's sexual history put women at increased risk for developing preinvasive and subsequent invasive lesions of the cervix, vagina, and vulva.

Sexual history and behaviors strongly correlates with risk of acquiring HPV infection and developing preinvasive lesions (66). Overall, the number of recent and total lifetime male partners increases the rate of HPV infection, particularly high-risk HPV infection (66,79–82). The most recent data from the U.S. Centers for Disease Control (CDC) data show that number of lifetime partners is an independent risk factor for all races except non-Hispanic Black women, where no independent correlation is seen (83).

Early onset of sexual activity has also been shown as an independent risk factor for HPV infection in some studies (81,83). Some studies suggest that frequency of intercourse with one's partner may also play a role (10). Characteristics of the

partner, including number of lifetime partners (79) and multiple coincidental partners, have all been implicated in risk of HPV acquisition (10). The rate of having new partners and having known a new partner for shorter periods of time before having vaginal intercourse are also associated with increased risk of HPV infection (66,79).

Additionally, co-infection with other sexually transmitted diseases and vaginal infections has been associated with increased susceptibility to HPV infection. Both bacterial vaginosis and trichomoniasis are associated with HPV infection although the correlation is not as strong with development of CIN (84,85). A history of herpes simplex virus infection and vulvar warts also increase the incidence HPV infection (66). A history of previous chlamydial infection has long been implicated in the development of invasive squamous cell carcinoma of the cervix (86–88). Hypotheses regarding pathogenesis include induction of squamous metaplasia at the transformation zone, increase in microabrasions, as well as interference with immune surveillance (88,89). More recent cohort studies have found that the role of chlamydia in carcinogenesis is likely related to both in promoting the acquisition and persistence of HPV infections (90–92). Chlamydia has not been implicated in the development of adenocarcinoma *in situ* (AIS) or invasive adenocarcinoma (88).

Tobacco

In 2004, the IARC added cervical cancer to the list of cancers causally related to smoking (93) based on analysis of numerous trials in the prior decade. As more epidemiologic and natural history trials were performed, conflicting data emerged on the association between cigarette smoking and HPV acquisition, persistence, and progression. Confounding variables have also been a factor; women who smoke are less likely to be compliant with screening guidelines (94) and more likely to have more social stressors (95).

Most studies agree, though, that current smoking increases the prevalence of and persistence of HPV infection, particularly those that have a high-risk HPV type (96–99). Additionally, most trials suggested delayed clearance of HPV infection in women who smoke (100,101). Compared to nonsmokers and former smokers, current smokers have higher high-risk HPV viral loads (102).

The effects of smoking on the development of lower genital tract neoplasia are multifactorial. Nicotine and other by-products of cigarette smoke have been readily identified in the cervical mucus of smokers (103). Benzo[a]pyrene, a known human carcinogen, has been found in cervical mucus and has been specifically noted to potentiate the HPV 16 and HPV 18 viral lifecycle (104). It has long been known that smoking causes a local immunological effect whereby the function of Langerhans' cells are significantly decreased, thus affecting the

innate immune system (105). Studies of women with preinvasive and invasive disease have shown that compared to nonsmokers, smokers show aberrant methylation of p16, a tumor suppressor gene (106). Other recently identified tumor markers in smokers with CIN include overexpression of cyclooxygenase-2 and Ki-67 and underexpression of p53, interleukin-10, and fragile histidine triad (107).

Oral Contraceptive Pills

The association between oral contraceptive pills (OCPs) on preinvasive and invasive diseases of the lower genital tract has been conflicting. The largest population-based study, which pooled data from trials involving over 50,000 women worldwide, did show an increased risk of preinvasive and invasive disease in women who were current users of OCPs, although this risk was eliminated when OCP use was discontinued (108). This study is criticized for its heterogeneity between trials and the possible confounding effects of sexual behavior in women on OCPs—thus, many have questioned the true association. Other large trials since then have shown that OCP use is not an independent risk factor for development of abnormal cytology, CIN, AIS, or invasive disease (109–111).

HIV and Immunosuppression

HIV infection is strongly associated with HPV infection. Additionally, HIV coinfection in one partner impacts the prevalence of HPV infection in the other partner (112). Higher incidence and prevalence as well as prolonged persistence of HPV have all been associated with women who are HIV positive (113). Rates of CIN are also higher among HIV positive women, independent of other risk factors (114). Additionally, CD4 count and HIV RNA levels correlate with high-risk HPV positivity (61). Although highly active antiretroviral therapy (HAART) has not been shown to definitively affect the incidence or persistence of HPV infections, it has been associated with better CIN outcomes and improves overall life expectancy of HIV positive women (115).

In addition to its effect on prevalence of HPV infection, other mechanisms related to coinfection of HPV and HIV have been proposed. Primarily, it is noted that a functional immune system is required to keep HPV in a latent and subclinical state. Thus HIV infection, in addition to other forms of immunosuppression, predisposes to progression and reactivation of HPV infection (61). Additionally, different molecular pathways have been proposed for HIV-related preinvasive lesions including a higher frequency of microsatellite instability in HIV associated CIN (116). Based on patterns of local pro-inflammatory immune markers, it appears that persistent HPV infection might make someone more susceptible to HIV infection as well.

Another group of women known to be at high risk for preinvasive HPV-associated lesions are transplant recipients and other patients on chronic immunosuppressive therapy such as those with Systemic Lupus Erythematosus. Small, early studies noted a higher incidence of HPV infections and up to 16 times the rate of invasive cervical cancer in women with a history of renal transplant compared with controls (117). However, these data are limited by less effective methods of HPV testing and lack of control for covariates. In a recent prospective 10-year trial of 48 women with renal transplants, no increased risk of HPV infection, high-grade cytology, or preinvasive lesions was observed (118). A large Swedish cohort study found that the rate of vulvar malignancy in women who had undergone solid organ transplant was 26 times higher than the general population. Additionally, the rate of vaginal cancer was 16 times higher. Rates of cervical cancer were not statistically higher and

preinvasive lesions were only marginally increased (119). A U.S. cohort of transplant recipients was analyzed and only vulvar carcinoma demonstrated a statistically significant higher incidence in transplant recipients. In fact, the incidence of vulvar carcinoma following a solid organ transplant was higher than the incidence of cervical cancer (7.5 vs. 5.8 per 100,000 person years) (120). This may reflect improved cervical cancer surveillance in this population. However, it may also reflect the different pathology of vulvar lesions in immunocompromised women. Smaller studies suggest rates of 90% to 100% HPV positivity in preinvasive and invasive vulvar lesions in women with transplants (121,122).

SECTION 4: PATHOLOGY OF PREINVASIVE LESIONS

Cervix

Formerly known as cervical dysplasia and carcinoma *in situ* (CIS), preinvasive squamous cell lesions of the cervix are now categorized as various levels of CIN. More specifically: mild, moderate, and severe dysplasia/CIS are now termed CIN 1, CIN 2, and CIN 3, respectively.

CIN Localization

The vast majority of CIN develops in the transformation zone of the cervix, located at the squamo-columnar junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. This area has been so-called “transformed” due to the process of metaplasia (Fig. 7.6). Prior to menarche, the transformation zone does not exist. The squamo-columnar junction occurs exactly at the level of the external cervical os. During menarche (as well as during pregnancy), the columnar epithelium of the endocervix appears on the ecto-cervix and is termed an “ectropion” or “cervical ectopy.” This columnar epithelium gradually becomes replaced by stratified squamous epithelium due to a variety of factors including alterations in pH and other hormonal changes. This area of former columnar, now squamous, epithelium that lies between the original squamocolumnar junction and the new squamocolumnar junction is termed the transformation zone. The transformation zone is the primary site for inducing cell-mediated immunity in the lower genital tract, and its role in the acquisition of not only HPV infections, but also HIV infections is still being elucidated (123,124).

Microscopic Appearance of CIN

Nuclear atypia is a prominent feature of CIN, which can occur at any level of dysplastic severity. It occurs as a result of enhanced proliferation, replication, and intracellular assembly of viral particles in HPV infected cells. The nuclei are hyperchromatic and frequently multinucleated; additionally, the nuclear outline is often irregular rather than round. The swollen appearance of the cells, often termed as koilocytes, is a result of viral particles present in the episomal area of the cell.

In addition to nuclear atypia, CIN 1 to 3 histology shows aberrant cytoplasmic differentiation. The basaloid cells, which are normally found as a single layer in contact with the basement membrane, replace the normal epithelium. These cells display nuclear crowding, loss of normal cell polarity, pleomorphism, and abnormal mitotic figures. The extent of these abnormal basaloid cells determines the grade of CIN. If the undifferentiated basaloid cells involve the lower third of the epithelium, the lesion is CIN 1; if these cells are present two-thirds of the way

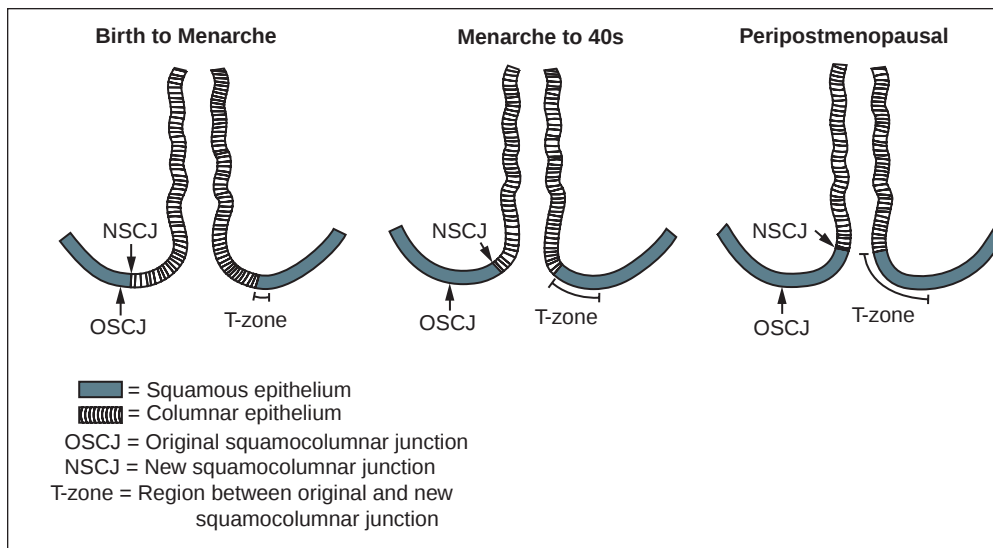


FIGURE 7.6. Impact of age on the location of the squamocolumnar junction. As females age, the location of the squamocolumnar junction on the cervix moves. The movement of the squamocolumnar junction defines the transformation zone.

through the epithelium, the lesion is CIN 2; and if the extent is greater than two-thirds, the lesion is termed CIN 3. In order to better classify the degree of CIN, molecular markers can be used by pathologists. For instance, p16^{INK4a} is a validated marker for biologically relevant CIN (125).

This classification system was developed when all of CIN was thought to be a spectrum of disease. Now we understand that CIN 1 usually represents a benign process that is merely a cytomorphologic representation of an active HPV infection; whereas higher-grade lesions, especially CIN 3, are truly premalignant. CIN 2 is a poorly reproducible category, with high levels of inter-observer variability (126). In one trial, agreement between pathologists was as low as 13% in the category of CIN 2 compared with 81% agreement with CIN 3 lesions (127). CIN 2 is now considered an equivocal diagnosis because it can include either benign HPV effects or precancerous lesions (125). In an analysis of a vaccine trial, agreement between biopsy and LEEP specimen improved when CIN 2 and CIN 3/AIS were grouped as a single predictive measure of high-grade disease (128). Due to limitations surrounding reproducibility, many institutions characterize lesions as either CIN 1 or CIN 2/3 (also known as CIN 2+); and often include additional molecular markers such as p16^{INK4a} and other proliferation markers to improve clinically relevant disease ascertainment (Fig. 7.7).

In CIN 1, the lower third of the epithelium displays nuclear atypia of immature basaloid cells while the remainder of the epithelium often shows the additional cytopathic effects, termed koilocytosis, which are directly related to an active HPV infection. Koilocytes are cells with atypical nuclei and perinuclear clearing, also known as vacuolization; they can be seen in both CIN 1 and CIN 2/3, although it is more common in CIN 1. The large, perinuclear vacuole is often a result of activation of viral E5 and E6 proteins (129).

Natural History of CIN

CIN 1 is the most common histologic diagnosis after colposcopic biopsy. Fortunately, very few of these lesions actually progress to a higher grade of CIN. Most will remain persistent or regress spontaneously as the HPV infection is cleared (130). In both prospective and retrospective trials, incidence of CIN 2/3 18 to 24 months after diagnosis of CIN 1 ranges from

4% to 10% (131,132). A retrospective analysis of the ASCUS-LSIL Triage Study (ALTS) (133) found that a diagnosis of CIN 1 on pathology (compared to a negative biopsy, or no biopsy taken) was not a risk factor for developing CIN 3. Therefore, CIN 1 is considered a nonneoplastic lesion and is not a disease that should require any extirpative treatment.

Without treatment, high-grade CIN has at least a 30% probability of becoming invasive cancer. This was shown in an unfortunate retrospective trial of a prospectively followed cohort of women followed over a 30-year period beginning in the 1960s in New Zealand. If adequately treated, however, very few women with CIN 2/3 will recur or develop invasive cancer (9).

Glandular Dysplasia and Adenocarcinoma In Situ

Although the majority of preinvasive cervical lesions are of squamous cell histology, approximately 3% represent precursors to invasive adenocarcinoma (134). While HPV 16 is the most commonly identified subtype in glandular lesions, HPV 18 causes a greater proportion of glandular as compared to squamous lesions (135). Contrary to popular conceptions regarding preinvasive glandular lesions, the majority are solitary. Multifocal (or “skip lesions”) do occur, but only in 10% to 15% of cases. Though glandular lesions can be found higher in the endocervical canal, the majority occur at the squamocolumnar junction (136).

Preinvasive glandular lesions can be divided into the categories of endocervical glandular dysplasia (EGD) and AIS. These categories differ by degree of nuclear stratification, nuclear atypia, and numbers of mitosis and apoptosis. Additionally, immunohistochemistry, such as staining for a proliferative marker, Ki-67, may also be used to help differentiate between the two categories (137). An additional category, termed glandular atypia, encompasses nonpremalignant lesions with atypia associated with inflammation or previous radiotherapy. Rare variants of AIS have been described including endometrioid, intestinal, serous, and clear cell histologies.

Histologically, AIS is characterized by enlarged glandular cells with large, hyperchromatic nuclei (Fig. 7.8). Unlike the cytopathic effect of koilocytosis seen in HPV infected squamous cells, endocervical cells show decreased cytoplasm and minimal intracellular mucin. Structurally, glandular cells are crowded

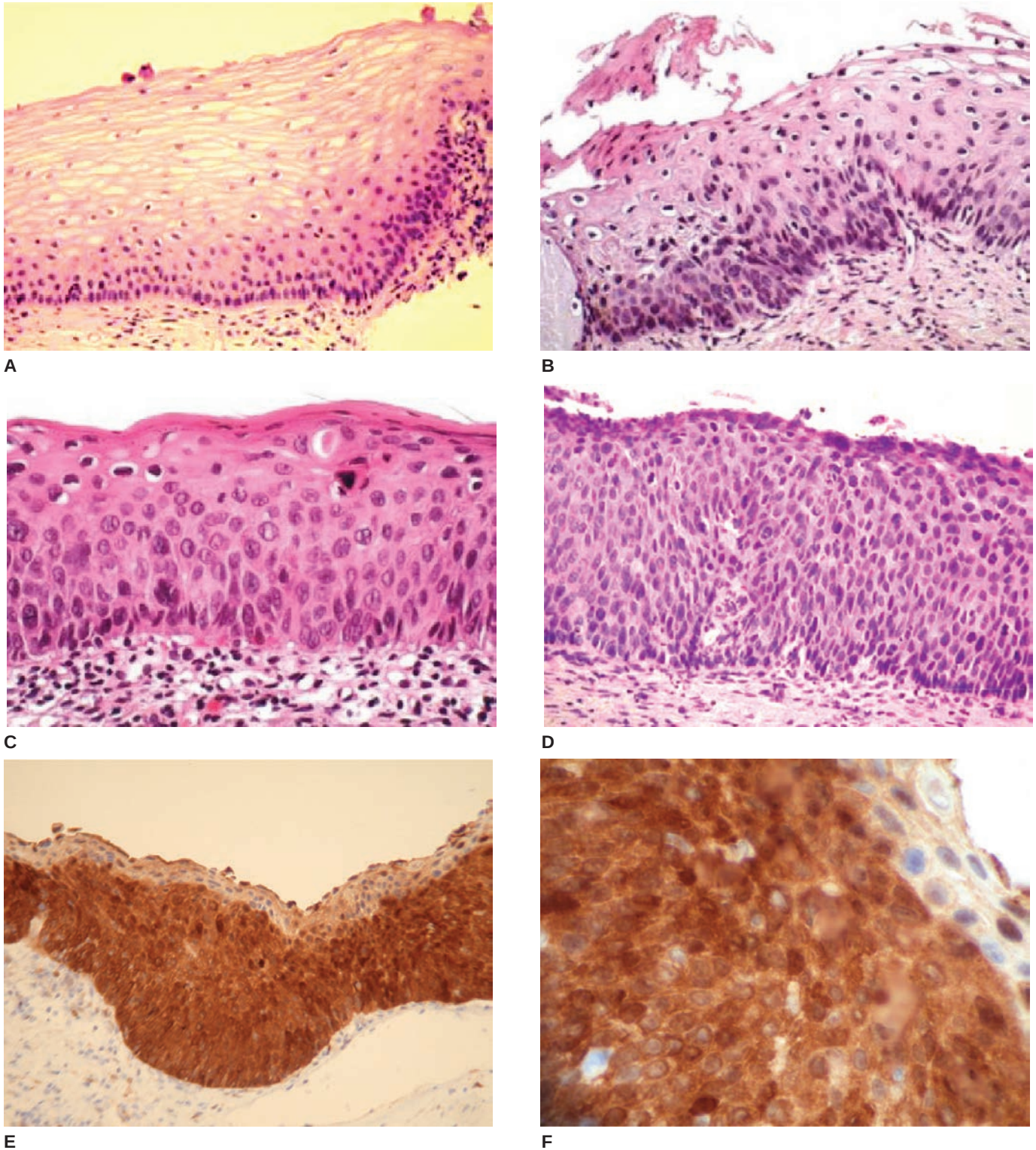


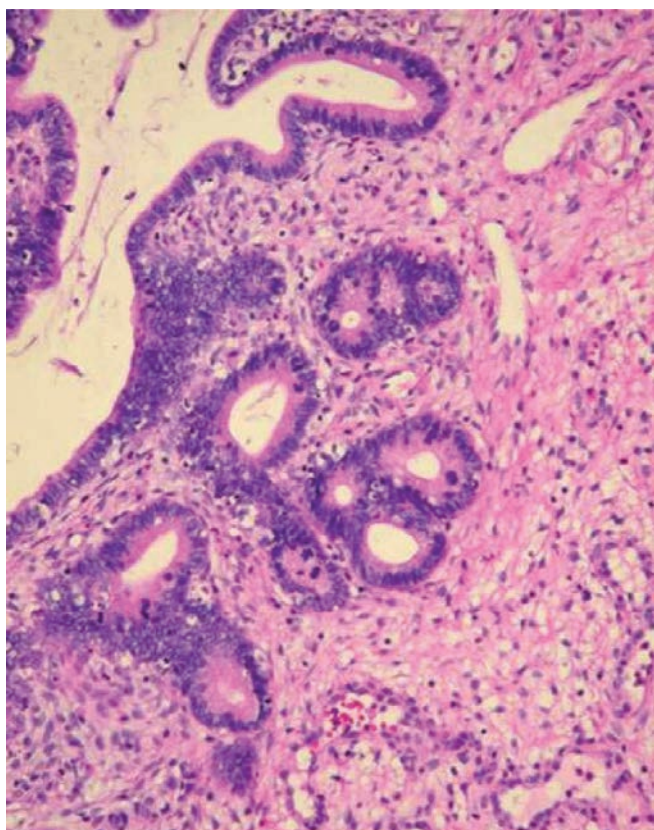
FIGURE 7.7. **A:** Normal squamous epithelium; **B:** CIN 1; **C:** CIN 2; **D:** CIN 3; **E:** Low-power view of P16 staining on cervical biopsy containing CIN 2/3; **F:** High-power view of p16 staining on cervical biopsy containing CIN 2/3.

Source: Images courtesy of University of Alabama at Birmingham.

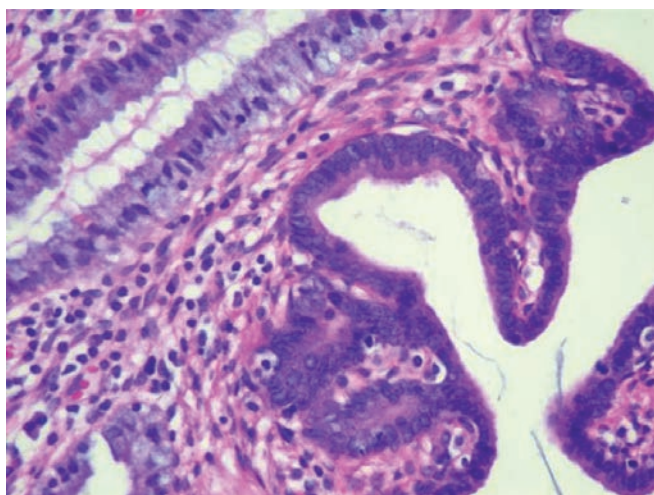
with pseudostratification. Unlike squamous lesions, apoptosis is a common feature in glandular lesions and is seen in higher frequency in AIS compared to invasive adenocarcinoma (138).

Diagnosing early invasive endocervical adenocarcinoma is sometimes more challenging than diagnosing squamous lesions due to the complex growth patterns of endocervical glands.

Atypical glands that extend greater than 5 mm from the uninvolved glands are usually termed invasive, whereas lesions within 5 mm are considered early invasive disease. Other features distinguish invasion from *in situ* lesions including stromal reaction (desmoplasia, inflammation), confluence of glands, and solid components.



A



B

FIGURE 7.8. Adenocarcinoma *in situ* (AIS). **A:** High-power view. **B:** Low-power view. Normal endocervical glands in the upper left.

Source: Images courtesy of University of Alabama at Birmingham

Vulva

Vulvar intraepithelial neoplasia (VIN) is increasing in incidence in the United States, with a 400% increase in preinvasive lesions and a 20% increase in invasive lesions between 1973 and 2000 (139). Classification of preinvasive vulvar disease has undergone many changes. In 2003, the WHO classified VIN in a 3-grade system for all types, similar to preinvasive cervical disease. Then, in 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) reclassified VIN into 2 categories: usual-type VIN, which is associated with HPV infection; and differentiated VIN, which is usually not associated with HPV

infection (140). VIN 1 was abandoned in terminology primarily due to its high rate of misclassification into clinically relevant disease. Usual-type VIN includes only high-grade VIN and is composed of warty, basaloid, and mixed histologies. In addition to being an HPV-associated lesion, usual-type VIN shares the same risk factors as those for CIN including tobacco use and immunodeficiency. Differentiated VIN, sometimes referred to as “keratinizing type,” occurs most commonly in older women and is often associated with lichen sclerosis. p53 mutations and microsatellite instability have been implicated in its pathogenesis. Five percent of women with lichen sclerosis develop invasive squamous cell carcinoma with an average interval of 10 years (141). Differentiated VIN has a greater propensity to progress to invasive disease, and time to progression is shorter than that of usual-type VIN.

The differential diagnosis for vulvar lesions is broad and diverse. Distinguishing benign from preinvasive lesions can be difficult by visual inspection alone and thus biopsy is usually necessary to establish diagnosis. Usual-type VIN appears as a sharply demarcated lesion that can exhibit various colorations including white, gray, red, and black. VIN is most commonly found at the introitus, on the labia minora, and around the anus. When the disease spreads beyond the anal verge, it is referred to as anal intraepithelial neoplasia, or AIN, and lesions are frequently multifocal (142). Microscopically, VIN resembles CIN and displays nuclear atypia and cytoplasmic differentiation.

Natural History of VIN

Based on retrospective reviews, an estimated 10% to 15% of untreated VIN will progress to invasive squamous cell carcinoma over many years (143,144). Additionally, up to 20% of women with high-grade VIN will have occult invasive disease at the time of surgery for preinvasive disease (145). Unlike CIN, regression of VIN is rare; one review noted only a 1% complete regression of VIN 3 (144).

Vagina

Vaginal intraepithelial neoplasia (VAIN) is another lesion that is part of the HPV spectrum in the lower genital tract. Its occurrence is less common and represents only 0.5% of all lower genital tract intraepithelial neoplasias. VAIN is most often found in the upper vagina and is most often multifocal. Many cases occur after hysterectomy and occult vaginal malignancy is uncommon (146). Recurrence is more common with multifocal disease and ranges from 20% to 60% after treatment with laser or 5-fluorouracil (146,147). Recurrence is uncommon after partial vaginectomy (147). HPV infection is implicated in the pathogenesis of over half of VAIN (148). The histologic features of VAIN are similar to those of CIN and VIN. Due to its infrequency, there are no current recommendations for vaginal cancer screening. Most screening recommendations do not recommend performing vaginal cuff cytology after a hysterectomy (149).

SECTION 5: SCREENING

With the advent of successful screening for preinvasive disease of the lower genital tract, effective treatments of precancerous lesions has also emerged, subsequently affecting the overall disease burden of invasive lower genital tract malignancies.

Cervical cancer screening is hailed as one of the major public health advances in the 20th century. Initially seeking determinants of the ovulation cycle in guinea pigs, Dr. George Papanicolaou evaluated the vaginal smear as an indicator of

hormone status. Eventually he studied human subjects and incidentally found a malignancy on a vaginal smear. More than a decade later, Dr. Papanicolaou and his colleague Dr. Herbert Traut published “The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus” which forever changed the landscape of cancer screening for women (150). The Papanicolaou, or Pap smear, is now used worldwide for cervical and vaginal cancer screening, and its utility and efficacy continue to be validated as newer molecular technologies emerge, particularly testing for HPV DNA.

It should be noted that the utility of the Papsmear as a screening test has not been based on randomized, controlled trials. Being the first such screening test in the modern era, the Pap smear never had to prove its clinical benefit through an evidence-based approach, as many modern screening tests are evaluated today.

Despite a lack of level I evidence, the epidemiologic data is quite convincing (151–154). In developed countries, the incidence of cervical cancer has declined dramatically since the acceptance and utilization of cervical cytology based-screening. In the United States, rates declined from 36.3 per 100,000 in the 1930s to 7.2 per 100,000 in the beginning of the 21st century—a reduction of over 80%. The greatest rate of decline occurred between the 1950s to 1970s when rates dropped by over 3% per year (155). This correlates with the widespread adoption of routine cervical cancer cytology-based screening programs in the United States.

However, despite the widespread acceptance of cervical cancer screening tests, it is estimated that there are still over 12,000 new cases of cervical cancer diagnosed in the United States annually (156). Reports estimate that 20% to 30% of cases will be in women who have had proper screening (156,157). Thus, as effective as the Pap smear may be, it is evident that many cases of cervical cancer and premalignant lesions are still undetected, suggesting that its use as a screening test can be further optimized.

There are elements inherent to cytology that may inhibit its success as a screening test. This includes poor cellularity due to collection or transfer. Also, Pap smears may be read as unsatisfactory due to inflammation, scant cellularity, or obscuring blood thereby limiting diagnostic ability. The rate of unsatisfactory Pap smears ranges from 1% to 8% (158,159) and on reevaluation, a significant number of these show cytologic atypia, including high-grade lesions and carcinoma (159). This is usually overcome with liquid-based cytology, which is the more commonly used cervical cytology platform due to the ability to also perform molecular testing for pathogens like HPV from the same collection vial. One of the suggested

improvements to overcoming the human error is the ability to run HPV testing, which is highly sensitive and is not dependent on any subjective evaluation.

Despite rigorous international standards, the interpretation of cytology is subject to inter-observer variability. Discrepancies between low- and high-grade lesions among various laboratories and personnel may be as high as 15% (160). Moreover, it is well established that the category of atypical squamous cells of undetermined significance (ASC-US) remains a poorly reproducible category. Attempts have been made to improve its low positive predictive value including HPV triage testing, but nonetheless, much variability exists regarding cytologic interpretation (126,161).

Even under the best circumstances when sampling is adequate, and interpretation is performed by experienced cytologists, the sensitivity and specificity of the Pap smear at baseline limits its functionality as a screening test. A pooled analysis of European and Canadian studies noted that though the specificity of the Pap smear in detecting high-grade dysplasia (CIN 2 or greater) was 96%, the sensitivity was only 53% (162). In another systematic review, the sensitivity of the Pap smear ranged from 30% to 87% and specificity ranged from 86% to 100% (163).

Currently, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society of Clinical Pathology (ASCP) recommend that women should begin cytology screening starting at age 21, regardless of risk factors (Table 7.2). Cytology should be performed every 3 years until age 30 (149). Based on modeling studies in this age group, and taking into consideration the natural history of the disease (including high rates of regression and long periods required before invasion), there is no increased risk of death due to cervical cancer associated with screening every 3 years versus every 2 years. Moreover, there is a 40% increase in the rate of colposcopy when screening is performed every 2 years compared to 3 years, with no increase in cancer detection with more testing (164).

At age 30, combined concurrent testing (or co-testing) with cytology and HPV testing is the preferred method of screening. If both tests are negative, screening can occur every 5 years (149). Co-testing improves sensitivity of detection of CIN 2/3 and lowers the false-negative rate of cytology alone (165,166). HPV testing also improves the detection of glandular lesions, which often go undetected with conventional cytology alone (167). If no HPV testing is performed, cytology alone every 3 years is acceptable. Women older than 65 and women with a previous hysterectomy for benign indications no longer need screening for cervical or vaginal cancer.

Table 7.2 Cervical Cancer Screening Recommendations

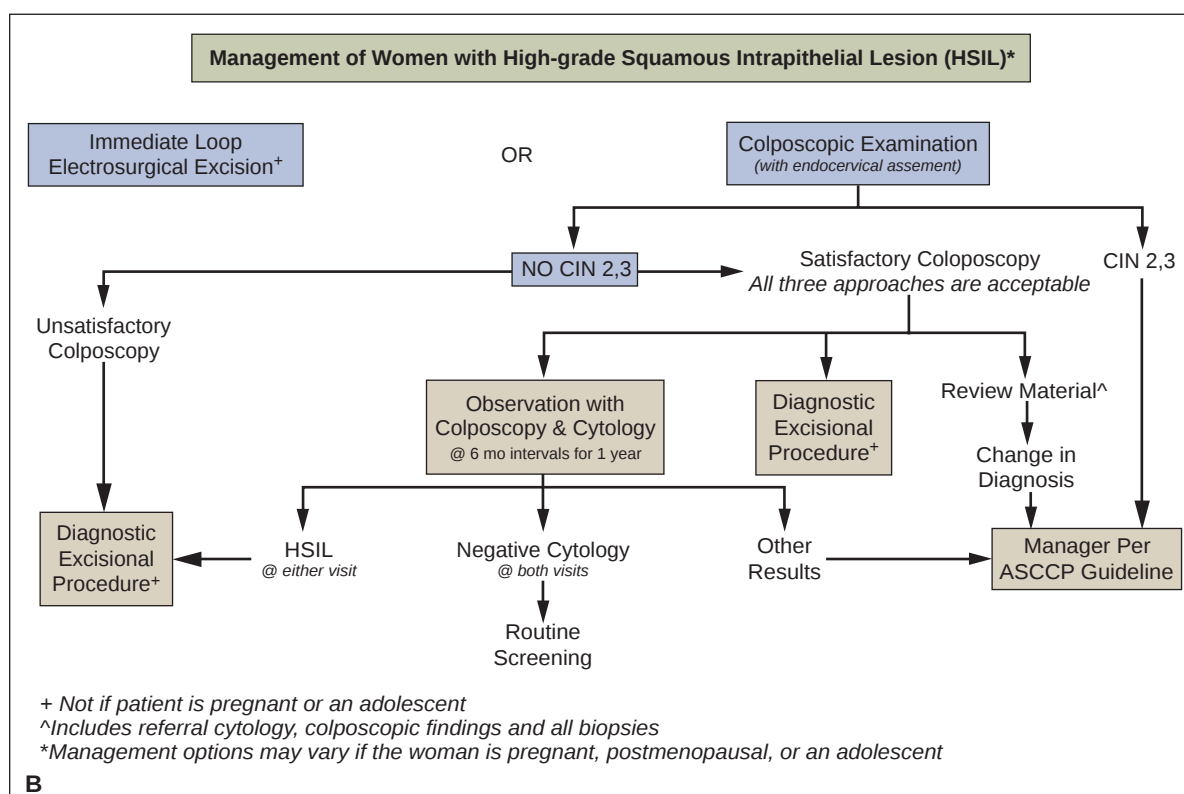
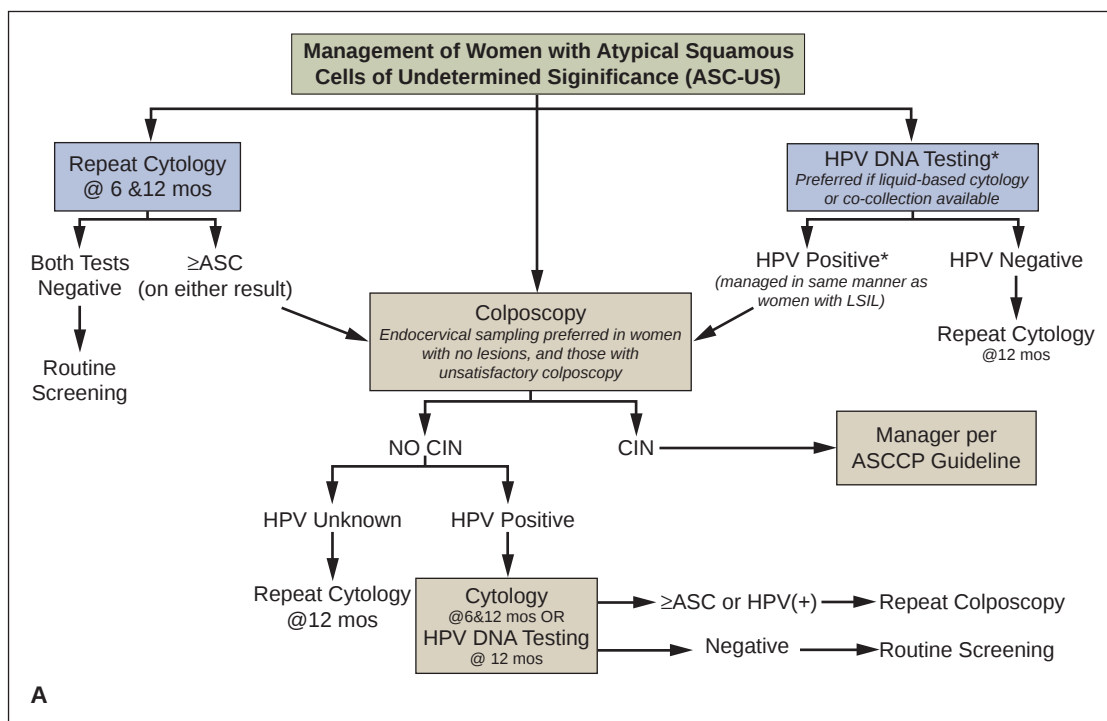
Age	Screening method	Comments
<21 years	No screening recommended	HPV testing is not recommended in this age group
21–29 years	Cytology alone every 3 years	HPV testing is not recommended in this age group
30–65 years	Preferred = “Co-testing” (HPV and Cytology) -or- Acceptable = Cytology alone every 3 years	
>65 years	No screening following adequate negative prior screening	If history of CIN 2+, continue screening for 20 years
After Hysterectomy	No screening	Applies only to women with no cervix and no history of CIN 2+
HPV Vaccinated	Follow age-specific recommendations (same as unvaccinated women)	

Source: Adapted from Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the prevention and early detection of cervical cancer. *J Low Genit Tract Dis* 2012;16(3):175–204, with permission.

Atypical Squamous Cells of Undetermined Significance

Figure 7.10 shows the distribution of Abnormal Cervical Cytology. ASC-US is the most common cytologic abnormality but the most poorly reproducible category (126). The rate of CIN 2/3 with ASC-US cytology varies depending on populations studied from 5% to 27%. However, because it is the

most common cytologic abnormality, half of all women with CIN 2/3 have a preceding diagnosis of ASC-US (168,169,170). Though only 0.2% of women with ASC-US cytology have invasive disease, women with cervical cancer often present with ASC-US cytology (171). Thus, further evaluation of women with this abnormality is warranted. The preferred approach to management of ASC-US is reflex high-risk HPV testing followed by colposcopy if the HPV test is positive (Fig. 7.9).



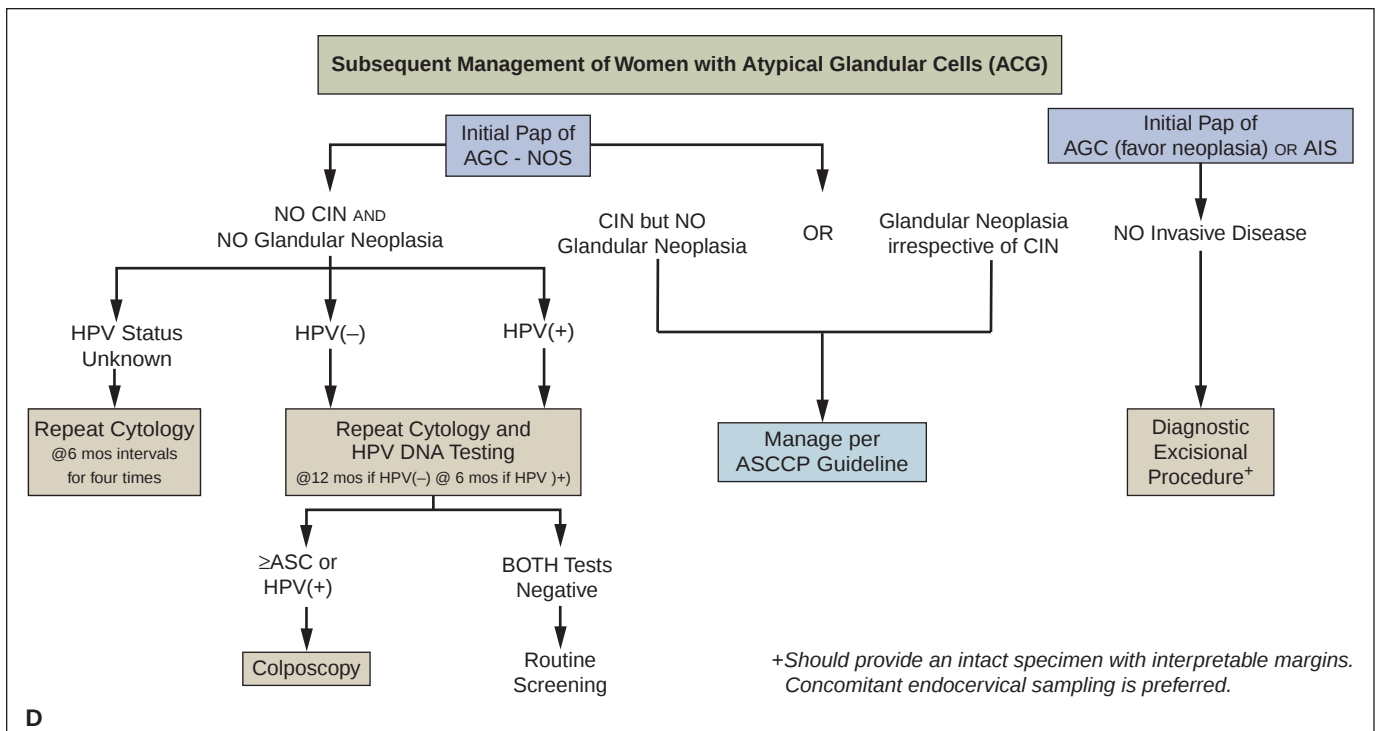
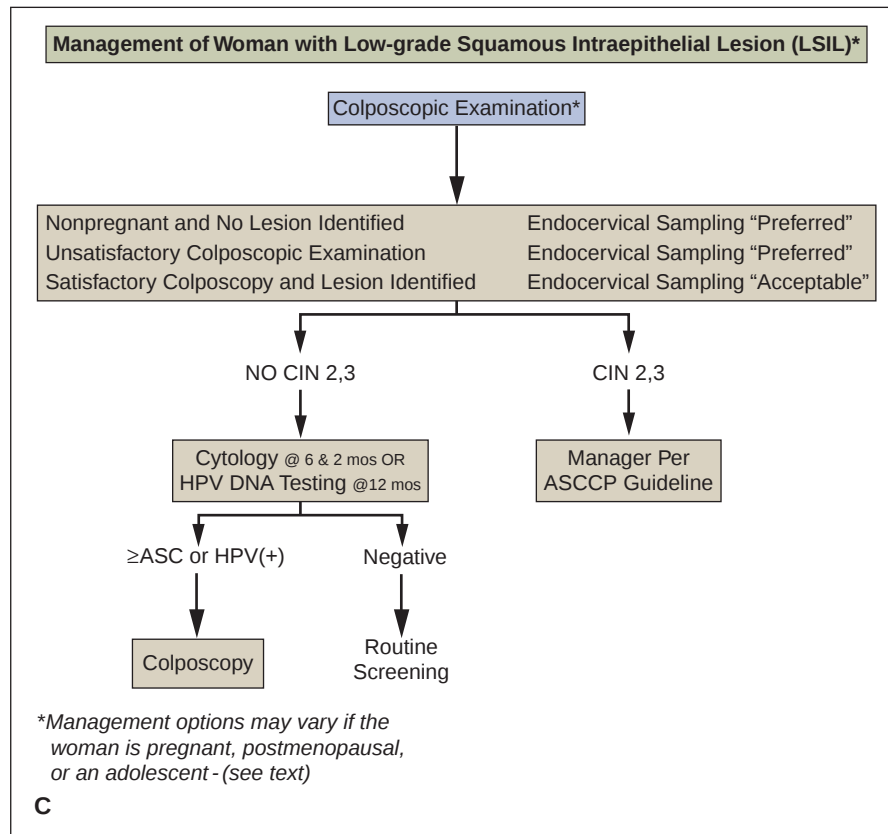


FIGURE 7.9. ASCCP Algorithms for Management of Abnormal Cytology.

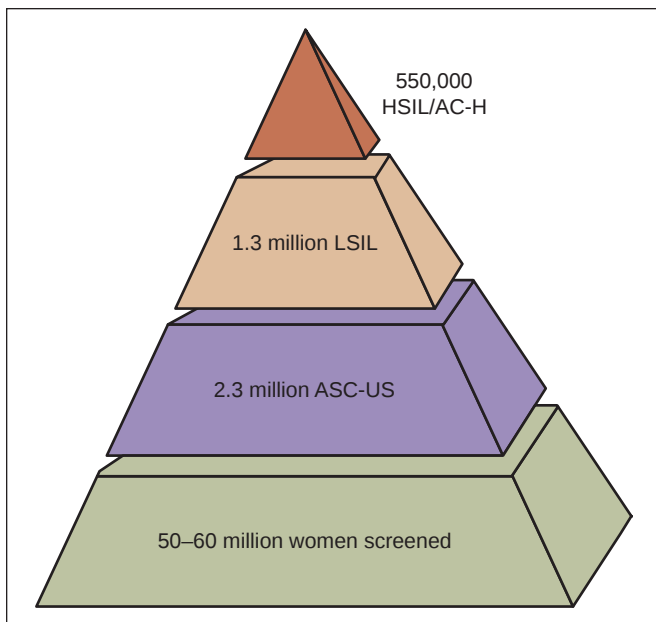


FIGURE 7.10. Distribution of Abnormal Cervical Cytology.

Source: Adapted from Davey DD, et al. Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med* 2004;128(11):1224–1229, with permission.

Among women who undergo reflex HPV testing, approximately 65% of women in their twenties will test HPV positive and only 31% of women over 30 years of age will be positive. HPV triage in women over 21 years of age with ASC-US cytology demonstrates high sensitivity for detection of CIN 2/3 and also reduces the number of unnecessary colposcopies by at least 50% (11). Approximately 15% of women with ASC-US cytology who are HPV positive have CIN 2/3 compared to less than 2% of women who are HPV negative (172). This is why it is recommended that a woman with an ASCUS HPV+ test undergo immediate colposcopy (HPV 173). Negative ASC-US cytology can be treated like a normal test and routine screening should follow. Annual cytologic follow up is not necessary (149).

Atypical Squamous Cells Cannot Exclude High-Grade SIL

Women with ASC-H cytology have a higher rate of CIN 2/3 than women with ASC-US (approximately 40% vs. approximately 15%, respectively) (168,172,174). The majority of specimens are HPV-positive and thus reflex HPV is not recommended; instead, immediate colposcopy should be performed (173).

Low Grade Squamous Intraepithelial Lesion

Roughly one-fourth of women with LSIL cytology have CIN 2/3, and most harbor a high-risk HPV infection (133). Therefore, colposcopy should be performed in all women with LSIL (Fig. 7.9). If no CIN 2/3 is identified, patients should be followed with either HPV testing in 1 year or repeat cytology at 6 and 12 months. The exception is postmenopausal women who have low rates of HPV infection and low rates of CIN 2/3 with LSIL cytology. In these women, HPV triage testing similar to women with ASC-US cytology is preferred (173).

High-Grade Squamous Intraepithelial Lesion

The rate of high-grade squamous intraepithelial lesion (HSIL) cytology is less than 1%, but it correlates strongly with high-grade cervical lesions (175). Management of HSIL includes either colposcopy or an immediate loop electrosurgical excisional procedure (LEEP) (Fig. 7.9). Up to two-thirds of women will have CIN 2/3 at the time of initial colposcopy for HSIL and over 90% of women will have CIN 2/3 when evaluated with an excisional procedure. Immediate LEEP is preferred in many institutions because of its cost-effective nature and reduced number of follow up exams (176,177).

Atypical Glandular Cells

Compared to atypical squamous cell cytology, atypical glandular cells (AGC) has a higher rate of both preinvasive and invasive disease. AGC is an uncommon diagnosis and is seen in less than 1% of cytologic specimens. Women older than 35 years of age are more likely to have invasive disease compared to women less than 35 years old. Overall, high-grade lesions, including AIS and invasive disease, are found in 9% to 38% of women with AGC (178,179). Following a diagnosis of AGC, colposcopy with endocervical sampling is recommended. Additionally, endometrial biopsy should be performed in women over the age of 35 or in women with risk factors for endometrial cancer (173).

Detection Methods

Molecular technologies for HPV detection have developed rapidly as routine clinical utility for such testing has expanded. The U.S. Food and Drug Administration (FDA) has approved five tests for detecting HPV. The first Hybrid Capture II (HCII) assay (Qiagen, Germantown, MD) was approved in 2003; it detects 13 high-risk HPV types through nucleic acid hybridization assays using signal amplification and chemiluminescence. In 2009, the FDA approved 2 additional HPV DNA tests: Cervista HPV HR (Hologic, Bedford, MA), which detects 14 high-risk types, and Cervista HPV 16/18 (Hologic, Bedford, MA), which detects HPV types 16 and 18. In 2011, the Cobas HPV test (Roche Molecular Systems, Pleasanton, CA) has been approved for the identification of HPV 16 and 18 while concurrently detecting 12 other high-risk HPV types. Most recently, the APTIMA HPV assay (GenProbe, San Diego, CA) was approved for cytology triage and cotesting. This assay detects the messenger RNA of the oncogenic E6 and E7 proteins of 14 high-risk HPV types (Table 7.3).

After over 60 years of cervical cancer screening with just the Pap smear alone, guidelines have been modified to reflect an improved understanding of the role of high-risk HPV in the development of cervical cancer and the role of HPV testing in cervical cancer screening.

The ASCCP recommends HPV testing in a variety of specific situations. These situations include triage of women 21 years or older with an ASC-US Pap smear, cotesting with cytology in women older than age 30, follow up after excisional procedures or ablation of CIN 2/3, management of postmenopausal women with LSIL, management of women with AGC on cytology, and follow-up for CIN 1 when it was preceded by a low-risk Pap smear (LSIL, ASC-US, ASC-H). Moreover, the ASCCP recommends genotyping assays, which specifically detect HPV 16 and 18, as a way to further triage women over the age of 30 with normal cytology and positive high-risk HPV tests. Women with negative cytology who are HPV 16 or HPV 18 positive should be referred for immediate colposcopy, whereas

Table 7.3 Cervical Cancer Screening

Name	Company	HPV Genotype Detection	Uses	FDA approval date
Digene Hybrid Capture 2 High-Risk HPV DNA Test	QIAGEN, Germantown, MD	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68	1. ASC-US triage 2. Co-testing in women >30 years old	March, 2003
Cervista HPV HR	Hologic, Bedford, MA	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68	1. ASC-US triage 2. Co-testing in women >30 years old	March, 2009
Cervista HPV 16/18	Hologic, Bedford, MA	16, 18	1. Triage for follow up of women >30 years old with negative cytology and positive high-risk HPV.	March, 2009
Cobas HPV Test	Roche Molecular Systems, Pleasanton, CA	Specifically identifies 16 and 18 while concurrently testing for 31, 33, 35, 39, 51, 52, 56, 58, 59 66 and 68	1. ASC-US triage 2. mCo-testing in women >30 years old 3. Triage for follow up of women >30 years old with negative cytology and positive high-risk HPV testing	April, 2011
APTIMA HPV Assay	Gen-Probe, San Diego, CA	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68	1. ASC-US triage 2. Co-testing in women >30 years old	February, 2012

Source: Adapted from Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the prevention and early detection of cervical cancer. *J Low Genit Tract Dis.*, 2012;16(3):175–204, with permission.

those who are high-risk HPV-positive but HPV 16 and HPV 18 negative can be followed in a year with repeat cytology or HPV testing (149).

Primary HPV testing as the sole screening modality has been investigated in multiple international trials, and shows promise in upfront screening strategies (166,180,181). In general, it has demonstrated improved sensitivity compared to cytology, although specificity may be lower. Because of its improved specificity over HPV testing alone, cytology may be used as a follow-up test after a positive HPV test (182). Because no large trials have evaluated the most effective strategies in managing the results of HPV testing in the primary screening setting in the United States, HPV testing is not yet recommended in the United States for use as a primary upfront screening test.

Additional Screening Strategies

In addition to cervical cytology and HPV testing from liquid-based cytologic specimens, other innovative techniques are being used in populations with limited access to standard screening approaches. In an attempt to make high-risk HPV testing more efficient, less invasive, and less costly, self-HPV testing has developed. Self-sampling demonstrates high concordance with physician collected samples (183). Prospective trials involving women who did not attend routine cervical screening programs in the Netherlands showed that, because of a higher participation rates, detection rate of CIN was higher than in the regularly screened population (184,185).

In developing nations where the cost of frequent follow-up exams and testing is prohibitive, visual inspection tests have emerged as an important method of screening and treatment. With a bright halogen lamp, visual inspection with acetic acid (VIA) or Lugol's iodine (VILI) is performed and positive lesions are referred to colposcopy with directed biopsy. Additionally, positive lesions can be treated immediately, bypassing the need for follow-up colposcopy. This is an efficient method of screening and treatment, and health care providers can be trained easily in visual inspection, thereby further improving its feasibility (186). Although significant verification bias exists in a

see-and-treat strategy, pooled analysis of trials utilizing visual inspection performed in developing nations revealed a sensitivity of 62% to 80% and specificity of 77% to 84% to detect high-grade CIN (187).

VIA and VILI with see-and-treat strategies appears to be cost-effective. A study that modeled screening strategies in India, Kenya, Peru, South Africa, and Thailand showed that screening women once per lifetime with visual inspection effectively reduced cervical cancer mortality by over 25% at an acceptably low cost in relation to each nation's gross domestic product (188). Population-based studies on VIA have yielded mixed results. In a south Indian population, cervical cancer mortality was reduced by 25% with VIA compared to no screening (189). In the largest prospective trial enrolling over 130,000 women in rural India, one-time screening methods of HPV testing, cytology, and VIA were compared. Compared with a control group, only HPV testing reduced the rate of cervical cancer (190). Thus once per lifetime HPV testing in women over 30 has been proposed as an effective method of cervical cancer reduction in low-resource settings (190).

SECTION 6: HPV VACCINATION

With an improved understanding of the role of HPV infection in the natural history of preinvasive and invasive lesions of the lower genital tract, prophylactic vaccination has emerged as an important element in cervical cancer prevention (Table 7.4).

The L1 capsid protein, which is 1 of 2 viral capsid proteins of the HPV virus, is the primary target for prophylactic vaccination. Vaccines consist of recombinant L1 proteins that form virus-like particles (VLPs), which are combined with different adjuvants. Adjuvants stimulate the immune system and increase the response to vaccination and are aluminum based. VLPs primarily induce a humoral response with neutralizing antibodies, but they also induce cell-mediated immune responses. Neutralizing antibody responses are logs higher than that generated from a response to a new HPV infection.

Table 7.4 HPV Vaccines

	Gardasil ^a	Cervarix ^b
VLP Types	HPV 6, 11, 16, 18	HPV 16, 18
Adjuvant	Aluminum Salt plus monophosphoryl lipid A	Aluminum Salt
Injection Schedule	Three injections: 0, 2, 6 months	Three injections: 0, 1, 6 months
FDA Approval	Females: prevention of vaginal, vulvar, and cervical cancer and their premalignant lesions (HPV 16, 18) Females and males: preventions of genital warts (HPV 6 and 11), anal cancer and premalignant lesions (HPV 16, 18)	Females: prevention of cervical cancer and premalignant cervical lesions (HPV 16, 18)
Additional Benefits	Safe in lactation	Safe in lactation Efficacy against HPV 31, 33, 45

^aMerck & Co., Inc., Whitehouse Station, NJ, USA.^bGlaxoSmithKline, Rixensart, Belgium.

Currently, 2 vaccines are approved in the United States for the prevention of cervical cancer. The quadrivalent vaccine (Merck & Co., Inc., Whitehouse Station, NJ, USA) contains VLPs to HPV types 6, 11, 16, and 18 and the bivalent vaccine (Glaxo Smith Kline, Rixensart, Belgium) contains VLPs to HPV types 16 and 18.

The FDA originally approved the quadrivalent vaccine in 2006 for girls and women aged between 15 and 25 years for the prevention of cervical cancer caused by HPV types 16 and 18, precancerous genital lesions caused by HPV types 6, 11, 16, and 18 and genital warts caused by HPV types 6 and 11. The federal advisory committee on immunization practices (ACIP) recommended routine vaccination of all 11- and 12-year-old girls. The three shot vaccination series can begin as young as age 9, and can be given to women up to age 26. In 2008, the quadrivalent vaccine was also approved for the prevention of vaginal and vulvar cancer in this same population. The following year, its use was expanded to the prevention of genital warts due to HPV type 6 and 11 in boys and men aged between 15 and 25. In 2010, the FDA further expanded the indications to include the prevention of anal cancer and associated premalignant lesions caused by these same HPV types. In 2011, the ACIP recommended routine vaccination of all boys, ages 11 and 12. The vaccine series can be given to boys as young as age 9 and up through age 22 for most men. The FDA approved the bivalent vaccine in 2009 for the prevention of cervical cancer and precancerous lesions caused by HPV 16 and 18 in women from 15 to 25 years of age. The ACIP recommendations for the bivalent vaccine mirror those for the quadrivalent vaccine, except the bivalent vaccine is not approved for use in males.

Multiple phase III trials have been conducted to evaluate the efficacy of these vaccines (191–193). These trials were blinded, placebo-controlled trials with endpoints that included development of CIN as well as external genital lesions for the quadrivalent vaccine. In an international trial that enrolled over 17,000 women aged between 16 and 26, the quadrivalent vaccine was 99% effective in preventing HPV 16 and 18 preinvasive or invasive lesions in a 3-year follow up period in women who were HPV naive at baseline. In an intention-to-treat analysis where women with preexisting infections were included, there was considerably less efficacy against incident of CIN 2/3 or AIS due to any HPV type, thus proving that it works primarily as a prophylactic vaccine (192). This trial also showed that the quadrivalent vaccine was effective in preventing 96% of CIN 1, 100% of VIN 1 and 99% of condyloma in HPV naive women (191).

The four-year follow-up of a bivalent HPV vaccine trial, which enrolled over 18,000 young women, showed similar efficacy against development of CIN 3 and AIS. Specifically, efficacy

against HPV 16- and 18-mediated CIN 3 lesions was 100% in women who were HPV negative at the time of vaccination. The vaccine was also effective against other lesions caused by HPV types 31, 33, and 45, which are closely related to HPV 16 and 18 (194). Specifically, in women who were HPV-negative at the time of vaccination, there was 93% efficacy against all CIN 3, irrespective of HPV type, as well as 100% efficacy against all AIS (195). High rates of efficacy even in non-HPV 16- or 18-mediated lesions suggest that the vaccine's effects may be more far reaching. Of note, these high clinical efficacy rates were associated with high cross-protective immune responses as well (196). HPV vaccination has not been shown to be therapeutic against preexisting HPV infections. Therefore, the HPV vaccine is most effective if it is administered prior to the onset of sexual activity. Additionally, the vaccine is not infectious and does not contain anything that would be teratogenic and is considered teratogenicity category B. Routine pregnancy testing prior to administration is not necessary and lactating women can safely receive the vaccine (197). Based on the natural history of HPV infection and development of preinvasive and invasive disease, it may take at least 15 years before there is a significant impact on the incidence of CIN 2/3 and perhaps 30 years before there is a change in cervical cancer incidence.

HPV vaccination programs are being instituted worldwide. HPV vaccination presents unique challenges in both high- and low-resource settings, including an older age of vaccination, a 3-dose regimen at a high cost relative to other childhood vaccines, and potential socio-cultural concerns about HPV being a sexually transmitted disease. Uptake of vaccination seems to be most affected by coverage of the vaccine at the state or national level. In the United States, it is estimated that almost 50% of adolescents received at least 1 dose and only 32% received all 3. Vaccine uptake varies significantly by state, likely a reflection of variability of state funding (198). Worldwide, rates are slightly higher in other high-resource settings. In Manchester, UK, the uptake of 2 doses was reported at 55%; 3-dose coverage in southern Australia was 69% and in Denmark, 62% (199–201). Despite many barriers to HPV vaccination, it is apparent that when communities make a focused effort to promote vaccination through financial coverage or public health awareness, high levels of vaccine uptake are noted (202).

Over 85% of cervical cancer cases occur in the developing world (203), yet patients in these nations are less likely to receive HPV vaccination. Despite its high cost relative to other childhood vaccines, in nations with high incidence, emerging models suggest that vaccination is cost-effective (204). Moreover, HPV vaccination has recently been made more affordable

at a subsidized price of 5 US dollars per dose (198). This has prompted research into the most effective strategies for large-scale vaccination. In a large international trial of developing nations, HPV vaccination programs were integrated into pre-existing health-center-based and school-based vaccination

programs in communities in India, Peru, Uganda, and Vietnam. Remarkably, complete vaccination (i.e., all 3 doses) was achieved in 68% to 96% of eligible girls (198). This study confirmed that a range of HPV vaccine delivery strategies were effective in achieving HPV immunization among eligible girls.

REFERENCES

1. Hariri S, Unger ER, Sternberg M, et al. Prevalence of genital human papillomavirus among females in the United States, the National Health And Nutrition Examination Survey, 2003–2006. *J Infect Dis*. 2011;204:566–573.
2. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA*. 2007;297:813–819.
3. Zur Hausen H. Condylomata acuminata and human genital cancer. *Cancer Res*. 1974;36:794.
4. Durst M, Gissmann L, Ikenberg H, et al. A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proc Natl Acad Sci USA*. 1983;80:3812–3815.
5. Boshart M, Gissmann L, Ikenberg H, et al. A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. *EMBO J*. 1984;3:1151–1157.
6. Bosch FX, Munoz N, Shah KV, Meheus A. Second international workshop on the epidemiology of cervical cancer and human papillomaviruses. *Int J Cancer*. 1992;52:171–173.
7. Greer BE, Koh WJ, Abu-Rustum NR, et al. Cervical cancer. *J Natl Compr Canc Netw*. 2010;8:1388–1416.
8. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189:12–19.
9. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 2008;9:425–434.
10. Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338:423–428.
11. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). *J Natl Cancer Inst*. 2002;94:102–107.
12. Bernard HU, Burk RD, Chen Z, et al. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology*. 2010;401:70–79.
13. Munoz N, Castellsague X, de Gonzalez AB, et al. Chapter 1: HPV in the etiology of human cancer. *Vaccine*. 2006;24(suppl. 3):S3/1–S3/10.
14. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—Part B: biological agents. *Lancet Oncol*. 2009;10:321–322.
15. Sen E, Alam S, Meyers C. Genetic and biochemical analysis of cis regulatory elements within the keratinocyte enhancer region of the human papillomavirus type 31 upstream regulatory region during different stages of the viral life cycle. *J Virol*. 2004;78:612–629.
16. Hubert WG, Kanaya T, Laimins LA. DNA replication of human papillomavirus type 31 is modulated by elements of the upstream regulatory region that lie 5' of the minimal origin. *J Virol*. 1999;73:1835–1845.
17. Horvath CA, Boulet GA, Renoux VM, et al. Mechanisms of cell entry by human papillomaviruses: an overview. *Virol J*. 2010;7:11.
18. Evander M, Frazer IH, Payne E, et al. Identification of the alpha6 integrin as a candidate receptor for papillomaviruses. *J Virol*. 1997;71:2449–2456.
19. Shafit-Keramat S, Handisurya A, Kriehuber E, et al. Different heparan sulfate proteoglycans serve as cellular receptors for human papillomaviruses. *J Virol*. 2003;77:13125–13135.
20. Culp TD, Budgeon LR, Marinkovich MP, et al. Keratinocyte-secreted laminin 5 can function as a transient receptor for human papillomaviruses by binding virions and transferring them to adjacent cells. *J Virol*. 2006;80:8940–8950.
21. Yoon CS, Kim KD, Park SN, et al. Alpha(6) Integrin is the main receptor of human papillomavirus type 16 VLP. *Biochem Biophys Res Commun*. 2001;283:668–673.
22. Da Silva DM, Fausch SC, Verbeek JS, et al. Uptake of human papillomavirus virus-like particles by dendritic cells is mediated by Fc gamma receptors and contributes to acquisition of T cell immunity. *J Immunol*. 2007;178:7587–7597.
23. Schelhaas M, Ewers H, Rajamaki ML, et al. Human papillomavirus type 16 entry: retrograde cell surface transport along actin-rich protrusions. *PLoS Pathog*. 2008;4:e1000148.
24. Day PM, Lowy DR, Schiller JT. Heparan sulfate-independent cell binding and infection with furin-precleaved papillomavirus capsids. *J Virol*. 2008;82:12565–12568.
25. Day PM, Lowy DR, Schiller JT. Papillomaviruses infect cells via a clathrin-dependent pathway. *Virology*. 2003;307:1–11.
26. Spoden G, Freitag K, Husmann M, et al. Clathrin- and caveolin-independent entry of human papillomavirus type 16-involvement of tetraspanin-enriched microdomains (TEMs). *PLoS One*. 2008;3:e3313.
27. Riley RR, Duensing S, Brake T, et al. Dissection of human papillomavirus E6 and E7 function in transgenic mouse models of cervical carcinogenesis. *Cancer Res*. 2003;63:4862–4871.
28. Wise-Draper TM, Wells SI. Papillomavirus E6 and E7 proteins and their cellular targets. *Front Biosci*. 2008;13:1003–1017.
29. Chellappan S, Kraus VB, Kroger B, et al. Adenovirus E1A, simian virus 40 tumor antigen, and human papillomavirus E7 protein share the capacity to disrupt the interaction between transcription factor E2F and the retinoblastoma gene product. *Proc Natl Acad Sci USA*. 1992;89:4549–4553.
30. Huang PS, Patrick DR, Edwards G, et al. Protein domains governing interactions between E2F, the retinoblastoma gene product, and human papillomavirus type 16 E7 protein. *Mol Cell Biol*. 1993;13:953–960.
31. Boyer SN, Wazer DE, Band V. E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. *Cancer Res*. 1996;56:4620–4624.
32. Longworth MS, Laimins LA. The binding of histone deacetylases and the integrity of zinc finger-like motifs of the E7 protein are essential for the life cycle of human papillomavirus type 31. *J Virol*. 2004;78:3533–3541.
33. Duensing S, Lee LY, Duensing A, et al. The human papillomavirus type 16 E6 and E7 oncoproteins cooperate to induce mitotic defects and genomic instability by uncoupling centrosome duplication from the cell division cycle. *Proc Natl Acad Sci USA*. 2000;97:10002–10007.
34. Thomas M, Pim D, Banks L. The role of the E6-p53 interaction in the molecular pathogenesis of HPV. *Oncogene*. 1999;18:7690–7700.
35. Thomas MC, Chiang CM. E6 oncoprotein represses p53-dependent gene activation via inhibition of protein acetylation independently of inducing p53 degradation. *Mol Cell*. 2005;17:251–264.
36. Nguyen ML, Nguyen MM, Lee D, et al. The PDZ ligand domain of the human papillomavirus type 16 E6 protein is required for E6's induction of epithelial hyperplasia in vivo. *J Virol*. 2003;77:6957–6964.
37. Massimi P, Gammoh N, Thomas M, et al. HPV E6 specifically targets different cellular pools of its PDZ domain-containing tumour suppressor substrates for proteasome-mediated degradation. *Oncogene*. 2004;23:8033–8039.
38. Favre-Bonvin A, Reynaud C, Kretz-Remy C, et al. Human papillomavirus type 18 E6 protein binds the cellular PDZ protein TIP-2/GIPC, which is involved in transforming growth factor beta signaling and triggers its degradation by the proteasome. *J Virol*. 2005;79:4229–4237.
39. Stoppler H, Hartmann DP, Sherman L, et al. The human papillomavirus type 16 E6 and E7 oncoproteins dissociate cellular telomerase activity from the maintenance of telomere length. *J Biol Chem*. 1997;272:13332–13337.
40. Veldman T, Horikawa I, Barrett JC, et al. Transcriptional activation of the telomerase hTERT gene by human papillomavirus type 16 E6 oncoprotein. *J Virol*. 2001;75:4467–4472.
41. Frattini MG, Laimins LA. The role of the E1 and E2 proteins in the replication of human papillomavirus type 31b. *Virology*. 1994;204:799–804.
42. Deng W, Lin BY, Jin G, et al. Cyclin/CDK regulates the nucleocytoplasmic localization of the human papillomavirus E1 DNA helicase. *J Virol*. 2004;78:13954–13965.
43. Loo YM, Melendy T. Recruitment of replication protein A by the papillomavirus E1 protein and modulation by single-stranded DNA. *J Virol*. 2004;78:1605–1615.
44. Ma T, Zou N, Lin BY, et al. Interaction between cyclin-dependent kinases and human papillomavirus replication-initiation protein E1 is required for efficient viral replication. *Proc Natl Acad Sci USA*. 1999;96:382–387.
45. Bouvard V, Storey A, Pim D, et al. Characterization of the human papillomavirus E2 protein: evidence of trans-activation and trans-repression in cervical keratinocytes. *EMBO J*. 1994;13:5451–5459.
46. Steger G, Corbach S. Dose-dependent regulation of the early promoter of human papillomavirus type 18 by the viral E2 protein. *J Virol*. 1997;71:50–58.

47. Jeon S, Allen-Hoffmann BL, Lambert PF. Integration of human papillomavirus type 16 into the human genome correlates with a selective growth advantage of cells. *J Virol*. 1995;69:2989–2997.
48. Cullen AP, Reid R, Campion M, et al. Analysis of the physical state of different human papillomavirus DNAs in intraepithelial and invasive cervical neoplasia. *J Virol*. 1991;65:606–612.
49. Corden SA, Sant-Cassia LJ, Easton AJ, et al. The integration of HPV-18 DNA in cervical carcinoma. *Mol Pathol*. 1999;52:275–282.
50. Ho CM, Lee BH, Chang SF, et al. Integration of human papillomavirus correlates with high levels of viral oncogene transcripts in cervical carcinogenesis. *Virus Res*. 2011;161:124–130.
51. Einstein MH, Cruz Y, El-Awady MK, et al. Utilization of the human genome sequence localizes human papillomavirus type 16 DNA integrated into the TNFAIP2 gene in a fatal cervical cancer from a 39-year-old woman. *Clin Cancer Res*. 2002;8:549–554.
52. Hopman AH, Smedts F, Dignef W, et al. Transition of high-grade cervical intraepithelial neoplasia to micro-invasive carcinoma is characterized by integration of HPV 16/18 and numerical chromosome abnormalities. *J Pathol*. 2004;202:23–33.
53. Tonon SA, Picconi MA, Bos PD, et al. Physical status of the E2 human papilloma virus 16 viral gene in cervical preneoplastic and neoplastic lesions. *J Clin Virol*. 2001;21:129–134.
54. Thorland EC, Myers SL, Gostout BS, et al. Common fragile sites are preferential targets for HPV16 integrations in cervical tumors. *Oncogene*. 2003;22:1225–1237.
55. Castle PE, Gravitt PE, Solomon D, et al. Comparison of linear array and line blot assay for detection of human papillomavirus and diagnosis of cervical precancer and cancer in the atypical squamous cell of undetermined significance and low-grade squamous intraepithelial lesion triage study. *J Clin Microbiol*. 2008;46:109–117.
56. Smith JS, Melendy A, Rana RK, et al. Age-specific prevalence of infection with human papillomavirus in females: a global review. *J Adolesc Health*. 2008;43:S5–S25, S25 e21–41.
57. Giuliano AR, Lazcano-Ponce E, Villa LL, et al. The human papillomavirus infection in men study: human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States. *Cancer Epidemiol Biomarkers Prev*. 2008;17:2036–2043.
58. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009–2010. *JAMA*. 2012;307:693–703.
59. Albero G, Castellsague X, Giuliano AR, et al. Male circumcision and genital human papillomavirus: a systematic review and meta-analysis. *Sex Transm Dis*. 2012;39:104–113.
60. Backes DM, Kurman RJ, Pimenta JM, et al. Systematic review of human papillomavirus prevalence in invasive penile cancer. *Cancer Causes Control*. 2009;20:449–457.
61. Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2005;97:577–586.
62. Gonzalez P, Hildesheim A, Rodriguez AC, et al. Behavioral/lifestyle and immunologic factors associated with HPV infection among women older than 45 years. *Cancer Epidemiol Biomarkers Prev*. 2010;19:3044–3054.
63. Rodriguez AC, Schiffman M, Herrero R, et al. Low risk of type-specific carcinogenic HPV re-appearance with subsequent cervical intraepithelial neoplasia grade 2/3. *Int J Cancer*. 2011;131(8):1874–1881.
64. Richardson H, Kelsall G, Tellier P, et al. The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiol Biomarkers Prev*. 2003;12:485–490.
65. Dalstein V, Riethmuller D, Pretet JL, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. *Int J Cancer*. 2003;106:396–403.
66. Moscicki AB, Hills N, Shiboski S, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. *JAMA*. 2001;285:2995–3002.
67. Ferreccio C, Van de Wyngaert V, Olcay F, et al. High-risk HPV infection after five years in a population-based cohort of Chilean women. *Infect Agent Cancer*. 2011;6:21.
68. Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet*. 2001;357:1831–1836.
69. Koutsky LA, Holmes KK, Critchlow CW, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med*. 1992;327:1272–1278.
70. Bae J, Seo SS, Park YS, et al. Natural history of persistent high-risk human papillomavirus infections in Korean women. *Gynecol Oncol*. 2009;115:75–80.
71. Bory JP, Cucherousset J, Lorenzato M, et al. Recurrent human papillomavirus infection detected with the hybrid capture II assay selects women with normal cervical smears at risk for developing high grade cervical lesions: a longitudinal study of 3,091 women. *Int J Cancer*. 2002;102:519–525.
72. Cuzick J, Arbyn M, Sankaranarayanan R, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine*. 2008;26(suppl. 10):K29–K41.
73. Castle PE, Wacholder S, Lorincz AT, et al. A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. *J Natl Cancer Inst*. 2002;94:1406–1414.
74. Kjaer SK, Chackerian B, van den Brule AJ, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiol Biomarkers Prev*. 2001;10:101–106.
75. Burchell AN, Tellier PP, Hanley J, et al. Human papillomavirus infections among couples in new sexual relationships. *Epidemiology*. 2010;21:31–37.
76. Bleeker MC, Hogewoning CJ, Berkhof J, et al. Concordance of specific human papillomavirus types in sex partners is more prevalent than would be expected by chance and is associated with increased viral loads. *Clin Infect Dis*. 2005;41:612–620.
77. Benevolo M, Mottolse M, Marandino F, et al. HPV prevalence among healthy Italian male sexual partners of women with cervical HPV infection. *J Med Virol*. 2008;80:1275–1281.
78. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med*. 2006;354:2645–2654.
79. Winer RL, Lee SK, Hughes JP, et al. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. 2003;157:218–226.
80. Sellors JW, Karwalajtys TL, Kaczorowski J, et al. Incidence, clearance and predictors of human papillomavirus infection in women. *CMAJ*. 2003;168:421–425.
81. Franco EL, Villa LL, Ruiz A, et al. Transmission of cervical human papillomavirus infection by sexual activity: differences between low and high oncogenic risk types. *J Infect Dis*. 1995;172:756–763.
82. Richardson H, Franco E, Pintos J, et al. Determinants of low-risk and high-risk cervical human papillomavirus infections in Montreal University students. *Sex Transm Dis*. 2000;27:79–86.
83. Saraiya M, Watson M, Wu X, et al. Incidence of in situ and invasive vulvar cancer in the US, 1998–2003. *Cancer*. 2008;113:2865–2872.
84. King CC, Jamieson DJ, Wiener J, et al. Bacterial vaginosis and the natural history of human papillomavirus. *Infect Dis Obstet Gynecol*. 2011;2011:319460.
85. Watts DH, Fazzari M, Minkoff H, et al. Effects of bacterial vaginosis and other genital infections on the natural history of human papillomavirus infection in HIV-1-infected and high-risk HIV-1-uninfected women. *J Infect Dis*. 2005;191:1129–1139.
86. Anttila T, Saikku P, Koskela P, et al. Serotypes of Chlamydia trachomatis and risk for development of cervical squamous cell carcinoma. *JAMA*. 2001;285:47–51.
87. Wallin KL, Wiklund F, Luostarinen T, et al. A population-based prospective study of Chlamydia trachomatis infection and cervical carcinoma. *Int J Cancer*. 2002;101:371–374.
88. Quint KD, de Koning MN, Geraets DT, et al. Comprehensive analysis of Human Papillomavirus and Chlamydia trachomatis in in-situ and invasive cervical adenocarcinoma. *Gynecol Oncol*. 2009;114:390–394.
89. Lehtinen M, Ault KA, Lyytikäinen E, et al. Chlamydia trachomatis infection and risk of cervical intraepithelial neoplasia. *Sex Transm Infect*. 2011;87:372–376.
90. Silins I, Ryd W, Strand A, et al. Chlamydia trachomatis infection and persistence of human papillomavirus. *Int J Cancer*. 2005;116:110–115.
91. Samoff E, Koumans EH, Markowitz LE, et al. Association of Chlamydia trachomatis with persistence of high-risk types of human papillomavirus in a cohort of female adolescents. *Am J Epidemiol*. 2005;162:668–675.
92. Shew ML, Fortenberry JD, Tu W, et al. Association of condom use, sexual behaviors, and sexually transmitted infections with the duration of genital human papillomavirus infection among adolescent women. *Arch Pediatr Adolesc Med*. 2006;160:151–156.
93. Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*. 2004;83:1–1438.
94. Byrne MM, Davila EP, Zhao W, et al. Cancer screening behaviors among smokers and non-smokers. *Cancer Epidemiol*. 2010;34:611–617.
95. Wilkerson JE, Bailey JM, Bieniasz ME, et al. Psychosocial factors in risk of cervical intraepithelial lesions. *J Womens Health (Larchmt)*. 2009;18:513–518.
96. Syrjanen K, Shabalova I, Petrovichev N, et al. Smoking is an independent risk factor for oncogenic human papillomavirus (HPV) infections but not for high-grade CIN. *Eur J Epidemiol*. 2007;22:723–735.
97. Vaccarella S, Herrero R, Snijders PJ, et al. Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys. *Int J Epidemiol*. 2008;37:536–546.
98. Collins S, Rollason TP, Young LS, et al. Cigarette smoking is an independent risk factor for cervical intraepithelial neoplasia in young women: a longitudinal study. *Eur J Cancer*. 2010;46:405–411.
99. Ho GY, Kadish AS, Burk RD, et al. HPV 16 and cigarette smoking as risk factors for high-grade

- cervical intra-epithelial neoplasia. *Int J Cancer*. 1998;78:281–285.
100. Giuliano AR, Sedjo RL, Roe DJ, et al. Clearance of oncogenic human papillomavirus (HPV) infection: effect of smoking (United States). *Cancer Causes Control*. 2002;13:839–846.
 101. Koshiol J, Schroeder J, Jamieson DJ, et al. Smoking and time to clearance of human papillomavirus infection in HIV-seropositive and HIV-seronegative women. *Am J Epidemiol*. 2006;164:176–183.
 102. Xi LF, Koutsky LA, Castle PE, et al. Relationship between cigarette smoking and human papilloma virus types 16 and 18 DNA load. *Cancer Epidemiol Biomarkers Prev*. 2009;18:3490–3496.
 103. Prokopczyk B, Cox JE, Hoffmann D, et al. Identification of tobacco-specific carcinogen in the cervical mucus of smokers and nonsmokers. *J Natl Cancer Inst*. 1997;89:868–873.
 104. Alam S, Conway MJ, Chen HS, et al. The cigarette smoke carcinogen benzo[a]pyrene enhances human papillomavirus synthesis. *J Virol*. 2008;82:1053–1058.
 105. Barton SE, Maddox PH, Jenkins D, et al. Effect of cigarette smoking on cervical epithelial immunity: a mechanism for neoplastic change? *Lancet*. 1988;2:652–654.
 106. Lea JS, Coleman R, Kurien A, et al. Aberrant p16 methylation is a biomarker for tobacco exposure in cervical squamous cell carcinogenesis. *Am J Obstet Gynecol*. 2004;190:674–679.
 107. Samir R, Asplund A, Tot T, et al. Tissue tumor marker expression in smokers, including serum cotinine concentrations, in women with cervical intraepithelial neoplasia or normal squamous cervical epithelium. *Am J Obstet Gynecol*. 2010;202(6):579.e571–577.
 108. Appleby P, Beral V, Berrington de Gonzalez A, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet*. 2007;370:1609–1621.
 109. Longatto-Filho A, Hammes LS, Sarian LO, et al. Hormonal contraceptives and the length of their use are not independent risk factors for high-risk HPV infections or high-grade CIN. *Gynecol Obstet Invest*. 2011;71:93–103.
 110. Syrjänen K, Shabalova I, Petrovichev N, et al. Oral contraceptives are not an independent risk factor for cervical intraepithelial neoplasia or high-risk human papillomavirus infections. *Anticancer Res*. 2006;26:4729–4740.
 111. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer*. 2007;120:885–891.
 112. Mbulawa ZZ, Coetzee D, Marais DJ, et al. Genital human papillomavirus prevalence and human papillomavirus concordance in heterosexual couples are positively associated with human immunodeficiency virus coinfection. *J Infect Dis*. 2009;199:1514–1524.
 113. De Vuyst H, Lillo F, Broutet N, et al. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev*. 2008;17:545–554.
 114. Wright TC Jr, Ellerbrock TV, Chiasson MA, et al. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstet Gynecol*. 1994;84:591–597.
 115. Bratcher LF, Sahasrabudhe VV. The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. *Infect Agent Cancer*. 2010;5:8.
 116. Wistuba 2nd, Syed S, Behrens C, et al. Comparison of molecular changes in cervical intraepithelial neoplasia in HIV-positive and HIV-indeterminate subjects. *Gynecol Oncol*. 1999;74:519–526.
 117. Halpert R, Fruchter RG, Sedlis A, et al. Human papillomavirus and lower genital neoplasia in renal transplant patients. *Obstet Gynecol*. 1986;68:251–258.
 118. Origoni M, Stefani C, Dell'Antonio G, et al. Cervical Human Papillomavirus in transplanted Italian women: a long-term prospective follow-up study. *J Clin Virol*. 2011;51:250–254.
 119. Adami J, Gabel H, Lindelof B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer*. 2003;89:1221–1227.
 120. Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011;306:1891–1901.
 121. Brown MR, Noffsinger A, First MR, et al. HPV subtype analysis in lower genital tract neoplasms of female renal transplant recipients. *Gynecol Oncol*. 2000;79:220–224.
 122. Meeuwis KA, Melchers WJ, Bouten H, et al. Anogenital malignancies in women after renal transplantation over 40 years in a single center. *Transplantation*. 2012;93(9):914–922.
 123. Pudney J, Quayle AJ, Anderson DJ. Immunological microenvironments in the human vagina and cervix: mediators of cellular immunity are concentrated in the cervical transformation zone. *Biol Reprod*. 2005;73:1253–1263.
 124. Scott ME, Ma Y, Kuzmich L, et al. Diminished IFN-gamma and IL-10 and elevated Foxp3 mRNA expression in the cervix are associated with CIN 2 or 3. *Int J Cancer*. 2009;124:1379–1383.
 125. Galgano MT, Castle PE, Atkins KA, et al. Using biomarkers as objective standards in the diagnosis of cervical biopsies. *Am J Surg Pathol*. 2010;34:1077–1087.
 126. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. *JAMA*. 2001;285:1500–1505.
 127. Carreon JD, Sherman ME, Guillen D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of population-based cervical samples. *Int J Gynecol Pathol*. 2007;26:441–446.
 128. Stoler MH, Vichnin MD, Ferenczy A, et al. The accuracy of colposcopic biopsy: analyses from the placebo arm of the Gardasil clinical trials. *Int J Cancer*. 2011;128:1354–1362.
 129. Krawczyk E, Supryniewicz FA, Liu X, et al. Koilocytosis: a cooperative interaction between the human papillomavirus E5 and E6 oncoproteins. *Am J Pathol*. 2008;173:682–688.
 130. Schiffman MH, Brinton LA. The epidemiology of cervical carcinogenesis. *Cancer*. 1995;76:1888–1901.
 131. Elit L, Levine MN, Julian JA, et al. Expectant management versus immediate treatment for low-grade cervical intraepithelial neoplasia: a randomized trial in Canada and Brazil. *Cancer*. 2011;117:1438–1445.
 132. Castle PE, Gage JC, Wheeler CM, et al. The clinical meaning of a cervical intraepithelial neoplasia grade 1 biopsy. *Obstet Gynecol*. 2011;118:1222–1229.
 133. Cox JT, Schiffman M, Solomon D. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. *Am J Obstet Gynecol*. 2003;188:1406–1412.
 134. Wang, S.S., et al., Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer*. 2004;100(5):1035–1044.
 135. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol*. 2010;11:1048–1056.
 136. Zaino RJ. Symposium part I: adenocarcinoma. *in situ*, glandular dysplasia, and early invasive adenocarcinoma of the uterine cervix. *Int J Gynecol Pathol*. 2002;21:314–326.
 137. Pavlakakis K, Messini I, Athanassiadou S, et al. Endocervical glandular lesions: a diagnostic approach combining a semi-quantitative scoring method to the expression of CEA, MIB-1 and p16. *Gynecol Oncol*. 2006;103:971–976.
 138. Moritani S, Ioffe OB, Sagae S, et al. Mitotic activity and apoptosis in endocervical glandular lesions. *Int J Gynecol Pathol*. 2002;21:125–133.
 139. Judson PL, Habermann EB, Baxter NN, et al. Trends in the incidence of invasive and *in situ* vulvar carcinoma. *Obstet Gynecol*. 2006;107:1018–1022.
 140. Sideri M, Jones RW, Wilkinson EJ, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med*. 2005;50:807–810.
 141. Carlson JA, Ambros R, Malfetano J, et al. Vulvar lichen sclerosis and squamous cell carcinoma: a cohort, case control, and investigation study with historical perspective; implications for chronic inflammation and sclerosis in the development of neoplasia. *Hum Pathol*. 1998;29:932–948.
 142. McNally OM, Mulvany NJ, Pagano R, et al. VIN 3: a clinicopathologic review. *Int J Gynecol Cancer*. 2002;12:490–495.
 143. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol*. 2005;106:1319–1326.
 144. van Seters M, van Beurden M, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol*. 2005;97:645–651.
 145. Hussein Zadeh N, Recinto C. Frequency of invasive cancer in surgically excised vulvar lesions with intraepithelial neoplasia (VIN 3). *Gynecol Oncol*. 1999;73:119–120.
 146. Diakomanolis E, Stefanidis K, Rodolakis A, et al. Vaginal intraepithelial neoplasia: report of 102 cases. *Eur J Gynaecol Oncol*. 2002;23:457–459.
 147. Dodge JA, Eltabbakh GH, Mount SL, et al. Clinical features and risk of recurrence among patients with vaginal intraepithelial neoplasia. *Gynecol Oncol*. 2001;83:363–369.
 148. Tsimplaki E, Argyri E, Michala L, et al. Human papillomavirus genotyping and e6/e7 mRNA expression in greek women with intraepithelial neoplasia and squamous cell carcinoma of the vagina and vulva. *J Oncol*. 2012;2012:893275.
 149. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the prevention and early detection of cervical cancer. *J Low Genit Tract Dis*. 2012;16(3):175–204.

150. Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. 1941. *Arch Pathol Lab Med.* 1997;121:211–224.
151. Quinn M, Babb P, Jones J, et al. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ.* 1999;318:904–908.
152. Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ.* 1999;318:1244–1245.
153. van der Aa MA, Pukkala E, Coebergh JW, et al. Mass screening programmes and trends in cervical cancer in Finland and the Netherlands. *Int J Cancer.* 2008;122:1854–1858.
154. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol.* 2011;12:663–672.
155. Wingo PA, Cardinez CJ, Landis SH, et al. Long-term trends in cancer mortality in the United States, 1930–1998. *Cancer.* 2003;97:3133–3275.
156. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62:10–29.
157. Subramaniam A, Fauci JM, Schneider KE, et al. Invasive cervical cancer and screening: what are the rates of unscreened and underscreened women in the modern era? *J Low Genit Tract Dis.* 2011;15:110–113.
158. Bentz JS, Rowe LR, Gopez EV, et al. The unsatisfactory thin prep pap test: missed opportunity for disease detection? *Am J Clin Pathol.* 2002;117:457–463.
159. Islam S, West AM, Saboorian MH, et al. Reprocessing unsatisfactory thin prep papanicolaou test specimens increases sample adequacy and detection of significant cervicovaginal lesions. *Cancer.* 2004;102:67–73.
160. Woodhouse SL, Stastny JF, Styer PE, et al. Interobserver variability in subclassification of squamous intraepithelial lesions: Results of the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med.* 1999;123:1079–1084.
161. Confortini M, Carozzi F, Dalla Palma P, et al. Interlaboratory reproducibility of atypical squamous cells of undetermined significance report: a national survey. *Cytopathology.* 2003;14:263–268.
162. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer.* 2006;119:1095–1101.
163. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med.* 2000;132:810–819.
164. Stout NK, Goldhaber-Fiebert JD, Ortendahl JD, et al. Trade-offs in cervical cancer prevention: balancing benefits and risks. *Arch Intern Med.* 2008;168:1881–1889.
165. Bulkman NW, Berkhof J, Rozendaal L, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet.* 2007;370:1764–1772.
166. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol.* 2010;11:249–257.
167. Anttila A, Kotaniemi-Talonen L, Leinonen M, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma *in situ* in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. *BMJ.* 2010;340:c1804.
168. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst.* 2001;93:293–299.
169. Manos MM, Kinney WK, Hurley LB, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA.* 1999;281:1605–1610.
170. Cox JT. The development of cervical cancer and its precursors: what is the role of human papillomavirus infection? *Curr Opin Obstet Gynecol.* 2006;18(suppl. 1):s5–s13.
171. Lonky NM, Sadeghi M, Tsadik GW, et al. The clinical significance of the poor correlation of cervical dysplasia and cervical malignancy with referral cytologic results. *Am J Obstet Gynecol.* 1999;181:560–566.
172. ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol.* 2003;188:1383–1392.
173. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 99: management of abnormal cervical cytology and histology. *Obstet Gynecol.* 2008;112:1419–1444.
174. Srodon M, Parry Dilworth H, Ronnett BM. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion: diagnostic performance, human papillomavirus testing, and follow-up results. *Cancer.* 2006;108:32–38.
175. Castle PE, Stoler MH, Solomon D, et al. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *Am J Clin Pathol.* 2007;127:805–815.
176. Dunn TS, Burke M, Shwayder J. A “see and treat” management for high-grade squamous intraepithelial lesion pap smears. *J Low Genit Tract Dis.* 2003;7:104–106.
177. Berdichevsky L, Karmin R, Chuang L. Treatment of high-grade squamous intraepithelial lesions: a 2- versus 3-step approach. *Am J Obstet Gynecol.* 2004;190:1424–1426.
178. Sharpless KE, Schnatz PF, Mandavilli S, et al. Dysplasia associated with atypical glandular cells on cervical cytology. *Obstet Gynecol.* 2005;105:494–500.
179. DeSimone CP, Day ME, Tovar MM, et al. Rate of pathology from atypical glandular cell Pap tests classified by the Bethesda 2001 nomenclature. *Obstet Gynecol.* 2006;107:1285–1291.
180. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med.* 2007;357:1579–1588.
181. Leinonen M, Nieminen P, Kotaniemi-Talonen L, et al. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. *J Natl Cancer Inst.* 2009;101:1612–1623.
182. Vesco KK, Whitlock EP, et al. Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the U.S. Preventive services task force. *Ann Intern Med.* 2011;155(10):698–705.
183. Petignat P, Faltin DL, Bruchim I, et al. Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? A systematic review and meta-analysis. *Gynecol Oncol.* 2007;105:530–535.
184. Gok M, Heideman DA, van Kemenade FJ, et al. HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. *BMJ.* 2010;340:c1040.
185. Bais AG, van Kemenade FJ, Berkhof J, et al. Human papillomavirus testing on self-sampled cervicovaginal brushes: an effective alternative to protect nonresponders in cervical screening programs. *Int J Cancer.* 2007;120:1505–1510.
186. Blumenthal PD, Lauterbach M, Sellors JW, et al. Training for cervical cancer prevention programs in low-resource settings: focus on visual inspection with acetic acid and cryotherapy. *Int J Gynaecol Obstet.* 2005;89(suppl. 2):S30–S37.
187. Sankaranarayanan R, Gaffikin L, Jacob M, et al. A critical assessment of screening methods for cervical neoplasia. *Int J Gynaecol Obstet.* 2005;89(suppl 2):S4–S12.
188. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. *N Engl J Med.* 2005;353:2158–2168.
189. Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet.* 2007;370:398–406.
190. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *N Engl J Med.* 2009;360:1385–1394.
191. Dillner J, Kjaer SK, Wheeler CM, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. *BMJ.* 2010;341:c3493.
192. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma *in situ*: a combined analysis of four randomised clinical trials. *Lancet.* 2007;369:1861–1868.
193. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet.* 2007;369:2161–2170.
194. Wheeler CM, Castellsague X, Garland SM, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol.* 2012;13:100–110.
195. Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol.* 2012;13:89–99.
196. Einstein MH, Baron M, Levin MJ, et al. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18–45 years. *Hum Vaccin.* 2011;7:1359–1373.

197. Committee opinion no. 467: human papillomavirus vaccination. *Obstet Gynecol.* 2010;116:800–803.
198. LaMontagne DS, Barge S, Le NT, et al. Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. *Bull World Health Organ.* 2011;89:821B–830B.
199. Watson M, Shaw D, Molchanoff L, et al. Challenges, lessons learned and results following the implementation of a human papilloma virus school vaccination program in South Australia. *Aust N Z J Public Health.* 2009;33:365–370.
200. Brabin L, Roberts SA, Stretch R, et al. Uptake of first two doses of human papillomavirus vaccine by adolescent schoolgirls in Manchester: prospective cohort study. *BMJ.* 2008;336:1056–1058.
201. Widgren K, Simonsen J, Valentiner-Branth P, et al. Uptake of the human papillomavirus-vaccination within the free-of-charge childhood vaccination programme in Denmark. *Vaccine.* 2011;29:9663–9667.
202. Hayashi Y, Shimizu Y, Netsu S, et al. High HPV vaccination uptake rates for adolescent girls after regional governmental funding in Shiki City, Japan. *Vaccine.* 2012;30(37):5547–5550.
203. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127:2893–2917.
204. Termrungruanglert W, Havanond P, Khemapech N, et al. Cost and effectiveness evaluation of prophylactic HPV vaccine in developing countries. *Value Health.* 2012;15:S29–S34.

SECTION II

DIAGNOSTIC AND THERAPEUTIC MODALITIES

CHAPTER

8

Perioperative and Critical Care

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INTRODUCTION

Surgery remains the mainstay of treatment for women with gynecologic malignancies. Ultimately, outcomes of the surgical intervention rest with the gynecologic oncologist in concert with anesthesiologists, nursing staff, stomal therapists, physical therapists, pharmacists, social workers, and the social network/support of the patient as well as others. Careful assessment of the patient prior to surgery can lead to improved outcomes and minimize surprises in the postoperative period. Should the need arise, prudent consultation with other medical specialists prior to or following surgery can further enhance patient care, and result in better outcomes.

The chapter has been divided into (2) sections: preoperative care/risk recognition and postoperative care/critical care. Within each section, clinical information has been arranged by organ system and recommendations are based upon evidence (when available). The critical care section provides basic yet practical information for the reader so that comanagement of the critically ill gynecologic oncology patient with an intensivist may be seamless.

PREOPERATIVE RISK ASSESSMENT

Initial Preoperative Evaluation

At the initial consultation for patients with known or suspected gynecologic malignancies, the gynecologic oncologist should take a thorough history, assessing for comorbid conditions, which may impact perioperative risk (1). Similarly, a thorough physical examination, looking for signs of diseases of which the patient is unaware, will aid in finding diseases that can impact surgical outcome. Review of accompanying medical records and radiographs is important. Ultimately, patients who will benefit from surgery are identified and will be deemed operative candidates, operative candidates who need further evaluation from specialists prior to surgery, or inoperable candidates.

Subsequent discussions should focus on the course of treatment. If surgical, the planned operative procedure should be described to the patient in nonmedical terminology. Attendant risks of the procedure, as well as alternatives for therapy (if they exist), should be described to the patient. The length of time for the operation and length of anticipated hospital stay should be estimated for the patient and her family. Further, time to recovery from the planned operative procedure should be estimated for the patient. These elements of the treatment plan constitute *informed*

consent, and should be documented in the medical record by the physician at the initial consultation. Preferably, this “consenting” should be done before the patient is in the preoperative holding area on the day of her surgery. Should further evaluation be needed from a specialist (e.g., a cardiologist or a pulmonologist), a letter outlining the proposed surgical intervention should be sent to the consultant. However, the impact of these consultations, or “preoperative clearances,” on perioperative outcomes is unclear (2–4).

Ideally, preoperative laboratory testing will be dictated by findings from the history and physical examination. Unfortunately, unnecessary and inappropriate preoperative testing has been done in an effort to reduce poor perioperative outcomes. However, evidence to support this practice is lacking and the cost to complete these unnecessary tests has been estimated to be over \$3 billion (5). In order to standardize preoperative testing, evidence-based guidelines have been developed (6). The National Institute for Health and Clinical Excellence (NICE), an independent organization in the United Kingdom that produces evidence-based guidelines for the promotion of good health and treatment of disease, developed guidelines for preoperative testing. These guidelines take into account the patient’s age, type of surgery, associated comorbidities, and the American Society of Anesthesiologists (ASA) grade for anesthesia risk (7) (Table 8.1). St. Clair et al. performed a retrospective study assessing adherence to the NICE guidelines for preoperative testing in patients having gynecological surgery between 2005 and 2007. The authors found that among 1,402 patients evaluated, inappropriate preoperative testing resulted in costs over \$418,000 (8).

If the patient’s condition requires the possibility of a stoma(s) (colostomy or urostomy), consultation with an enterostomal therapist for marking of the planned stoma(s) should be considered. During this visit, the therapist will take into account the location of the patient’s waist, abdominal creases, how she wears her clothing, the types of clothing she wears, and the location of the future stoma when she stands or sits. In addition, the therapist can initiate education on the function and care of the stoma(s).

Should the proposed surgery result in a marked change of body image or possible sexual dysfunction (e.g., exenteration, radical vulvectomy, or vaginal reconstruction), consultation with prior patients who have successfully recovered from similar operations may be warranted. In addition, these patients may benefit from psychological counseling prior to their surgery.

Assessment of Cardiac Risk

Any gynecologic oncologist must be aware of the underestimation of cardiac disease in women when evaluating cardiac risk preoperatively. In the past decade, a great deal of literature has

Table 8.1 National Institute for Health and Clinical Excellence Recommendations for Preoperative Testing

Study	Age (years)	Recommendation
Chest X-ray	Any age	Cardiovascular surgery
	60 or older	Grade 4 surgery and ASA 3 or greater with cardiovascular disease
Electrocardiogram	16–39	ASA 2 or greater with cardiovascular disease or cardiovascular surgery
	40–59	As above, plus grade 4 surgery if ASA 2 or greater with renal disease, or ASA 3 with respiratory disease
	60–79	As above, plus grade 2 surgery if ASA 2 or greater with renal disease, or ASA 3+ with respiratory disease or grade 3 surgery or greater
	80 or older	Consider deferring if grade 1 surgery
Full blood count	16–59	ASA 3 with renal disease, or grade 3 or greater surgery
	60 or older	As above, plus grade 2 or greater surgery
Hemostasis	16 or older	Never recommend, may be considered
Renal function	15–59	ASA 2 or greater with renal disease, ASA 3 or greater with cardiovascular disease, ASA 2 or greater with cardiovascular disease with grade 3 or greater surgery, ASA 3 or greater with respiratory disease, with grade 3 or greater surgery
	60 or older	As above, plus ASA 2 with cardiovascular disease, with grade 2 or greater surgery, or any grade 3 surgery
Urinalysis	16 or older	Never recommended, may be considered

ASA, American Society of Anesthesiologists.

ASA grade: ASA 1, normal/healthy; ASA 2, mild systemic disease; ASA 3 severe systemic disease.

Surgery grade: grade 1, minor surgery; grade 2, intermediate surgery; grade 3, major surgery; grade 4, extensive surgery.

Source: From St. Clair CM, Shah M, Diver EJ, et al. Adherence to evidence-based guidelines for preoperative testing in women undergoing gynecologic surgery. *Obstet Gynecol.* 2010;116(3):694–700, with permission.

been published on this subject. In 2001, the National Heart, Lung, and Blood Institute (NHLBI) launched the Heart Truth Project to promote education about heart disease among women (9). Statistics have shown that only one of three primary physicians correctly cited coronary artery disease as a leading cause of death in women. Similarly, studies have demonstrated that women are less often counseled on cardiac risk factors, less often prescribed lipid-lowering medications, less often offered invasive procedures, and less often prescribed cardiac rehabilitation. There is a lack of health care provider knowledge of the guidelines for prevention of cardiovascular disease (CVD) in women (10). Further, compared to men, women who had a

Table 8.2 Multifactorial Index of Cardiac Risk

Risk factor	Points
S3 gallop or increased jugular venous pressure	11
Myocardial infarction in previous 6 months	10
More than 5 premature ventricular ectopic beats per minute	7
Rhythm other than sinus or premature atrial contractions	7
Age >70 years	5
Emergency noncardiac operative procedure	4
Significant aortic stenosis	3
Poor general health status	3
Abdominal or thoracic surgery	3
Possible total	53

Source: Adapted from Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297:845–880, with permission.

myocardial infarction (MI) had a greater interval from onset of pain until arrival at hospital, were less likely to be treated with thrombolytics and β -blocking agents, were less often evaluated with invasive methods, had higher rates of reinfarction, and had greater mortality (9).

In the assessment of perioperative risk, cardiac risk factors are certainly one of the top concerns for clinicians. There have been a number of reviews and different systems created for the purposes of assessing cardiac risk for patients undergoing noncardiac surgery (10–13). Realize that approximately 1 in 12 patients (>65 years old) will have significant coronary artery disease (14). It is estimated that over 30% of patients undergoing major elective surgery have at least one cardiac risk factor (15).

Cardiac risk indices have been published by at least 10 different investigators (16). Goldman et al. published the Multifactorial Index of Cardiac Risk (MICR) in 1977 (17). This risk index was the first large, prospective, multivariate analysis of patients undergoing noncardiac surgery. They used definite endpoints of cardiac death, ventricular tachycardia, pulmonary edema, and myocardial infarction. The MICR involves nine independent risk factors to create a point risk index and predict morbidity and mortality (Tables 8.2 and 8.3). One weakness of this index is underestimating risk in vascular surgery patients. Nonetheless, these criteria have been validated and have stood the test of time. In response to a shift in the literature from calculation of risk with indices to clinical decision making, especially in regard

Table 8.3 Multifactorial Index of Cardiac Risk, Cardiac Risk Class, Morbidity, and Mortality

Cardiac Risk	Total Points	Morbidity (%)	Mortality
Class I	0–5	0.7	0.2
Class II	6–12	5.0	1.6
Class III	12–25	11.5	2.3
Class IV	>26	22.2	55.6

Source: Adapted from Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297:845–850, with permission.

Table 8.4 Classification of CVD Risk in Women

Risk Status	Criteria
High risk	Established coronary heart disease Cerebrovascular disease Peripheral arterial disease Abdominal aortic aneurysm End-stage or chronic renal disease Diabetes mellitus 10-year Framingham global risk >20% ^a
At risk	≥1 major risk factors for CVD, including: Cigarette smoking Poor diet Physical inactivity Obesity, especially central adiposity Family history of premature CVD (CVD at <55 years of age in male relative and <65 years of age in female relative) Evidence of subclinical vascular disease (e.g., coronary calcification) Metabolic syndrome Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
Optimal risk	Framingham global risk <10% and a healthy lifestyle, with no risk factors

CVD, coronary vascular disease.

^aOR at high risk on the basis of another population-adapted tool used to assess global risk.

Source: Adapted from Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481–1501, with permission.

to the need for preoperative evaluation, the American College of Cardiology/American Heart Association (ACC-AHA) guidelines were developed (18). Recently, the AHA updated guidelines for CVD prevention in women (19). This document provides risk classification of coronary vascular disease (CVD), based upon clinical criteria and/or the Framingham 10-year global risk score (20) (Table 8.4). This CVD risk stratification has not been assessed specifically for preoperative risk assessment, but provides classification of women who may need further (noninvasive or invasive) evaluation.

Clearly, the approach to the patient must include a careful history and physical examination. Initially, age greater than 70 years was thought to be a risk factor for cardiac morbidity, but a recent clinical trial showed no increased independent risk for cardiac complications (20). Any prior history of cardiac disease such as angina, MI, arrhythmia, congestive heart failure, or valvular disease must be evaluated. Patients with unstable angina, recent myocardial infarction, class III-IV heart failure, decompensated congestive failure, or aortic stenosis present the highest risk. These patients will likely require further invasive testing. Severe aortic stenosis must be identified preoperatively because the risk of perioperative morbidity is as high as 30% (21).

In patients without overt cardiac risks, other factors are considered to be helpful for uncovering subclinical disease. Classically, these risk factors are smoking, hyperlipidemia, hypertension, and diabetes mellitus.

In 2007, the ACC-AHA published revised guidelines to direct invasive, interventional evaluations (14). The classification defines clinical predictors as minor, intermediate, and major. In addition, the guidelines now utilize functional capacity in terms of metabolic equivalents (METs), with a level <4 being considered poor. The ability to climb one flight of stairs or walk up a hill would classify the patient in the >4 group (14).

Testing available for further evaluation includes both invasive and noninvasive methods. The routine resting electrocardiogram is a valuable screening tool for patients over the age of 40. It can potentially identify a prior myocardial infarction, which may prompt further evaluation of coronary artery disease. Echocardiography can predict postoperative congestive heart failure (CHF) in patients with ejection fractions (EFs) less than 35% (22). Unfortunately, echocardiography cannot reliably predict ischemia, but may be quite useful in the evaluation of valvular diseases and for follow-up of patients with known left ventricular (LV) dysfunction. Additionally, elevated preoperative brain natriuretic peptide (BNP) is an independent predictor of 30-day adverse cardiovascular outcomes after noncardiac surgery (23). Exercise or pharmacological stress testing provides valuable information for perioperative ischemic risk. Nuclear scintigraphy with evaluation of perfusion defects has shown a positive predictive value of 12% to 16% and a negative predictive value of 99% (24). Dobutamine stress echocardiography has shown similar predictive values.

The ACC-AHA recommendations provide a way to segregate patients who should have their surgery delayed for further cardiac evaluation because of a recent MI, who should have their CHF optimized, or who should optimize control of dysrhythmias. In selected patients, coronary revascularization, angioplasty, stent placement, or valve replacement may be prudent before the planned noncardiac surgery (18).

The risk of reinfarction after a recent MI is directly related to the interval between the MI and an event, which could precipitate an MI. However, these rates have been declining due to improved perioperative care. Reinfarction rates have dropped from 37% in patients undergoing noncardiac surgery within 3 months following MI to 5% to 10%, more recently. Reinfarction rates reduce further as the interval from the original MI increases, with rates of reinfarction being 2% to 3% and 1% to 2%, 4 to 6 months and greater than 6 months, following the acute event, respectively (25). Elective surgery should be postponed for 6 months following an acute MI, however an urgent operation may be performed 4 to 6 weeks after infarction if stress testing is favorable and the patient receives cardiac monitoring in the perioperative period.

Perioperative β -Blockade

In 1996, a multicenter, randomized, placebo-controlled trial was published that evaluated the use of β -blockade with atenolol versus placebo in patients undergoing noncardiac surgery. Although no differences in perioperative mortality or MI were seen, the atenolol group had significantly fewer ischemic episodes (24% vs. 39%). Furthermore, at 6 months and at 2 years, the atenolol group had decreased mortality (9 vs. 21 deaths) and decreased number of cardiac events (16 vs. 32) (26). The Peri Operative ISchemic Evaluation (POISE) trial showed that the use of β -blockers in the perioperative period reduces the risk of the composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest at 30 days. However, it also shown that bradycardic episodes and hypotensive events result in an increase in death and strokes (27). Based on the findings of these studies, patients with or at risk for coronary artery disease may receive some benefit from perioperative β -blockade use; however, the clinician must be aware of the potential adverse outcomes.

PULMONARY RISK ASSESSMENT

Postoperative pulmonary complications represent a significant cause for morbidity and mortality in patients undergoing elective surgery. Approximately 25% of deaths within the early postoperative period (first week) are related to pulmonary issues. Pulmonary complications after major abdominal surgery range from 20% to 30% (28). Laparotomy results in a 45% decrease in vital capacity and a 20% reduction in functional residual capacity (FRC) (29). When the patient is in the supine position, FRC is reduced below alveolar closing volume (i.e., the volume at which point alveoli start closing), which results in atelectasis (30).

When examining risk factors for postoperative pulmonary problems, a number of issues surface. General medical status (e.g., functional status, obesity, nutrition) is related to postoperative pulmonary complications (PPCs) (31). A history of congestive heart failure, renal failure, poor mental status, and immunosuppression are all associated with a higher PPC rate (32). Surgical issues such as the type of procedure (open or minimally invasive), the type of incision (thoracic and upper abdominal being worse than midline or lower abdominal), duration of anesthetic (>2 hours), the use of a nasogastric tube (increased risk), and the use of parenteral (increased risk) versus epidural (decreased risk) analgesics are all correlated with PPC incidence (33). All patients undergoing noncardiothoracic surgery should be evaluated for the presence of the following risk factors for PPCs in order to receive pre- and postoperative interventions to reduce risk: chronic obstructive pulmonary disease (COPD), congestive heart failure, American Society of Anesthesiologists (ASA) class of II or greater, functionally dependent, and age older than 60 years (34). In terms of direct pulmonary risk factors, the most common preexisting pulmonary disease is COPD (32). These patients retain carbon dioxide, have poor gas exchange, and have an increased residual volume. Smoking, history of dyspnea, pneumonia, and sleep apnea are other risk categories. Patients with asthma and other restrictive lung diseases (low forced vital capacity [FVC] with normal forced expiratory volume in the first second of expiration [FEV₁/FVC ratio) have minimal increased risk for PPCs (33).

When interpreting the usual preoperative radiographic and laboratory values, several caveats must be kept in mind. A preoperative chest radiograph in normal adults has no predictive value other than providing essential baseline data for an at-risk patient. Arterial blood gas analysis in prospective trials has not been shown to be useful in providing risk stratification. However, it is useful in providing baseline data for patients with preexisting disease such as COPD (35). A low serum albumin (<35 g/L) is a powerful marker of increased risk and should be considered in patients with one or more risk factors for PPCs (36). Preoperative pulmonary function tests (PFTs) are rarely useful for risk stratification and not routinely indicated prior to surgery. A consensus statement from the American College of Physicians in 2006 recommended that preoperative PFTs or chest radiography may be appropriate in patients with a previous diagnosis of COPD or asthma (34). Such testing may provide valuable baseline data and aid in risk stratification for patients with moderate to severe COPD who are undergoing major abdominal surgery.

Perioperative strategies for reducing risk of PPCs include lung expansion techniques, smoking cessation, and optimization of gas exchange. Although preoperative and postoperative incentive spirometry has shown mixed results in reducing the rate of pulmonary complications, it continues to be widely recommended (37), and it should be considered as a preventive strategy for any patient undergoing laparotomy. In order to maximize patient compliance, preoperative counseling and education are necessary. Clearly, COPD must be optimized with control of infection and maximizing medical regimens. Reactive airway disease should be prevented with the use of perioperative inhalation therapy such

as β agonists. Steroid therapy is generally reserved for patients already utilizing them as part of their medical regimen. These steroid-dependent patients will need stress-dose steroids to prevent insufficiency (see “Adrenal Suppression” section below). Prophylactic antibiotics are not indicated in COPD patients to prevent pulmonary infections.

Smokers have significantly more postoperative complications including pneumonia, surgical-site infections, and death (38). Smoking-cessation programs have had an unclear effect on PPCs (39). Although the data consist of poorly controlled trials, it appears that short-term abstinence (<8 weeks from the time of surgery) may actually increase the complication rate (40). Abstinence for greater than 10 weeks showed complication rates similar to nonsmokers (41). Unfortunately, the long-term success rate of smoking-cessation programs is low, and in the case of malignancy, the gynecologic oncologist rarely has the opportunity to delay the operation for 8 to 10 weeks.

ENDOCRINOLOGIC RISK ASSESSMENT

Diabetes

The prevalence of diabetes has reached epidemic proportions in the United States. In 2011, the Centers for Disease Control and Prevention (CDC) reported that 25.8 million people or 8.3% of the population have diabetes (42). Diabetes accounts for the fourth leading comorbid condition among hospital discharges (43). One-fifth of surgical patients will have diabetes and people with known diabetes have a 50% risk of undergoing surgery at some point in their lifetime (44). Interestingly, one-third to one-half of patients hospitalized are unaware that they have diabetes and are currently receiving no treatment. It is only during preoperative evaluation for elective surgery or acute hospitalization that these patients will be diagnosed (45). Because of this prevalence, some authors have suggested that all surgical patients be regarded as dysglycemic until proven otherwise (46). Understanding the basic physiology of diabetes and how it impacts perioperative risk is crucial for the surgeon.

There are two types of diabetes. Type 1 diabetes occurs as a result of insulinopenia, with all type 1 diabetics being insulin dependent. In the absence of sufficient insulin, these patients develop ketoacidosis. Type 1 diabetics account for approximately 10% of all diabetics. Type 2 diabetes occurs as a result of insulin resistance and impaired insulin secretion. Type 2 diabetics may be treated with diet alone, oral hypoglycemic agents, noninsulin injectable medications, or insulin. These patients account for approximately 90% of all diabetics (47). However, approximately 30% of hospitalized patients will have a prediabetic condition consisting of impaired fasting glucose levels or impaired glucose tolerance (45). Thus, perioperative glycemic control will be dictated by known (or newly discovered) diabetic status.

When evaluating patients with known diabetes for surgery, attention should be directed toward the patient's diabetic status (i.e., type of glucose control; number of hypoglycemic events, etc.) and the long-term complications caused by diabetes since this end organ damage can impact perioperative outcome. Most complications of diabetes are related to microvascular changes, such as diabetic retinopathy, neuropathy, nephropathy, and CVD (48). In addition to a thorough history and physical examination, preoperative studies should include an electrocardiogram to rule out a prior “silent” MI (especially in patients with diabetes for more than 10 years), serum creatinine, blood urea nitrogen, urinary analyses to assess renal function and glycosylated hemoglobin (HbA_{1c}) to evaluate recent glycemic

control. HbA_{1c} levels reflect the level of hyperglycemia that red blood cells (RBC) have been exposed. Because the average lifespan of an RBC is 120 days, the HbA_{1c} is an indicator of glycemic control over that period of time (47). As mentioned earlier, because of the prevalence of dysglycemia among hospitalized adults in the United States, measurement of HbA_{1c} as a screening for diabetes, may identify patients with undiagnosed diabetes or impaired glucose metabolism (46). HbA_{1c} levels ≤6.5% are associated with good long-term glucose control and have been associated with decreased rates of infectious complications across a variety of surgical procedures (49,50). However, HbA_{1c} levels >6.5% are diagnostic for diabetes and evidence of poor glycemic control in known diabetics (51,52). Ultimately, the type of diabetes, preoperative glycemic control, the extent and magnitude of the intended surgery, the elective or emergent nature of said surgery, and other comorbid medical conditions will affect the metabolic changes these patients face intra- and postoperatively (46).

Another entity which has come to light in the last decade among hospitalized patients is that of stress induced hyperglycemia (SIH). This disease is defined as an inpatient fasting glucose measurement ≥126 mg/dL or a random glucose measurement of more than 200 mg/dL, which returns to normal after discharge (44,53). A growing body of evidence suggests that SIH and diabetic hyperglycemia are different diseases (54) and SIH confers a higher risk of adverse outcomes, such as an increased risk of in-hospital mortality (52,55,56) and longer lengths of stay compared to nondiabetic or hyperglycemic diabetic patients (53).

The armamentarium available for treatment of diabetes has increased over the last decade. Type 1 diabetics will most likely be using a combination of insulin therapies for glycemic control, whereas type 2 diabetics may be on oral therapy alone, insulin therapy alone, injectable noninsulin therapy alone, or some combination therapy of all the aforementioned agents. Table 8.5 outlines these drugs and timing for stopping these medications prior to surgical procedures because of the pharmacological half-lives of these drugs (57).

The physiologic changes that diabetic patients encounter during surgery result in a hyperglycemic state. The stress of surgery increases secretion of epinephrine, norepinephrine, cortisol, and growth hormone, all of which directly antagonize insulin action (46–48). In addition, gluconeogenesis and lipolysis are increased with mobilization of glucose precursors, and a net protein catabolism ensues. Glycemic control perioperatively will depend upon the type of diabetes or impaired glucose tolerance the patient has, as well as the medications that have/have not be utilized to control such disease states. Recently the Clinical Guidelines Subcommittee of The Endocrinology Society published treatment guidelines for non-critically ill patients hospitalized and subsequently found to be hyperglycemic (known diabetes versus unknown). The authors would direct the reader to review these guidelines, but recommendations from this group, for perioperative care of patients with hyperglycemia undergoing surgical interventions, are listed in Table 8.6 (58).

There are several case-control studies that demonstrate an increased risk for adverse outcomes in patients undergoing elective noncardiac surgery who have either preoperative or postoperative hyperglycemia (59–63). Postoperative glucose levels greater than 200 mg/dL are associated with prolonged hospital stays and increased risk of postoperative complications including wound infections and cardiac arrhythmias (60–62). Although diabetic patients with vascular disease are at risk of silent postoperative MI and acute renal failure, postoperative infections (respiratory, urinary, wound infections, etc.) account for about two-thirds of all postoperative complications and 20% of all postoperative deaths among diabetics undergoing surgery (49). Hyperglycemia has been shown to impair phagocytic function and chemotaxis of granulocytes when glucose levels are higher than 250 mg/dL (64).

Table 8.5 Management of Diabetes Medications Before Surgery in Patients Who Must Be NPO

Medication Type	Night before Surgery	Morning of Surgery
Oral Agents		
Sulfonyl-urea		Hold
Glyburide	Give with meal	
Glipizide		
Glimepiride		
Metformin (contraindicated in women with creatinine levels >1.4)	Hold	Hold; can induce lactic acidosis and should be held in patients' procedures that require IV contrast
Thiazolidinediones	Hold	Hold; Can cause fluid retention in the postoperative period
Rosiglitazone		
Pioglitazone		
Meglitinides	Give with meal	Hold
Repaglinide		
Nateglinide		
α Glucosidase inhibitors	Give with meal	Hold
Acarbose		
Miglitol		
Dipeptidyl peptidase-IV inhibitor	Give with meal	Hold
Sitagliptin		
Noninsulin Injectable		
Incretin mimetics	Give 30–60 minutes before meal	Hold
Exenatide		
Amylin analog	Give immediately before meal	Hold
Pramlintide		
Insulin		
Regular Insulin	Give full dose	Give half dose
Humulin ®R		
Novolin ®R		
ReliOn ®R		
NPH Insulin	Give full dose	Give half dose
Humulin ®N		
Novolin ®N		
ReliOn ®N		

Continued

Table 8.5 Management of Diabetes Medications Before Surgery in Patients Who Must Be NPO (continued)

Medication Type	Night before Surgery	Morning of Surgery
Premixed Insulins	Give full dose	Give half dose
Humulin ®70/30		
Novolin ®70/30		
Humalog ®75/25		
Novolog ®70/30		
Rapid-acting Insulin	Give full dose with meals	Hold
Aspart		
Glulisine		
Lispro		
Inhaled Insulin		
Basal Insulin (long-acting)	If patient is on basal insulin and rapid-acting insulin, give full dose. If patient is on oral diabetes medication plus basal insulin or basal insulin only, give half dose	If patient is on basal insulin and rapid-acting insulin, give full dose. If patient is on oral diabetes medication plus basal insulin or basal insulin only, give half dose
Glargine		
Detemir		
Continuous subcutaneous insulin pump	Continue current settings	Switch to continuous insulin infusion and titrate

Source: From Meneghini LF. Perioperative management of diabetes: translating evident into practice. *Cleveland Clin J Med*. 2009;76(4):S53–S59 and Khan NA, Ghali WA, Spratt SE, et al. Perioperative management of diabetes mellitus. Physicians' Information and Education Resources. American College of Physicians, 31 Aug. 2009, 26 Apr. 2012. <http://pier.acponline.org/physicians/public/periopr879/tables/periopr879-tl.html>, with permission.

Although glycemic control is important, the jury is still out on when control should be achieved (pre-, intra-, or postoperatively or throughout the entire perioperative period), what glucose levels should be achieved for maximum benefit, and which insulin regimen is most effective (46). The landmark publication by Van den Berghe et al. in 2001 showed, in a randomized, prospective fashion, that aggressive glycemic control through intensive insulin therapy (IIT) (maintaining glucose levels between 80 and 110 mg/dL) versus conventional insulin therapy (glucose levels between 180 and 200 mg/dL) in critically ill postoperative patients (more than 60% were cardiac surgery patients) reduced episodes of septicemia and in-hospital mortality by 46% and 34%, respectively (65). Despite the enthusiasm for tighter glucose control, subsequent studies over the last decade, with a heterogeneous population of acutely ill patients, have failed to confirm the results of Van den Berghe's work (46,53). In fact, the multinational, multidisciplinary Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial in 6104 ICU patients reported increased mortality rates (27.5% [IIT] vs. 24.9% [control]) in patients who were kept at blood glucose levels of 81 to 108 mg/dL versus <180 mg/dL. The increased mortality was driven by increased rates of

Table 8.6 Perioperative Blood Glucose Control: An Endocrine Society Clinical Practice Guideline

Recommendation Number	
5.3.1	All patients with type 1 diabetes who undergo minor or major surgical procedures receive either continuous insulin infusion or subcutaneous basal insulin with bolus insulin as required to prevent hyperglycemia during the perioperative period
5.3.2	Patients with diabetes should discontinue oral and noninsulin injectable antidiabetic agents before surgery with initiation of insulin therapy in those patients that develop hyperglycemia during the perioperative period
5.3.3	When instituting subcutaneous insulin therapy in the postsurgical setting, basal (for patients who are NPO) or basal bolus (for patients who are eating) insulin therapy is the preferred approach. Sliding scale insulin (SSI) should not be used

Source: Umpierrez GE, Hellman R, Korytkoski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2012;97:16–38.

hypoglycemia (blood glucose <40 mg/dL) among patients with the tightest blood glucose control (6.8% [IIT] vs. 0.5% [control], respectively) (66). Because of the NICE-SUGAR study, and others (53), recommendations for blood glucose targets have relaxed somewhat depending upon the setting of the patient. Intravenous (IV) insulin therapy should be instituted in critically ill patients when blood glucose levels exceed 180 mg/dL, and for non-critically ill patients when blood glucose levels exceed 140 mg/dL (67), to maintain blood glucose at these levels while minimizing hypoglycemia. Attaining these levels of glycemic control will depend upon the patient's type of diabetes, her medical condition, and her oral intake status. Individual institutional policy will vary as to where patients may receive IV insulin therapy (ICU vs. step-down units vs. routine hospital floors). If the patient is receiving IV insulin, then transition to a subcutaneous route must be started before discontinuing the IV route. Most patients can be converted to long-acting basal insulin, with the dose usually being 50% to 80% of the prior day's IV insulin dose. An insulin regimen utilizing a subcutaneous basal/bolus approach outperforms traditional sliding scale regular insulin regimens. Umpierrez et al. expanded their previous work (68) by conducting a prospective randomized trial comparing subcutaneous basal/bolus insulin replacement to traditional subcutaneous sliding scale insulin (SSI) replacement for patients with type 2 diabetes undergoing general surgery, not expected to be admitted to the ICU, and whose glucose levels exceeded 140 mg/dL. In the group randomized to the basal/bolus insulin, the starting daily dose was 0.5 U/kg/day, with half of the dose being given as basal insulin (insulin glargine) once daily and half given as rapid-acting insulin analog (glulisine) in fixed doses prior to meals. If the patient was NPO, then the insulin glargine dose was given and the insulin glulisine was held until meals were resumed. For supplementation, the rapid-acting analog was used. Among the 211 patients studied, those in the basal/bolus group received higher daily doses of insulin, had lower daily mean blood glucose levels (27 mg/dL lower), had the same risk of hypoglycemic episodes (blood glucose levels <40 mg/dL), and more often achieved the glycemic goal of <140 mg/dL.

Table 8.7 Basal/Bolus Insulin Treatment Protocol

Starting Insulin Doses	Supplemental Insulin (Insulin Glulisine)				Insulin Adjustment
Discontinue all oral anti-diabetic and noninsulin injectable medications	Give supplemental insulin glulisine according to the sliding scale (below) for blood glucose >140 mg/dL				If the fasting and predinner BG is between 100–140 mg/dL and no hypoglycemia the previous day: no changes
Starting total daily dose (TDD): 0.5 units/kg-actual body weight	If patient is able and expected to eat, give supplemental glulisine before each meal and at bedtime following the “usual” column				If the fasting and predinner BG is between 140–180 mg/dL and no hypoglycemia the previous day: increase insulin TDD by 10% every day
*Reduce TDD to 0.3 units/kg actual body weight in patients ≥70 years of age and/or serum creatinine ≥2.0 mg/dL	If the patient is not able to eat, give supplemental glulisine every 6 hours (6–12–6–12) following the “sensitive” column				If the fasting and predinner BG is >180 mg/dL and no hypoglycemia the previous day: increase insulin TDD by 20% every day
Give half of the TDD as insulin glargine, at the same time once daily and half as insulin glulisine in three equally divided doses before each meal. Hold insulin glulisine if patient not able to eat	Blood Glucose (mg/dL)	Insulin Sensitive (units)	Usual (units)	Insulin Resistant (units)	If the fasting and predinner BG is between 70–99 mg/dL and no hypoglycemia: decrease insulin TDD by 10% every day If the patient develops hypoglycemia BG <70 mg/dL: decrease insulin TDD by 20%
	141–180	2	4	6	
	181–220	4	6	8	
	221–260	6	8	10	
	261–300	8	10	12	
	301–350	10	12	14	
	351–400	12	14	16	
	>400	14	16	18	

TDD-total daily dose; BG-Blood Glucose

Source: Adapted from Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with Type 2 diabetes undergoing general surgery (RABBIT 2 Surgery). *Diabetes Care*. 2011;34:256–261, with permission.

In addition, the basal/bolus group had fewer wound infections, pneumonias, episodes of bacteremia, respiratory failure, and acute renal failure as compared to the SSI group. There also was a nonsignificant trend toward fewer postsurgical ICU admissions and shorter ICU stays than in the SSI group (69). Table 8.7 demonstrates the basal/bolus method to control hyperglycemia in type 2 diabetics postoperatively.

Thyroid Disorders

When patients give history of hypothyroidism or hyperthyroidism during evaluation for surgery, thyroid-stimulating hormone (TSH) and thyroxine (T4) levels should be obtained. The primary objective is to determine if the patient is euthyroid or not, prior to surgical intervention so as to avoid the complications of myxedema or thyroid storm in the postoperative period.

Hypothyroidism is a common condition in the United States, affecting approximately 1% of all patients and 5% of the population over the age of 50 and it develops 10 times more often in women than men (70). Decision to operate on patients with hypothyroidism will depend upon the level of hypothyroidism and the urgency of the surgery. Hypothyroidism can influence many physiologic functions, such as myocardial function, respiration, gastrointestinal motility, hemostasis, and free water balance (46,71). Although there have been no prospective, randomized studies looking at the surgical outcome of hypothyroid patients versus controls, several retrospective case-matched control studies have evaluated hypothyroid patients undergoing surgery. A study by Weinberg et al. demonstrated no differences between hypothyroid and euthyroid controls for perioperative complications. In addition, no differences in outcome were seen when hypothyroidism was stratified by thyroxine levels. The investigators concluded that patients with mild to moderate hypothyroidism should not be denied needed surgery in order to correct the metabolic problem. They further

stated that insufficient numbers of patients with severe hypothyroidism precluded recommendations for perioperative care of these patients (72). In another retrospective study, Ladenson et al. reviewed perioperative complications among hypothyroid patients undergoing surgery, finding more intraoperative hypotension in noncardiac surgery, more heart failure in cardiac surgery, and more gastrointestinal and neuropsychiatric complications. They also noted that patients were unable to mount fever in the face of infection, although infection rates were not different. Further, no differences were found in the duration of hospitalization, perioperative arrhythmias, delayed anesthesia recovery, pulmonary complications, or mortality (73).

Patients with mild to moderate hypothyroidism requiring urgent surgery may have it without delay. These patients may have more minor complications of ileus, postoperative delirium, or infection without fever. Patients with severe hypothyroidism (myxedema coma, decreased mentation, pericardial effusions, heart failure, or very low levels of thyroxine) who are to undergo urgent/emergent surgery will need intravenous levothyroxine (200–500 µg given during 30 minutes) followed by daily doses of 50 to 100 µg intravenously. These patients will likely need stress-dose glucocorticoids (see “Adrenal Suppression” section) started prior to, during, and continued after surgery due to coexisting adrenal insufficiency (or due to the fact that intravenous replacement with levothyroxine may precipitate adrenal insufficiency) (46,73,74).

Myxedema coma is a rare condition, with an incidence of 0.22 per million patients per year. Most of the cases (80%) occur among hospitalized, elderly (older than 60 years) women with long-standing hypothyroidism, but it can occur at any age (75). A majority of the cases will occur in the postoperative period due to inciting causes such as infections, cold exposure, sedatives, analgesics, and other medications. The mortality from this disease is high (80%), but has been decreasing in recent years due to increased awareness, testing, and improved perioperative care (76–78). Myxedema coma is characterized by severely depressed

mental status, seizure, hypothermia, bradycardia, hyponatremia, heart failure, and hypopnea. Although maintenance of normothermia by warming is tempting, the resulting vasodilatation may cause cardiovascular collapse in patients with intravascular volume depletion, cardiac insufficiency, and pericardial effusion/tamponade, and should be performed carefully if at all (76). Myxedema coma is a medical emergency and necessitates urgent administration of levothyroxine. An initial intravenous bolus of 200 to 500 µg should be given, followed by 50 to 100 µg intravenously daily. Dehydration is frequently present and aggressive volume resuscitation with dextrose and normal saline should be instituted. Intravenous glucocorticoids should be administered (50 mg hydrocortisone IV, 4 times daily) because of frequent adrenal insufficiency. Resolution of symptoms, if properly treated, should begin within 24 hours.

Patients using thyroid replacement preparations can have their doses held during the immediate postoperative period until they are able to tolerate oral intake, as the half-life of these drugs is 5 to 9 days (71).

The causes of hyperthyroidism are many, but the most common cause is Graves disease. This autoimmune disorder, caused by an antibody directed to thyroid-stimulating hormone receptors, results in increased thyroid hormone production. The clinical signs of hyperthyroidism include tachycardia, atrial fibrillation, fever, tremor, goiter, and ophthalmopathy (47). Most complications occurring in hyperthyroid patients undergoing surgery involve cardiac function, as T4 and T3 have direct inotropic and chronotropic effect on the heart and a vaso-dilatory effect on peripheral vasculature, resulting in the activation of the renin-angiotensin-aldosterone system. All of these events result in a high cardiac output state, which increases cardiac work and oxygen requirements and can result in myocardial infarction (75). Arrhythmias are very common in the face of hyperthyroidism, with atrial fibrillation occurring in 10% to 20% of patients (79–82). Again, level of control prior to the operation will determine the perioperative outcome for the patient. Patients with controlled hyperthyroidism should be instructed to take their antithyroid medications in the morning of the day of surgery. Patients with mild hyperthyroidism may have surgery with preoperative beta-blockade. However, patients with moderate or severe disease should have surgery canceled until a euthyroid state is attained (83).

The greatest perioperative risk for patients who have undiagnosed hyperthyroidism or who are inadequately treated, is a rare, yet life-threatening condition known as thyroid storm. This “thyroid emergency” usually occurs intraoperatively or 48 hours postoperatively. The mortality of thyroid storm is 10% to 75% and requires treatment in a critical care environment (70). Symptoms are nonspecific and include hyperpyrexia, tachycardia, delirium, nausea and vomiting, and diarrhea (84). Treatment of thyroid storm is aimed at stopping production of thyroid hormone and treating the systemic effects of the decompensated patient. Antithyroid medications such as carbimazole, methimazole, and propylthiouracil (PTU) are used to inhibit the new synthesis of thyroid hormones. Unfortunately, there are no IV preparations for these compounds, so they must be administered enterally or per rectum as retention enemas or suppositories. Recent guidelines from the American Thyroid Association and the Association of Clinical Endocrinologists recommend that propylthiouracil be started with a loading dose of 500 to 1000 mg followed by 250 mg every 4 hours, and methimazole should be administered at daily doses of 60 to 80 mg (85). Administering these drugs in this sequence will provide more rapid clinical improvement because propylthiouracil has the added advantage of inhibiting conversion of T4 to T3, which methimazole does not do. These drugs prevent synthesis of new thyroid hormone, but will not stop release of stored thyroid hormone. Either inorganic iodine or lithium carbonate (for patients who are allergic to iodine; 300 mg orally every 6 hours) must be given. Lugol’s solution or a saturated solution of potassium iodide (3–5 drops

orally, every 6 hours) may be used, but must not be given sooner than 1 hour after the administration of the thionamide dosage; otherwise thyroid hormone synthesis will be enhanced by the iodine treatment. In severe cases of thyroid storm, plasmapheresis and therapeutic plasma exchange may be needed. β -blockade is critical to ameliorate the manifestations of thyroid excess and does so by correcting the heart rate, reducing cardiac oxygen demand, decreasing agitation, convulsions, psychotic behavior, and tremors. Propranolol is the most commonly used agent and dosages of 60 to 80 mg given orally every 4 hours or 0.5 to 1 mg IV followed by subsequent doses of 2 to 3 mg every several hours are recommended. Another theoretic benefit of β -blockade is the inhibition of conversion of T4 to T3. One other medication which has a high therapeutic benefit is the administration of corticosteroids, which not only inhibits the conversion of T4 to T3, but also treats adrenal insufficiency which may have occurred due to the rapid turnover of cortisol. Acetaminophen is preferred to salicylates, as the latter may exacerbate thyrotoxicosis by decreasing thyroid protein binding and increasing free T3 and T4. Finally, a thorough search for the precipitating cause of the thyroid storm should be undertaken immediately, with the most common cause in the perioperative period being infection (75).

Adrenal Suppression

How patients respond to stress is directly related to the hypothalamic-pituitary axis (HPA), and any defect in this cycle can have dramatic effects in the perioperative period. The most common cause of primary adrenal insufficiency (AI) is autoimmune adrenalitis, where the adrenal cortex is destroyed and the patient’s endogenous production of glucocorticoid steroids is reduced or ceases. Secondary AI is characterized by atrophy of the adrenal cortex as a result of deficient adrenocorticotrophic hormone (ACTH) stimulation. The most common cause of secondary AI is administration of exogenous corticosteroids which feeds back to cause a decrease in hypothalamic corticotropin-releasing hormone and subsequent decreased pituitary ACTH secretion. Although there is remarkable variability in individual response to a particular dose and length of treatment with steroids, in general, any patient who received the equivalent of 20 mg per day of prednisone for more than 5 days is at risk for HPA suppression. If the duration of steroid treatment is 1 month or longer, the patient will have HPA suppression, which can last for 6 to 12 months after stopping therapy. Whereas an equivalent dose of prednisone 5 mg (or less) for any period of time will not usually suppress the HPA axis (86–88). Assessment of adrenal function (ACTH stimulation tests) in the perioperative period has not been shown to be sensitive or specific in identifying patients who are at risk for AI and who might respond to supplemental corticosteroids (89–92).

Recently, Marik and Varon performed a meta-analysis of the world literature concerning perioperative stress doses of corticosteroids for patients who take corticosteroids chronically. Their search revealed two randomized controlled trials (RCTs) and seven cohort studies, for a total of 315 patients. Although the number of patients is small, the two RCTs showed no differences in the hemodynamic profiles of patients receiving stress doses of corticosteroids, compared to patients receiving only their usual daily dose of corticosteroid. Similarly, in 5 of the 7 cohort studies, patients who continued to receive their usual daily doses of corticosteroids without additional stress doses, did not develop unexplained hypotension or adrenal crisis perioperatively. The remaining 2 cohort studies each had 1 patient who stopped their usual daily dose of corticosteroid preoperatively, and each developed unexplained postoperative hypotension, which responded to hydrocortisone and fluid therapy. The authors recommend that patients receiving therapeutic doses of corticosteroids, who undergo surgery, do not routinely need

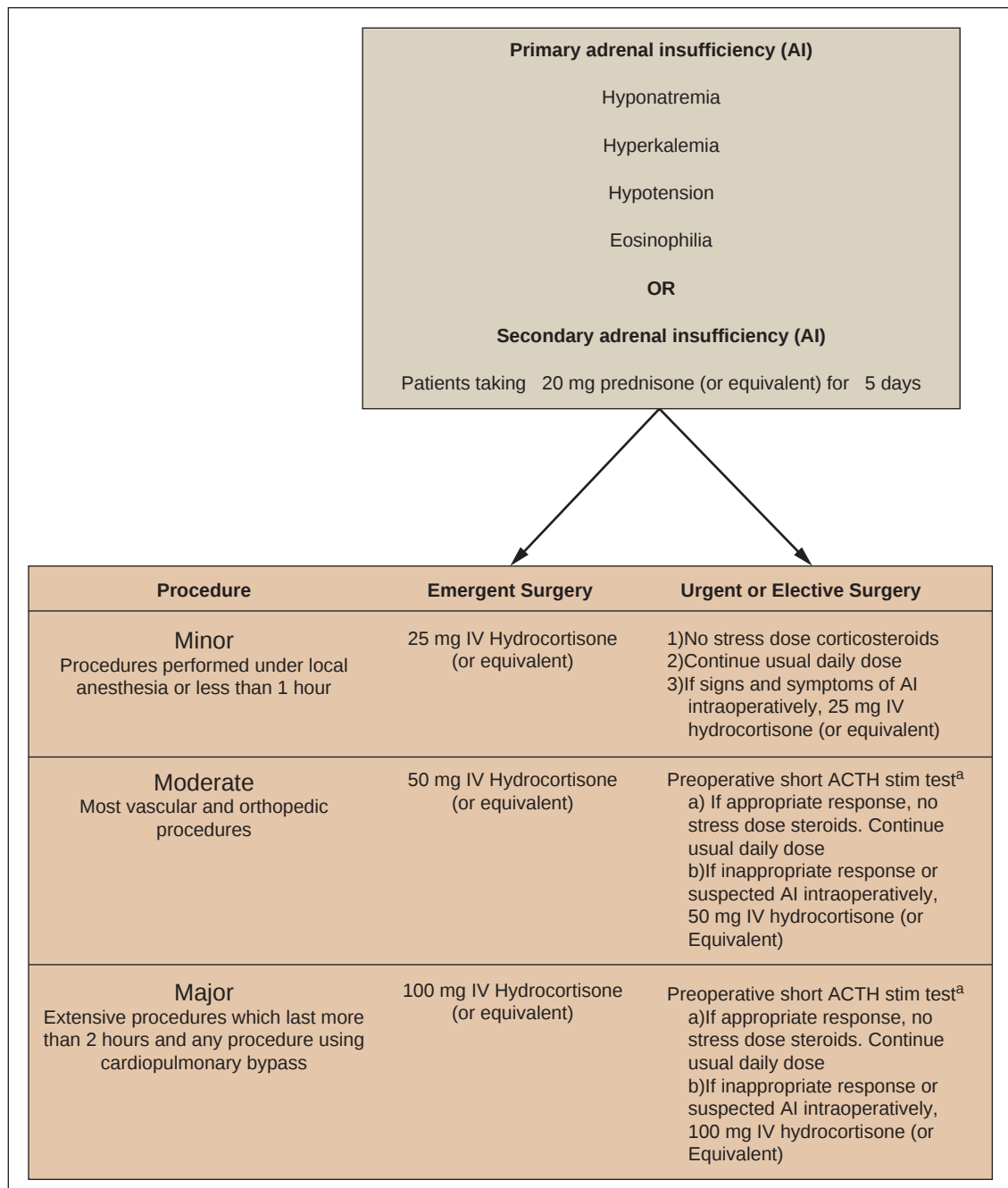


FIGURE 8.1. Algorithm for adrenal insufficiency.

^aThe short ACTH stimulation involves IV administration of 250 µg synthetic ACTH (Cortrosyn™, cosyntropin) followed by plasma cortisol collection 30 minutes later. Normal cortisol levels after stimulation greater than 18 µg/dL.

When given intraoperatively, steroid doses are continued every 8 hours for 48 hours.

Source: Adapted from Kohl BA, Schwartz S. How to manage perioperative endocrine insufficiency. *Anesthesiol Clin*. 2010;28:139–155, with permission.

stress doses of corticosteroids as long as their usual daily dose is continued. In addition, adrenal function testing is not recommended for these patients because the test is overly sensitive and does not predict which patient will develop adrenal crisis. Further, patients who have primary adrenal insufficiency and who are taking physiological replacement doses of corticosteroids will require supplemental stress doses of corticosteroids in the perioperative period (93).

Figure 8.1 outlines an algorithm that may be helpful in guiding clinicians in their decision-making about stress-dose steroids for patients who take them chronically. Giving stress dose glucocorticoids needs to be weighed against the potential side effects

of the drug (such as poor wound healing, fluid retention, and increased risk of infection) versus the benefits of supporting the HPA axis in a surgically stressed patient.

RENAL RISK ASSESSMENT

Chronic kidney disease (CKD) affects over 13 million Americans (20 years and older; CKD stage 2 or worse) (94), with most having a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² (95). The most common form of renal failure facing the

surgeon is acute kidney injury (AKI) occurring during the postoperative period, which will be discussed below in the section on postoperative/critical care. Since 2002, a uniform classification system for CKD was introduced, stratifying CKD into 5 stages based on estimation of GFR and documentation of renal injury (95). Class 5 CKD, or end-stage renal disease (ESRD), includes patients who require renal replacement therapy (usually dialysis) for treatment (94). With the aging population, increasing prevalence of diabetes and hypertension, and advances in dialytic therapy, the number of patients living with CKD is increasing (94). Therefore, surgeons must be cognizant of the potential perioperative risks associated with these patients.

The predominant causes of CKD are diabetes and hypertension, accounting for 71% of all patients who are dialysis dependent (94). Patients with these underlying diseases tend to have other comorbid conditions such as coronary artery disease and peripheral vascular disease. Evaluation of CKD patients undergoing surgery should focus on four areas: cardiac evaluation, fluid and electrolyte management, anemia, and bleeding diatheses. Of course, glycemic control for diabetics and blood pressure control for hypertensive patients is obvious.

CVD has long been recognized as the leading cause of death among ESRD patients, which occurs in 50% of patients (94,96, 97). However, patients with other stages of CKD, even minor derangements, have an increased risk of CVD. A recent study correlated stage of CKD with odds ratios (ORs) for cardiovascular risk, demonstrating a graded increase in risk with increasing stage of CKD (OR-15 for Stage I to OR 20 to 1000 for stage V) (97). The disease factors which contribute to CVD among CKD patients include microalbuminuria/proteinuria, hypertension, diabetes, dyslipidemia, and smoking (98). In addition, many CKD patients will have coronary artery disease (23% to 40%) (99–101), and many ESRD patients (70% to 80%) will develop ventricular hypertrophy due to hypertension and severe anemia. This hypertrophy results in a decreased myocardial capillary density and diastolic and systolic dysfunction, all of which leads to disturbances in intra-ventricular conduction, electrical excitability, and ventricular arrhythmias (102). Therefore, these patients may benefit from a formal cardiac clearance from a cardiologist prior to surgical intervention.

The capacity of the failing kidney to maintain volume and electrolyte homeostasis is achieved through adaptive processes, which are limited in their ability to respond to physiological stresses, placing well-compensated patients, in the premonitory state, at increased risk of fluid and electrolyte disturbances during the perioperative period (103). Intraoperative and perioperative fluid management in the patients with CKD must therefore take into account the reduced capacity for both water excretion and conservation. Excessive free water administration must be avoided to prevent iatrogenic hypotonicity, while providing sufficient free-water to prevent hypertonicity. Electrolyte status should be monitored frequently and water administration adjusted if hypo- or hypernatremia ensues (104). ESRD patients who are dependent upon dialysis will need to be euolemic prior to surgery. Thus, communication with the patient's nephrologist is paramount. Details about the operation should be discussed, with planned preoperative dialysis (without heparin 24 hours prior to surgery) and postoperative dialysis on the day of surgery for large intraoperative fluid loads. Electrolytes should be monitored in the immediate postoperative period, with hyperkalemia being aggressively managed with dialysis, or medically if necessary. Acute hyperkalemia may be treated with glucose and insulin, which will drive the Na/K-ATPase pump resulting in an increase of intracellular potassium and lowering of extracellular potassium. Ten milliliters of calcium gluconate can afford cardioprotection and membrane stabilization in patients with abnormal electrocardiograms (ECGs) (105). Decreasing total body potassium is the final step in the treatment of hyperkalemia. In non-oliguric patients, renal potassium excretion may be enhanced

with loop-acting diuretics. Sodium polystyrene sulfonate (Kionex®, Kayexalate®) may be used as an exchange resin in the gastrointestinal tract. Forty grams dissolved in 80 mL of sorbitol (or more to promote elimination) and given orally will bind one millimole of potassium for each gram given. Alternatively, 50 to 100 g of sodium polystyrene sulfonate may be dissolved in 200 mL of water and may be given rectally as a retention enema by inserting a Foley catheter into the rectum and filling the balloon (104). These administrations should be repeated every 2 to 4 hours until the potassium level is in a normal range (see section below on potassium derangements). Caution with the use of this resin in postoperative patients is urged, as intestinal necrosis has been reported (106).

Most patients with CKD have or will develop anemia due to erythropoietin deficiency during the course of their disease and, prior to the introduction of erythropoietin stimulating agents (ESAs), were transfusion dependent. In recent years, the use of ESAs has come under scrutiny. Recent reviews have demonstrated that raising the hemoglobin levels above 11 g/dL in patients with CKD resulted in a 1.14-fold increase in the odds ratio of death. These results highlight the need to carefully manage hemoglobin levels with ESAs within a recommended range of 9 to 11 g/dL (107,108). In urgent situations, transfusion of blood is necessary to maintain hemoglobin prior to and during surgery.

CKD patients have an increased risk for bleeding complications. Platelet dysfunction caused by renal failure is multifactorial, with retained uremic toxins, abnormal binding of von Willebrand factor, abnormal platelet arachidonic acid metabolism, and excess vascular prostacyclin and nitric oxide production all being implicated (109). The bleeding time provides the best correlation with risk of clinical bleeding in CKD patients. If a patient has demonstrated prior bleeding because of uremic platelet dysfunction, these patients must be treated with 1-deamino-8-D-arginine vasopressin (dDAVP) intravenously, or intranasally and with cryoprecipitate to prevent bleeding during surgery (110). In addition, patients may be treated with intravenous conjugated estrogens (0.6 mg/kg) if they are given 4 to 5 days prior to surgery (104,111).

Furthermore, with reduced or absent renal function, these patients metabolize drugs such as antibiotics, anesthetics, and analgesics poorly. Drug administration in ESRD must be done judiciously with careful attention to the pharmacokinetics of particular drugs. Multiple guidelines exist that can direct drug dose reductions for patients with ESRD (112,113).

HEPATIC RISK ASSESSMENT

An increasing number of patients with chronic liver disease, advanced or end stage, will require non-liver transplant surgery (114). Reasons for this increase are; an aging population, better long-term survival of patients with liver cirrhosis, and continuously improving outcomes after surgery and critical care medicine (115). Historically, liver dysfunction was related to chronic viral or alcoholic hepatitis. While the incidence of these conditions has not changed dramatically in recent years, the rising rate of obesity has led to nonalcoholic fatty liver disease, which is increasingly recognized as the most common cause of chronic liver disease (CLD) in the United States (116).

As mentioned earlier, thorough preoperative evaluation of patients includes a comprehensive history and physical examination, with laboratory testing based upon historical and physical findings. Routine testing of liver function or coagulation in asymptomatic patients rarely yields abnormal results or changes in perioperative management (7). However, patients with history of liver disease, jaundice, blood transfusions, the use of alcohol or other recreational drugs, hepatitis, or physical findings of icterus, hepato-splenomegaly, palmar erythema, or spider nevi should be tested to rule out occult or active liver diseases (115).

Table 8.8 Child-Turcotte-Pugh (CTP) Classification of Liver Disease and Operative Mortality

Component	Score		
	1 Point	2 Points	3 Points
Ascites	None	Controlled with medication	Treatment-refractory
Encephalopathy	Absent	Grade I–II; Controlled with medication	Grade III–IV; treatment refractory
Albumin g/L	>3.5	2.8–3.5	<2.8
Bilirubin mg/dL	<2	2–3	>3
INR	<1.7	1.7–2.3	>2.3
CTP Classification	Class A (5–6 points)	Class B (7–9 points)	Class C (10–15 points)
90 day Mortality risk (abdominal surgery)	2%–10%	2%–30%	12%–76%

Source: Adapted from Hanje AJ, Patel T. Preoperative evaluation of patients with liver disease. *Nat Clin Pract Gastroenterol Hepatol.* 2007;4:266–276; Muir AJ. Surgical clearance for the patient with chronic liver disease. *Clin Liver Dis.* 2012;16:421–433; and Hoetzel A, Ryan H, Schmidt R. Anesthetic considerations for the patient with liver disease. *Curr Opin Anesthesiol.* 2012;25(3):340–347, with permission.

Patients with acute hepatitis (viral or alcohol-induced) should have their surgery delayed until the acute phase of the disease process has passed and liver function tests have returned to normal. Mortality rates among these patients can range from 10% to 58% if surgery is pursued. Patients with acute liver failure/fulminant liver failure, defined as the development of jaundice, coagulopathy, and hepatic encephalopathy within 26 weeks in a patient with acute liver injury and without pre existing liver disease, are critically ill, and all surgery other than liver transplantation is contraindicated in these patients (117). Contrarily, patients with chronic infectious hepatitis, which is stable, tolerate surgery with minimal mortality (114,118,119). Of course the operator should practice universal precautions with all surgical interventions, regardless of the patient's known infectivity status.

Assessing the severity of the underlying liver disease is important to determine perioperative outcome, and has been correlated to two classification systems; the Child-Turcotte-Pugh (CTP) classification and the model of end-stage liver disease (MELD) score. The Child-Turcotte score was the first predictor of surgical risk/mortality for patients undergoing surgical intervention; specifically, patients having portacaval shunts. The system was modified by Pugh and colleagues to include prothrombin time in place of the subjective assessment of nutritional status, for use in patients undergoing esophageal transections for bleeding varices (120,121). Although widely known for classifying liver disease, this system has been criticized for utilizing subjective variables (ascites and encephalopathy) in developing a score. However, the CTP score correlates with mortality in patients undergoing differing types of surgery (115,122) (Table 8.8). The MELD score was originally devised as a prognostic measure of short-term mortality in patients with cirrhosis undergoing placement of a transjugular intrahepatic porto-systemic shunt (TIPS) (123). The MELD score is derived from a complex formula which incorporates three biochemical variables (serum total bilirubin, serum creatinine, and the international normalized ratio [INR]) and assigns the patient a score of 8 to 40 (Table 8.9). The risk of morbidity and mortality in patients with liver disease depends upon the type of surgery and has been correlated to

Table 8.9 Model for End-stage Liver Disease (MELD) Score

$$\text{MELD Score} = (9.6 \times \log_e[\text{Creatinine}]) + (3.8 \times \log_e[\text{Bilirubin}]) + 11.2 \times \log_e[\text{INR}] + 6.4$$

Creatinine levels above 4.0 mg/dL, are assigned 4.0 mg/dL. Levels under 1.0 mg/dL are assigned 1.0 mg/dL. If the patient has had dialysis twice in the previous week, the value is assigned 4.0 mg/dL

Bilirubin levels below 1.0 mg/dL are assigned 1.0 mg/dL

INR levels below 1.0 are assigned 1.0

The maximum score is 40. Scores calculated greater than 40, are assigned a value of 40.

MELD Score	Less than 10	10–15	Greater than 15
	Low Risk	Intermediate Risk	1. High Risk
30 Day Mortality (Abdominal/cardiac/orthopedic surgery)	5%–5.7%	10%	2. >50%

Source: Adapted from Hanje AJ, Patel T. Preoperative evaluation of patients with liver disease. *Nat Clin Pract Gastroenterol Hepatol.* 2007;4:266–276; Malik SM, Ahmad J. Preoperative risk assessment for patients with liver disease. *Med Clin N. Am.* 2009;93:917–929, and Friedman LS. Surgery in the patient with liver disease. *Trans Am Clin Climatol Assoc.* 2010;121:192–204, with permission.

the aforementioned classification systems (Tables 8.8 and 8.9) (122). However it is likely that over the last two decades, mortality rates have decreased, despite the absence of large studies confirming this assumption (115).

Patients with cirrhosis of the liver also have coagulopathies, which need to be corrected prior to surgery. Vitamin K, fresh frozen plasma, or cryoprecipitate may be administered to correct the prothrombin time to within 3 seconds of normal. Figure 8.2 presents an algorithm for patients with liver disease facing surgery.

Finally, selection of medications in patients with hepatic dysfunction needs to be done carefully, from types of perioperative antibiotics to anesthetic agents and analgesics. Patients with liver dysfunction are particularly susceptible to anesthetic effects such as changes in hepatic metabolism of medications and changes in hepatic blood flow. Alterations of the type and the dose of an agent are necessary to avoid postoperative hepatic dysfunction and hepatitis. Postoperative pain management with narcotic agents needs to be reduced by as much as 50% to account for the altered hepatic metabolism in these patients (124).

PREOPERATIVE NUTRITIONAL ASSESSMENT

There is a clear correlation between degree of malnutrition and increased risk of perioperative complications in cancer patients undergoing surgery (125). The broader consideration of nutrition in the gynecologic cancer patient is discussed in Chapter 32. The intent of this section is to present the concepts of preoperative nutritional evaluation and support of the gynecologic oncology patient undergoing surgery. Early refeeding and enteral and parenteral nutritional support in the postoperative patient will be discussed later.

The incidence of malnutrition among cancer patients has been estimated to be 20% to 80%, with the prevalence among gynecologic oncology patients being approximately 20%. For example, ovarian cancer patients are 19 times more likely to have moderate malnutrition when compared to patients with other

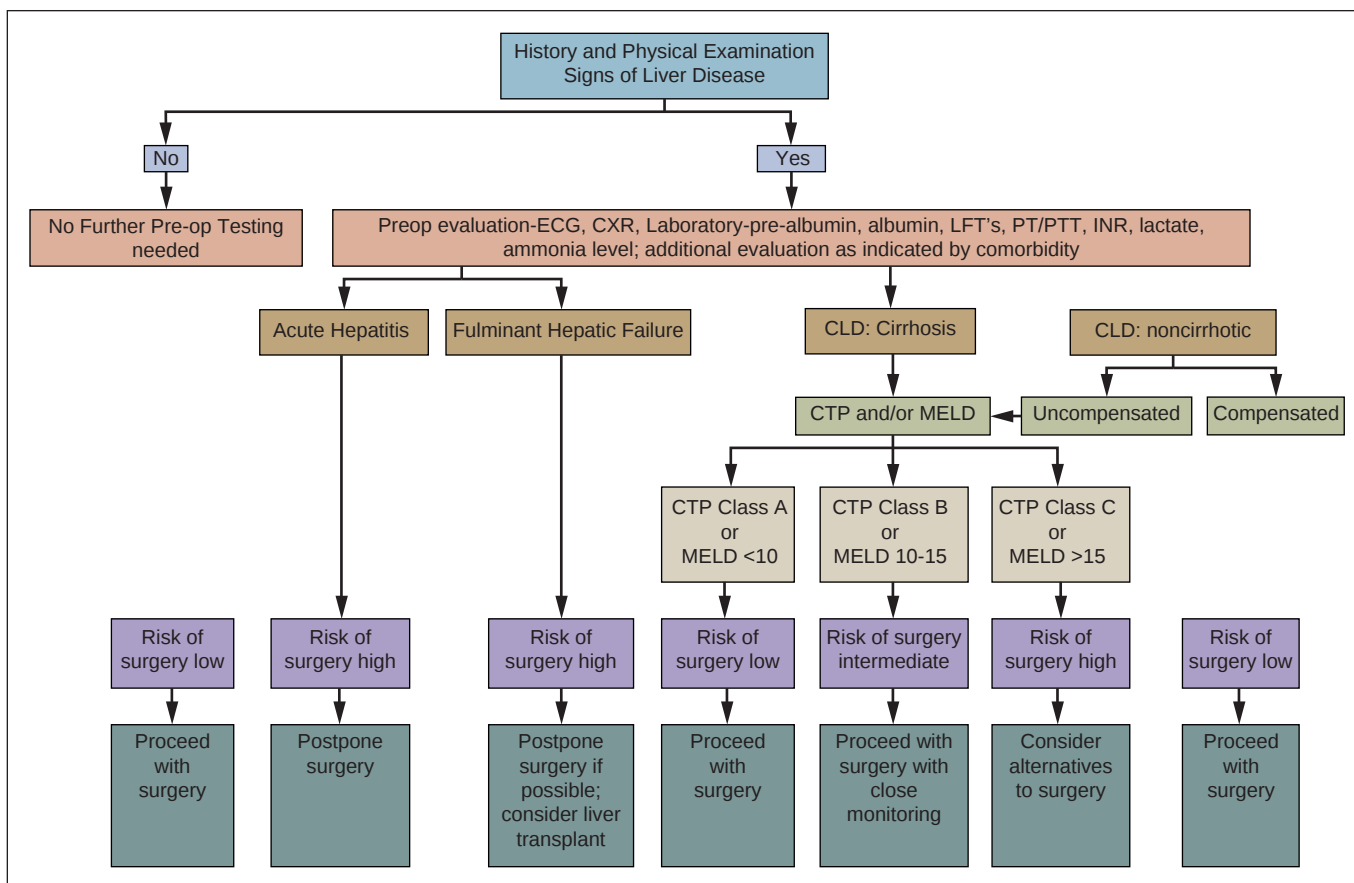


FIGURE 8.2. Preoperative evaluation and risk stratification in suspected liver disease.

ECG, electrocardiogram; LFTs, liver function tests; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; PT, prothrombin time; PTT, partial prothrombin time; INR, international normalization ratio; CLD, chronic liver disease; CTP, Childs–Turcotte–Pugh; MELD, model of end-stage liver disease.

Source: Adapted from Hanje AJ, Patel T. Preoperative evaluation of patients with liver disease. *Nat Clin Pract Gastroenterol Hepatol*. 2007;4:266–276 and Hoetzel A, Ryan H, Schmidt R. Anesthetic considerations for the patient with liver disease. *Curr Opin Anesthesiol*. 2012;25(3):340–347.

gynecological malignancies or benign conditions (126,127). Among malnourished gynecologic oncology patients, patients have been found to have an increased risk of postoperative complications, longer lengths of stay, hospital readmissions, reoperations, earlier cancer recurrences, and residual tumor after initial surgery (127–129). The methods for assessing malnutrition has varied among investigators and has included weight loss over a given time, various objective anthropometric parameters (e.g., weight loss, body mass index, triceps skinfold thickness, and arm circumference), biochemical testing (e.g., serum albumin, prealbumin, total protein, transferrin, hemoglobin, and vitamins), and immunologic testing (skin sensitivity tests) (Table 8.10) (130).

Nutrition screening refers to the initial clinical evaluation that can quickly identify patients at high risk for malnutrition and who, later, may undergo a more formal and extensive nutritional assessment. Such instruments are the Malnutrition Screening Tool (MST) and the Malnutrition Universal Screening Tool (MUST), which have been used in oncology patients (Table 8.11). Logically, identifying patients at nutritional risk, by screening, will mark them for subsequent formal nutrition assessment, and identify opportunities for medical nutrition therapy, which ultimately should improve patient outcomes. Unfortunately, this sequence of assumptions has never been subjected to prospective confirmation in clinical trials (131).

Many nutrition assessment tools have been developed, including subjective and objective data to assign risk, and some have been validated in cancer patients, including gynecologic cancer patients. Those instruments that have been used in cancer patients

include the Subjective Global Assessment (SGA), the Patient-Generated Subjective Global Assessment (PG-SGA), Nutrition Risk Index (NRI), the Mini Nutritional Assessment (MNA), Prognostic Nutritional Index (PNI), and the Nutritional Risk Screening 2002 (NRS-2002) (Table 8.11). Although just examples

Table 8.10 Measurement of Nutritional Depletion

Parameters	Depletion		
	Mild	Moderate	Severe
Triceps skin fold (TSF) % Standard	50–90	30–50	<30
Mid-arm muscle circumference (MAMC) % Standard	80–90	70–80	<70
Albumin g/dL	3.0–3.4	2.1–3.0	<2.1
Total lymphocyte count (TLC) Cmm	1200–1500	800–1200	<800
Weight loss, % initial			
In 1 week	<1	1–2	>2
In 1 month	<2	2–5	>5
In 3 months	<5	5.0–7.5	>7.5
In 6 months	<7.5	7.5–10.0	>10.0

Table 8.11 Nutritional Screening and Assessment Tools

Tool	Components
Screening Instruments	
Malnutrition Screening Tool (MST)	3 items: weight, percentage weight loss, appetite
Malnutrition Universal Screening Tool (MUST)	3 items: BMI, percentage weight loss, acute disease effect
Nutritional Risk Screening 2002 (NRS-2002)	4 items: reduced BMI, percentage weight loss, decreased dietary intake, acute disease effect
Assessment Instruments	
Patient-Generated Subjective Global Assessment (PG-SGA)	Patient (4 questions): weight history, symptoms, food intake, activity level Health care provider: metabolic demand, diagnosis and comorbidities, physical examination
Subjective Global Assessment (SGA)	History and physical examination to assign nutrition score
Prognostic Nutritional Index (PNI)	Equation: PNI Score (%) = $158 - 16.6$ (albumin level in gm/dL) $- 0.78$ (triceps skin fold in mm) $- 0.2$ (transferrin level in mg/dL) $- 5.8$ (Grade of delayed hypersensitivity)
Nutrition Risk Index (NRI)	Equation: $NRI = 1.519$ (serum albumin; g/dL) $+ 41.7$ (current weight/usual weight) $\times 100$
Mini Nutritional Assessment (MNA)	18 items: Screening portion (6 questions): food intake, weight loss, mobility stress, BMI; Assessment (12 questions): medical history, eating habits, anthropometric measurements

Source: Adapted from Huhmann MB and August DA: Reivew of American Society for Parenteral and Enteral Nutrition (ASPEN) clinical guidelines for nutrition support in cancer patients: nutrition screening and assessment. *Nutr Clin Pract.* 2008;23:182–188, with permission.

of the many assessment tools available, none has emerged as the “gold standard” for nutritional screening and/or nutritional assessment among cancer patients, and their use depends upon which organization endorses a particular tool.

The SGA tool, originally described by Detsky in 1987, uses history and physical examination to assign a nutrition risk score. The PG-SGA was adapted from the SGA by Ottery, and later modified by McCallum and Polisen to give a numerical score of 0 to 47, specifically for the oncology population (132–135). It consists of two sections, one of which is done by the patient. This portion elicits information related to weight history, symptoms, food intake, and activity level. The other section, completed by a health care professional, includes an evaluation of metabolic demand, diagnosis, and comorbidities in relation to nutrition requirements and elements of physical examination. Every portion of the tool is given a numeric score, including the patient's portion, which is used to triage intervention. Laky and colleagues in 2007 showed, in a prospective fashion, that the PG-SGA could be easily administered to identify gynecological cancer patients at risk for malnutrition. Their work established a prevalence of malnutrition among their patients in Brisbane, Australia. Among 145 patients with known or suspected gynecologic cancer, 116 patients were classified as well nourished (PG-SGA A), 29 patients were moderately malnourished (PG-SGA B), and none of the patients were severely malnourished (PD-SGA C). These investigators found that ovarian cancer patients were 19 times more likely to be

malnourished, compared to patients with other gynecologic malignancies or benign conditions. In addition, they found that preoperative serum albumin levels correlated with the PG-SGA B score among ovarian cancer patients, similar to other previous reports (128,129,135), and may be a good indicator of malnutrition among gynecologic cancer patients in the absence of a full nutritional assessment (126). In 2008, Laky found that the scored PG-SGA, albumin level, triceps skinfold thickness, and total-body potassium could predict the SGA better than chance. The authors concluded that the scored PG-SGA is the most appropriate tool for identifying malnutrition in gynecologic cancer patients.

The NRI was used to stratify nutrition risk in the Veterans Affairs Total Parenteral Nutrition Cooperative Study Group trial of perioperative parenteral nutrition. It is a simple equation that uses albumin and weight to classify individuals as either well nourished or malnourished. The equation:

$$NRI = 1.519 (\text{serum albumin; g/dL}) + 41.7 (\text{current weight/usual weight}) \times 100$$

A score less than 100 is considered malnourished (31). This particular tool has not been studied in gynecologic oncology patients.

The MNA is an 18-item tool that is divided into two sections: screening and assessment. The screening segment contains 6 questions related to food intake, weight loss, mobility, stress, and body mass index. If this score is 11 or less, then a health care provider will complete the remaining 12-item assessment. A total score of <17 indicates malnutrition and a score between 17 and 23.5 indicates risk for malnutrition. This instrument has been validated in the elderly population, but its use among cancer patients is limited and nonexistent among gynecologic cancer patients.

The PNI is an objective evaluation of nutritional status which includes anthropometric measurements and laboratory testing and an assessment of cell mediated immunity by testing to mumps, tuberculin and *Candida* (the grade of response is 0 nonreactive; 1 <5 mm induration; 2 ≥5 mm induration) (136). The information gathered is put into the formula below:

$$\begin{aligned} \text{PNI Score (\%)} = & 158 - 16.6 (\text{albumin level in g/dL}) - \\ & 0.78 (\text{triceps skin fold in mm}) - \\ & 0.2 (\text{transferrin level in mg/dL}) - \\ & 5.8 (\text{Grade of delayed hypersensitivity}) \end{aligned}$$

If the PNI is <40%, then the patient is determined to have normal nutritional status; PNI 40% to 49% indicates mild malnutrition; PNI >50% is severe malnutrition. Santoso et al. compared this objective, yet cumbersome and expensive, method to the SGA for gynecologic malignancies. They found that agreement between the two methods was only fair to moderate, with the SGA methodology trending toward underreporting when compared to the objective method (137).

The NRS 2002 was developed to include measures of current malnutrition and disease severity. This scoring system assesses current malnutrition by scoring the amount and duration of weight loss, reduced BMI, and recent decrease in dietary intake. In addition, the severity of illness is graded as a reflection of increased nutritional requirements. A score is calculated for each part of the assessment and added together for the final score. A score ≥3 indicates the need to start nutritional support. This NRS 2002 is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) for the screening of hospitalized patients and has been widely accepted in Europe. It is important to note that this tool is useful in identifying patients who will benefit from nutrition intervention, but does not categorize the risk of malnutrition. This tool has not been evaluated among patients with gynecological malignancies undergoing surgery (138).

Currently, the American Society of Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) do not recommend routine nutrition support therapy (NST-parenteral or enteral) in

patients undergoing major cancer operations. The risks and costs of routine perioperative NST outweigh benefits in terms of surgical outcomes in cancer patients (125,138).

Several RCTs have been done to evaluate NST in cancer patients undergoing surgery. The largest trial, the Veterans Affairs Cooperative Study, randomized 395 surgical (abdominal or noncardiac thoracic surgeries) patients, mostly male, to receive at least 7 days of preoperative and 3 days of postoperative TPN or to receive no perioperative nutritional supplementation. The TPN group had a greater number of infectious complications, mostly among patients classified as borderline or mildly malnourished compared to the unfed patients (14.1% vs. 6.4%). However, a subset of severely malnourished patients derived benefit from lower operative complication rates (5% vs. 43%, $p = 0.03$) without incurring an increase in infectious complications. The overall 30- and 90-day mortality rates were not different between the groups (31). Meijerink et al. completed a trial of preoperative nutrition among 151 patients undergoing surgery for gastric or colorectal cancer and randomized to preoperative TPN versus enteral nutrition (EN) versus standard oral diet (SOD). The authors found that there was no difference in mortality among the groups. However, patients who were severely malnourished and received either TPN or EN had fewer intra-abdominal abscesses than the MOD, but there was a difference in infectious morbidity between the TPN and EN groups (140). A similar study by Bozzetti et al. randomized severely malnourished patients undergoing resection of gastric or colonic malignancies to 10 days of preoperative and 9 days of postoperative TPN or SOD with hypocaloric TPN postoperatively only. The TPN only group showed lower noninfectious postoperative complication rates and mortality (141). And finally Wu et al. randomized 468 patients to pre- and postoperative TPN/EN versus postoperative hypocaloric PN among moderately to severely malnourished patients undergoing surgery for gastrointestinal cancers. The investigators found fewer complications, lower mortality, and shorter lengths of stay among the full nutrition support group (142). Because of the findings of these trials, ASPEN and ESPEN suggest that perioperative NST may be beneficial in moderately or severely malnourished patients if administered for 7 to 14 days preoperatively. The potential benefits of NST must be weighed against the potential risks of the NST itself and of delaying the operation. The authors direct the reader to reviews of these recommendations, which have been done by Huhman and August (for ASPEN) (125) and Braga et al. (for ESPEN) (139).

PREPARATION FOR SURGERY

Medication Management

In preparation for surgery, patients may need to decrease or stop taking certain medications, especially those associated with higher incidence of anti-coagulation risks. Appropriate notice and clear instructions should be given to patients in this case, as some medications require several days of cessation to produce desired results. It will take approximately 4 days after warfarin therapy is discontinued for the international normalized ratio (INR) to reach 1.5 for those patients with INR levels between 2.0 and 3.0. Many patients on warfarin do not need to be covered with heparin therapy preoperatively. Administration of treatment-dose intravenous heparin or low-molecular-weight heparin (LMWH) while the INR is subtherapeutic is recommended for patients with a history of mechanical mitral valve, ball and cage valve, acute venous, or arterial thromboembolism within 3 months of surgery, or atrial fibrillation with a history of thromboembolic stroke (143). A thorough discussion pertaining to usage of over-the-counter medications and herbal supplements

is crucial in presurgery medication management. Patients should be counseled on the use of nonprescription medications, such as aspirin, nonsteroidal anti-inflammatories, ginkgo biloba, saw palmetto, garlic, ginseng, and vitamin E, as they have antiplatelet components and may enhance bleeding risk (144, 145). If possible, anemia should be corrected preoperatively. The use of recombinant human erythropoietin with concurrent iron and folic acid supplementation 2 to 3 weeks preoperatively has been shown to reduce allogeneic blood transfusions in patients undergoing elective surgery (146). It has been estimated that 60% of all blood transfused in the United States is given to surgical patients.

Numerous studies have shown the benefit of starting medications, such as statins and β -blockers, in the preoperative setting to reduce cardiac risk (147). The perioperative use of β -blockers has been shown to reduce the incidence of postoperative myocardial ischemia, myocardial infarction, and cardiac mortality by decreasing myocardial oxygen consumption and workload, although this has not been studied specifically in the morbidly obese population (147). Current ACC/AHA guidelines recommend that β -blockers should be continued in patients undergoing surgery who are receiving β -blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA class I guideline indications (148). For high-risk patients not receiving β -blockade, therapy should start before elective surgery, with the dose titrated to achieve a heart rate at rest of 50 to 60 beats/minute (149). The perioperative use of β -blockers in high-risk patients undergoing major noncardiac surgery is supported by the published data. However, studies have questioned the benefits of this approach in moderate-risk patients and report that the potential harm in low-risk groups might outweigh the benefit, stressing the importance of patient selection (150).

Statins have also been shown to be effective cardioprotective drugs in the perioperative setting (147). Statins have been shown to act as plaque stabilizers and therefore possibly decrease the risk of thromboembolic events (147,151). With their low side effect profile and well-documented benefits, statins should be strongly considered for all obese patients with elevated serum cholesterol or triglycerides (152).

Close to 2 million patients undergo coronary angioplasty each year in western countries, and >90% of these patients will have coronary stents placed as part of their intervention (153,154). Patients with bare metal stents are normally taking low-dose aspirin 81 mg. It is recommended that they stop taking aspirin 7 days before surgery (155,156).

Patients with drug-eluting stents take oral aspirin 81 mg, or even aspirin 325 mg, and, for the first 12 months after stent placement, daily oral clopidogrel 75 mg (156,157). Ideally, these patients should not undergo elective surgery, within the first 12 months after stenting. After the first 12 months, both medications are recommended to be stopped 7 days before surgery to reduce the risk of intra- and postoperative bleeding (155).

It is not uncommon for gynecologic oncology patients to undergo neoadjuvant chemotherapy. Most gynecologic oncologists would agree that the timing of surgery in relation to chemotherapy is crucial. In most cases, the surgical intervention should replace a cycle of chemotherapy. With regard to bevacizumab, special considerations should be taken into account since there is the added risk of bowel perforation and poor wound healing. The incidence, type, and timing of postsurgical bleeding events and wound-healing complications were assessed in surgical patients in the AVastin And DOcetaxel (AVADO) and Avastin THERapy for advaNced breAst cancer (ATHENA) trials. Both study protocols followed recommendations to withhold bevacizumab for at least 6 weeks before elective surgery, and to wait 28 days (or until the wound was fully healed) after major surgery before recommencing bevacizumab therapy (158). Another study by Erinjeri et al. investigated how the timing of administration of bevacizumab affected the risk of wound healing in patients undergoing chest-wall port placement. They concluded the risk

of a wound dehiscence requiring a chest wall port explant in patients treated with bevacizumab was inversely proportional to the interval between bevacizumab administration and port placement, with significantly higher risk seen when the interval is less than 14 days (159). Scappaticci et al. assessed postoperative wound healing complications in two randomized trials of 5 mg/kg bevacizumab in colorectal cancer treatment. Bevacizumab administered in combination with 5-fluorouracil/leucovorin-based chemotherapy 28 to 60 days after primary cancer surgery caused no increased risk of wound healing complications compared with chemotherapy alone. While wound healing complications were increased in patients who had major surgery during bevacizumab therapy, the majority of bevacizumab-treated patients experienced no complications (160).

Blood Banking

Patients and their families are taking a more proactive role in their health care and thereby are entering into surgeries knowledgeable of risks and expecting alternative options. Preoperative counseling should include discussion of the potential for blood transfusions and associated risks. Transfusion rates of approximately 5% have been reported for patients undergoing abdominal hysterectomy for benign disease (160,161). Radical procedures performed for the treatment of gynecologic malignancies are associated with an estimated blood loss of 1,000 mL or greater. Transfusion rates for patients undergoing radical hysterectomy have been reported as high as 80% (162), but rates of 10% to 20% are more typical in the recent literature. The risk of transfusion-transmitted infection of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus from red blood cell transfusion is estimated at 1:2.1 million units, 1:250,000 units, and 1:1.9 million units, respectively (163). Although these rates have significantly decreased in the last decade with the introduction of new screening technologies, transmission of other agents, bacterial contamination, transfusion reactions, increased infection complications, and immunosuppression remain risks of allogeneic blood transfusion (164,165). One alternative both physicians and patients have turned to is the use of donor blood in the perioperative period.

Since the mid-1980s, preoperative autologous blood donation (PABD) has been utilized in order to avoid allogeneic blood transfusion in patients undergoing elective surgery where excessive blood loss is anticipated. Although this practice decreases homologous blood use, 15% of autologous donors will still receive allogeneic transfusions, and 50% of units collected are not used and must be discarded (166). Furthermore, PABD greatly increases the likelihood of any transfusion being necessary and is not without medical risks. Severe reactions during autologous donation occurred at a rate of 0.32% per unit collected and 0.75% per donor. Serious incidents during blood collection that required hospitalization were 12 times more likely in PABD compared to allogeneic donors (167). Transfusions to the wrong recipient, bacterial contamination, febrile nonhemolytic reactions, and allergic reactions have also been reported with autologous transfusion. The cost-effectiveness of PABD has been found to be extremely poor and has steadily deteriorated over the decade (166–169).

Acute normovolemic hemodilution (ANH) is an autologous blood-procurement strategy that is equivalent to PABD in reducing allogeneic transfusion needs. Its clinical utility has been extensively studied in patients undergoing radical prostatectomy, total joint replacement, and, more recently, major colorectal surgery. During ANH, blood is procured in the holding or operating room and replaced simultaneously with colloid and crystalloid until a target hematocrit level of 28% is reached or blood volume of 1,500 mL is removed (170). The patient's blood becomes diluted and the amount of actual red cell mass lost

during surgery is reduced. ANH obviates the costs of blood testing, storage, or wastage because all blood collected during ANH is kept in the operating room and returned to the patient before the end of surgery. It is simple to perform and more convenient for the patient. Since the blood is collected at point-of-care there is no possibility for clerical error or contamination. ANH has been shown to be a cost-effective yet underutilized strategy to reduce allogeneic blood transfusions (170–172). ANH in which the blood is kept in a continuous circuit with the patient is often a workable alternative for a Jehovah's Witness patient (170,173).

The utilization of erythropoietin in oncology patients should on a case by case basis due to recent evidence of adverse effects in oncology patients (174).

Bowel Preparation

It is generally accepted that full mechanical bowel preparation is indicated when intestinal injury or bowel resection is anticipated. Mechanical bowel cleansing is considered to be a crucial factor in preventing postoperative infectious complications and disruption of bowel anastomosis. In addition to the decreased risk of infection, mechanical bowel preparation has several advantages. It facilitates palpation of the entire colon during laparotomy. It may decrease operative time by enabling the surgeon to work with a clean bowel and improve handling during bowel anastomosis or repair. Furthermore, removal of solid material from the gastrointestinal tract prior to laparoscopy may improve exposure and lessen the chance of injury secondary to manipulation of a heavy and distended feces-laden colon with the relatively traumatic laparoscopic grasping instruments.

Historically, clearing the colon in preparation for surgery was a complicated procedure requiring several days of clear liquid diet, cathartics, enemas, and preoperative hospitalization. The introduction of polyethylene glycol (PEG) electrolyte solution in the early 1980s revolutionized bowel preparation (175). PEG is an iso-osmotic solution with uniquely designed electrolyte concentrations that result in virtually no net absorption of ions or water, and large volumes can be administered without significant fluid or electrolyte alterations. Several randomized studies have demonstrated that bowel cleansing with PEG can be performed safely as an outpatient preparation prior to colorectal surgery without increasing complication rates (176). Although effective, bowel preparation with PEG has some disadvantages related to patient tolerance and compliance. It requires oral intake of 4 L of a salty-tasting solution over a relatively short period of time. Many patients experience nausea, vomiting, and abdominal bloating and discomfort, and are unable to drink the required volume.

Sodium phosphate is an osmotic cathartic that provides quality bowel cleansing while avoiding the need to ingest a large volume of solution (177,178). Generally, a 45-mL dose (or two doses taken 4 hours apart) is taken with at least four glasses of clear liquid with each dose. Colonic cleansing with this method may cause intravascular volume contraction in some patients. A randomized, blinded study showed that rehydration with a carbohydrate-electrolyte "sport" drink resulted in significantly less intravascular volume contraction as compared to rehydration with water (179). A meta-analysis of 8 blinded studies that compared sodium phosphate to PEG for colonoscopy preparation suggests that sodium phosphate is an effective, better tolerated, and less costly regimen (180). Comparisons between these 2 preparations have also been studied in patients undergoing colorectal surgery, with similar results (178,181). Contraindications for the use of sodium phosphate include patients with renal insufficiency, symptomatic CHF, and liver failure with ascites (182). Hyperphosphatemia, hypernatremia, hypocalcemia, and hypokalemia have been reported after bowel preparation with sodium phosphate, but generally without clinical

significance (177,178,180,183). However, serious and fatal metabolic derangements have been reported, and caution should be used in elderly patients or when prescribing multiple dose regimens (182–185). The FDA suggests obtaining posttreatment laboratory evaluation (basic metabolic panel, calcium, phosphate), especially if more than 45 mL is taken in a 24-hour period (182). Low-volume bowel preps are now available, such as Suprep (sodium sulfate, potassium sulfate, and magnesium sulfate). Generally, the risk of electrolyte abnormalities are lower with these newer preps; however, posttreatment laboratory evaluation should be considered (186).

Although regarded as being essential in preventing complications of colorectal surgery, the necessity of mechanical bowel cleansing has been strongly disputed for the past 15 years. The claims that preoperative mechanical bowel preparation reduces anastomotic leakage and SSI are based on observational studies and expert clinical experience. Since 1992, several prospective randomized trials reported that elective colon and rectal surgery may be performed safely without mechanical bowel preparation. All patients in these trials received systemic antibiotics. However, the majority of these trials were greatly underpowered, with a 60% or greater chance that a type II error occurred (187,188). In 2006, Bucher et al. published a meta-analysis of 1,297 patients from 7 randomized, controlled trials and concluded that mechanical bowel preparation does not reduce the incidence of infectious complications and may be harmful with respect to leakage at the anastomosis (189). Another meta-analysis of 1,592 patients (9 trials) came to the same conclusions and stated that the dogma that mechanical bowel preparation is necessary before elective colorectal surgery should be reconsidered (190). In a survey of members of the American Society of Colon and Rectal Surgeons, essentially all routinely used mechanical bowel preparation, although 10% questioned its importance. Of the 515 surgeons who responded to the questionnaire, 47% routinely used sodium phosphate, 32% routinely used PEG, and 14% alternated between the 2 agents (191).

The importance of appropriate intravenous antimicrobial prophylaxis in patients undergoing colorectal surgery is well established and was discussed earlier in this chapter. There are conflicting opinions and data regarding whether preoperative oral antibiotics as part of a bowel preparation add any additional benefit for reduction of SSI (192,193). Although there are still strong proponents of this practice (194), oral antibiotic usage with preoperative mechanical bowel cleansing is declining (191).

Infection Prophylaxis

The use of prophylactic antimicrobials plays a large role in reducing the rates of surgical site infections (SSIs) and should be used in clean or clean-contaminated operations, which include most procedures performed by gynecologic oncologists. Radical pelvic surgery introduces women to a higher risk of postoperative infection secondary to several potential factors: lengthened operating time, average of age of patient requiring this specific surgery, increased blood loss, anemia, potential hypothermia, probable poor nutritional status, the presence of tumor, prior pelvic irradiation, diabetes, obesity, peripheral vascular disease, and a history of postsurgical infection (195,196). Prophylactic antibiotics should provide coverage consistent with the microbial milieu most likely to be encountered. In gynecologic oncology surgery, the most common infecting organisms are coliforms, enterococci, streptococci, clostridia, and bacteroides.

Several guidelines for antibiotic prophylaxis in surgery have been published (195,197,199,200). Most reports recommend cefazolin for gynecologic procedures. Although no longer available, cefotetan had been the preferred antibiotic for prophylaxis in longer radical gynecologic operations, as well as for

prophylaxis prior to colorectal surgery, due to longer half-life and broad spectrum coverage (198). An appropriate alternative for surgical procedures with a higher chance of bowel resection or injury is cefazolin plus metronidazole or ampicillin-sulbactam (200). Cefoxitin is another option, but availability has been limited. Most patients with a penicillin allergy can be treated with cefazolin; however, when allergy prohibits the administration of a cephalosporin, alternative regimens are clindamycin with gentamicin, a fluoroquinolone, or aztreonam (197). Itani et al. reported on a randomized, double-blinded trial in patients undergoing elective colorectal surgery that suggested ertapenem as an effective alternative to cefotetan (201). Ertapenem has received FDA approval for prophylaxis for elective colon resection; however, the 2006 Medical Letter guidelines caution against the routine use of ertapenem for surgical prophylaxis due to cost and concerns that this practice may result in increased rates of antibiotic resistance (200).

When considering dosing orders to achieve and maintain effective tissue levels, parenteral antibiotics should be given within 1 hour (between 1 and 2 hours for fluoroquinolones and vancomycin) prior to skin incision as a loading dose (197). For patients weighing >70 kg, the dosage should be doubled (i.e., cefazolin 2 g intravenously [IV]) or weight-based dosing should be used. Repeat doses should be given intraoperatively for surgeries lasting longer than 3 to 4 hours or when blood loss exceeds 1,000 mL (198,200). Guidelines from the National Surgical Site Infection Project recommend that prophylactic antibiotic use for abdominal or vaginal procedures end within 24 hours of the operation (197). The majority of the published evidence supports the use of an appropriately timed administration of a single dose of antibiotic and indicates that repeat doses postoperatively are unnecessary and subject the patient to the potential emergence of resistant organisms (195,197,198,200).

The American College of Surgeons and the National Surgical Quality Improvement Plan employ a prospective, peer-reviewed database to quantify 30-day risk-adjusted surgical outcomes that encompass such variables as preoperative risk factors and postoperative mortality and morbidity, allowing comparison of outcomes among all hospitals in the program. Enrolled hospitals abstract case data into the database, the data are quantified, and the database generates comprehensive semiannual reports to the hospitals as well as real-time, continuously updated, online benchmarking reports (202).

Surgical site infections account for nearly 40% of nosocomial infections in surgical patients and occur in up to 20% of patients undergoing abdominal surgery (195,197). They are a significant source of postoperative morbidity, resulting in longer hospital stays, increased rates of intensive care unit admissions, hospital readmissions, and subsequently increased costs. Mortality rates increase 2 to 3 times for patients with an SSI as compared to patients who do not develop an SSI (203,204). In addition to the administration of preoperative antimicrobial prophylaxis, preoperative skin preparation is used to reduce the risk of SSI by decreasing the microbial count at the projected site of incision. A meta-analysis of 6 trials concluded that although whole-body scrubs or showers with antiseptic agents such as chlorhexidine or povidone-iodine prior to surgery reduce bacterial counts on the skin, this practice did not reduce wound infection rates (205). Surgical infection occurrences are noted to be influenced by both patient and operative environmental factors. Therefore, patients undergoing surgery should be instructed to bathe or shower normally the night or morning prior to surgery, removing any debris from the skin surface and decreasing environmental contaminants.

Inappropriate hair removal techniques can traumatize the skin and provide an opportunity for colonization of microorganisms. There is no evidence that hair removal prior to surgery will prevent or reduce SSI. To the contrary, meta-analysis evaluating hair removal techniques demonstrated a twofold increase in SSI when patients underwent hair removal by shaving versus clipping

(206). Hair is generally sterile and therefore does not need to be removed unless the hair around the incision will interfere with the operation. When hair removal is necessary, the simplest and least irritating method of hair removal is an electric or battery-powered clipper with a disposable head (195,206). Some infection control experts advocate removing all razors from hospitals and operating rooms (207).

Special Considerations for Obese Patients

A heightened awareness of potential comorbidities should be extended when preparing morbidly obese patients for surgery. Coexisting disorders, such as coronary artery disease, hypertension, obesity-hypoventilation syndrome, obstructive sleep apnea, adult-onset diabetes mellitus, pulmonary hypertension, gastroesophageal reflux, impaired cardiac function, and hypercoagulability are common in morbidly obese patients and may be undiagnosed at the time of surgery. Certain symptoms of such comorbidities may not manifest themselves until the patient undergoes physiologic stress related to surgery and thereby contribute to increased perioperative morbidity and mortality. For example, baseline pulmonary function studies of markedly obese patients demonstrate mild hypoxemia; decreased vital capacity, tidal volume, and expiratory reserve volume; increased resistance; and ventilation-perfusion inequalities (208). During the postoperative period, severe hypoxemia may occur secondary to sedation, pain, immobility, atelectasis, and anemia, leading to cardiac arrhythmia or ischemia. A thorough preoperative medical history and physical examination should be performed to increase the findings of coexisting disease and minimize surgical risk. A comprehensive review of the pathophysiology associated with morbid obesity is beyond the scope of this chapter, and we direct the reader elsewhere for a thorough review (209).

Surgery in morbidly obese patients poses many challenges for teams on both sides of the surgical drape. The primary concern of the anesthesiologist is gaining adequate control of the airway. The combined problems of increased aspiration risk, rapid oxygen desaturation caused by decreased functional residual capacity, baseline hypoxemia, and increased oxygen demand, in addition to technical difficulties due to anatomic fat deposits, make intubation a high-risk procedure. An awake, fiberoptic-assisted intubation is often the technique of choice for obtaining an airway. Extubation should be delayed until the patient is fully awake and ideally sitting upright (210). There are technical operating room and instrumentation issues, which need to be addressed as well. Standard operating tables, stretchers, and hospital beds have weight limits, which have prompted specifically designed wider and sturdier models for the obese patient. Staff and patient safety during transfer of the patient from the operating table to the bed or gurney is also a concern in the extremely obese patient and must be taken into consideration. Proper retractors and extra-long instruments are essential and may not be available in all hospitals. Although these practical considerations are ostensibly mundane, failure to prepare will obviate a successful outcome, add frustration to all involved, and possibly put the patient at risk.

Recent reports in the gynecologic oncology literature suggest performing panniculectomy to improve exposure of the peritoneal cavity and pelvic structures (211–213). Although this is a relatively straightforward procedure, it does require some experience and planning for optimal results. Hospital credentialing of surgical privileges may require the involvement of a plastic surgeon or proctoring until proficiency is demonstrated. In addition, since panniculectomy is considered a cosmetic procedure, many insurers may require prior authorization with documentation of medical necessity, or they may deny any reimbursement.

CRITICAL CARE AND POSTOPERATIVE MANAGEMENT

Cardiovascular Issues

Monitoring Issues

There are many tools at the hands of the modern-day clinician when it comes to monitoring the cardiovascular function of the patient. Clinical examination, heart rate, blood pressure, and ECG are a few. In the critical care setting, the addition of the arterial catheter, central venous pressure, and pulmonary artery catheter increases sophistication. Most patients in the ICU can be managed with simple clinical parameters. Fluid status can be assessed by daily weights, pulse rate, blood pressure, and urine output. Continuous ECG monitoring is helpful for detecting arrhythmias and ischemia. Central venous pressure (CVP) is often used for assessment of volume status and a crude estimation of cardiac function. If a patient has a central line, then a port can be continuously transduced for CVP. It is a common mistake among novices to evaluate a single reading of CVP rather than reviewing the trend. When the CVP is correlated with volume status, the resulting graph is a scatter graph (i.e., no correlation). There is correlation only over time and in response to fluid challenges, transfusion, or therapy. One must remember that the CVP is a pressure measurement and not the desired measurement of volume (preload). Therefore, only crude estimations of fluid status can be made. When the status of a patient's cardiac output or fluid state is unclear, a minimally invasive hemodynamic monitor or an invasive pulmonary artery (PA) catheter (e.g., Swan-Ganz catheter) may be helpful. A minimally invasive hemodynamic monitor connects to an existing arterial catheter and performs continuous self-calibration. The sensor provides information on stroke volume, stroke volume variation, and cardiac output (214).

Pulmonary artery catheters are placed via a central vein (subclavian or jugular) as a central line. The catheter has a balloon-tipped transducer and is "floated" into the pulmonary artery. Waveforms of the right ventricle, pulmonary artery, and pulmonary capillary wedge pressure (PCWP) are directly visualized as the catheter progresses through the heart (Fig. 8.3), and confirmed placement is verified by chest radiograph (Fig. 8.4). Complications of placement include pneumothorax, arrhythmia, line sepsis (2%), and rarely, pulmonary artery rupture. The PA catheter allows the measurement of cardiac output and oxygen delivery and estimation of preload by obtaining the pulmonary artery occlusive pressure (PAOP) or PCWP, the "wedge."

A number of formulas for calculation of hemodynamic parameters are crucial in utilizing the PA catheter for the care of the critically ill patient (Table 8.12). Assessment of preload is desirable for determining fluid administration or diuretic requirements for patients. The ideal measure of preload would be left ventricular end-diastolic volume; however, since this is unobtainable with current technology, intensivists settle for "the wedge" as an estimation. By inflating the balloon placed in the pulmonary artery, a direct column of standing fluid exists between the left atrium, through the pulmonary vasculature, and back to the balloon (transducer). The PAOP can be measured and is a crude reflection of left atrial pressure. If the PAOP is elevated, the preload is adequate (or excessive), and if it is low, the patient may be volume depleted. These measurements, as previously mentioned with CVP, are dynamic and trend is important. For example, if the PAOP is low and a fluid bolus is given, the PAOP should increase if the diagnosis of volume depletion was correct.

Thermodilution techniques are used to calculate cardiac output by injecting saline via a proximal port in the PA catheter and measuring the thermal changes at the distal tip of the PA catheter. By combining the preload assessment provided by the

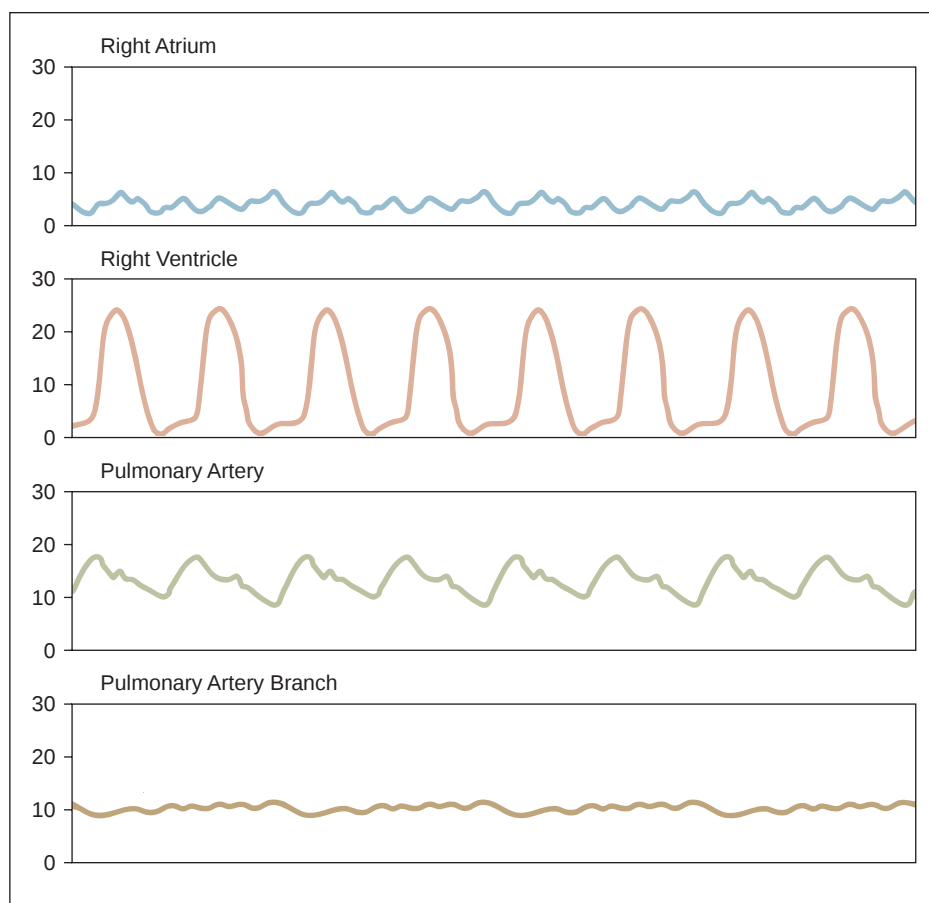


FIGURE 8.3. Pulmonary artery catheter wave-form readings as the catheter passes through the heart into the pulmonary artery. Y-axis is reading in millimeters of mercury (mm Hg).

PAOP and the calculated cardiac output, differentiation between volume depletion and cardiogenic disease states can be made (see section on shock). Newer PA catheters have been developed that can calculate right ventricular ejection fraction.

By taking a blood sample from the tip of the PA catheter, the most desaturated blood in the body is retrieved. In normal circulation, the blood from the superior vena cava and the inferior vena cava mix, and the blood from the coronary sinus is

added to give a sample known as the mixed venous blood. By evaluating the oxygen saturation of this blood, oxygen delivery can be calculated (Table 8.12). This measurement is perhaps the most important function of the PA catheter, and current technology allows this function to be continuous via an infrared sensor at the tip of the PA catheter. For example, if oxygen delivery is determined to be low, there are only 3 situations that the clinician can influence: increase cardiac output (with fluid, chronotropes, or inotropes), increase the hemoglobin, or increase the oxygen saturation. In a patient with a major operation and medical comorbidities, the measurement of a normal oxygen delivery provides reassurance to the clinician that end organs are being perfused.

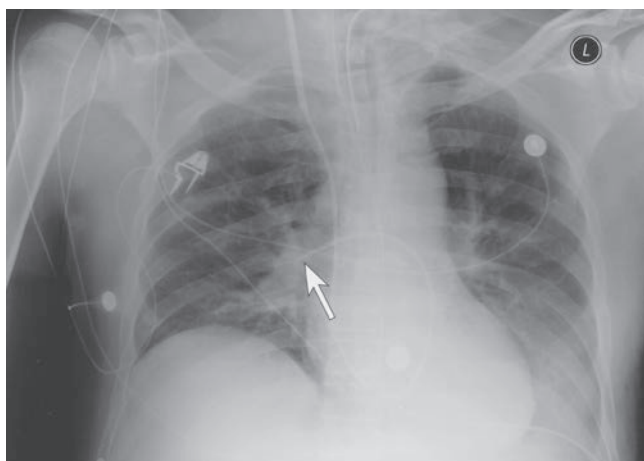


FIGURE 8.4. Chest radiograph showing proper placement of pulmonary artery catheter in the pulmonary artery (arrow shows tip of pulmonary catheter).

Table 8.12 Hemodynamic formulas

Cardiac output (CO) = stroke volume (SV) $\times$ heart rate (HR) [4–8 L/min]

Cardiac index (CI) = CO/body surface area (BSA)

Systemic vascular resistance (SVR) = $\frac{\text{Mean arterial pressure (MAP)} - \text{Central venous pressure (CVP)}}{\text{CO}} \times 80$ [800–1200 dyne/s/cm²/m²]

Arterial O₂ content (CaO₂) = (1.36) (hemoglobin) (oxygen saturation) + 0.003 (partial pressure of oxygen) [20 mL O₂/dL]

O₂ delivery (DO₂) = CO $\times$ CaO₂ $\times$ 10 [600–1000 mL O₂/min]

O₂ availability (O₂AVI) = CI $\times$ CaO₂ $\times$ 10 [500–600 mL/min/m²]

O₂ extraction ratio = $\frac{(\text{CaO}_2 - \text{CvO}_2)}{\text{CaO}_2} \times 100$ [25%]

Values in brackets are normal values.

Calculation of the systemic vascular resistance (SVR) is also possible with a PA catheter. Because the SVR is a calculated value and not directly measured, inaccuracies are inherent and overinterpretation of this value is cautioned. Rather than relying on the calculated SVR, the clinician should have complete understanding of the measured blood pressure and cardiac output and the ramifications therein to make therapeutic decisions (SVR combines the 2 previously mentioned measured variables).

In one study of ovarian cancer patients undergoing cytoreductive surgery, 18% of patients had indications for PA catheter use (214). Because of the issues of volume status in these patients, PA catheter placement for postoperative fluid management may be especially helpful.

Acute Postoperative Myocardial Infarction

MI usually manifests with acute chest discomfort, elevated cardiac enzymes (troponin, creatinine phosphokinase [CPK], etc.), and ECG changes. Dyspnea, diaphoresis, nausea, and anxiety may also be associated. Risk factors that increase mortality from postoperative MI include female gender, advanced age, tachycardia, hypotension, and CHF (215,216). Treatment includes ICU monitoring with continuous ECG monitoring, supplemental oxygen, immediate oral aspirin 325 mg administration, sublingual nitroglycerin, and morphine sulfate as needed until pain resolves. β -blockers have been shown to decrease mortality by decreasing fatal arrhythmias and they are also part of the early treatment regimen. An evaluation for heparin therapy or thrombolytics can be made in consultation with a cardiologist.

Congestive Heart Failure

Patients with known CHF will be risk stratified, as previously mentioned, before major elective surgery. However, in the postoperative setting, CHF will present in a number of ways (165). Patients with CHF are in a continuous hypervolemic state, and issues of fluid balance (strict “ins” and “outs”) will be paramount during the perioperative period. In difficult cases, insertion of a PA catheter can be very helpful. Judicious fluid administration guided by the PAOP as well as selective use of inotropic support for augmentation of the cardiac output will aid the clinician in a successful outcome in these difficult patients (217).

Inotropes and Vasopressors

A variety of hemodynamically active drugs is available to support the cardiovascular function of patients in the perioperative period (218). In the broadest sense, these drugs can be categorized as vasopressors, which elevate blood pressure, and inotropes, which enhance cardiac output (219). When faced with a patient in whom oxygen delivery is low and an increase in cardiac output is desired, inotropes such as dopamine or dobutamine should be used. Dopamine, at lower doses, activates dopaminergic receptors and increases circulation in mesenteric, cerebral, and renal vascular beds. At intermediate doses, dopamine stimulates β -receptors in the heart and peripheral circulation. This activation causes tachycardia, increased stroke volume, and increased cardiac output. Increasing cardiac output in this fashion also increases demands for myocardial oxygen and could precipitate angina or MI (220). At high doses, dopamine acts as an α -agonist, causing vasoconstriction. Dobutamine is a β -1 agonist with much greater inotropic effect than dopamine, and causes peripheral arterial vasodilation, decreasing afterload (this dilation is abrupt and can cause hypotension in some patients). It is the drug of choice for severe heart failure.

Epinephrine is a potent sympathomimetic with varying effects based on the dose. The drug has β -mimetic effects at lower doses and α -mimetic effects at higher doses. Epinephrine causes

an acute increase in myocardial oxygen demand and is mainly reserved for cardiac arrest or severe circulatory failure. Norepinephrine and phenylephrine are pure α -mimetic agents, utilized for vasoconstriction (neurogenic shock). In most situations of shock, fluid resuscitation is preferred to administration of α -agents. Although these agents will give a false sense of security that the blood pressure is normal, one must remember that the vasoconstriction underperuses capillary beds, leading to an increased incidence of renal hypoperfusion (acute renal injury), splanchnic hypoperfusion (resulting in translocation of gut flora), and a myriad of other problems (220,221).

Vasopressin has emerged as an option similar to epinephrine, with some important differences. This antidiuretic hormone in high doses provides potent vasoconstriction and leads to improved cerebral and coronary blood flow in shock states. Unlike epinephrine, there is less increase in myocardial oxygen demand and less propensity for inducing arrhythmias.

Amrinone (or inamrinone) is a phosphodiesterase inhibitor that provides a positive inotropic effect on cardiac musculature while causing vasodilation. It is used in refractory cardiac failure.

Valvular Disease

In a recent study, approximately 4% of patients undergoing elective, noncardiac surgery were found to have clinically significant valvular disease. Important considerations in perioperative management are directed at patients with aortic stenosis (AS) and the level of associated ventricular failure. Aortic stenosis is an independent risk factor for poor operative outcome, as previously mentioned (222). Patients with severe AS need valve replacement before elective surgery, whereas patients with mild to moderate AS need careful anesthetic control of blood pressure. The presence of ejection systolic murmurs requires assessment of left ventricular function for the presence of congestive heart failure with echocardiography (223). Treatment and support will be related to support of ventricular function. Avoidance of systemic hypotension in the perioperative period is essential. Recently, the American Heart Association reviewed its recommendations for universal prophylactic antibiotic administration for prevention of endocarditis in patients with valvular disease and artificial valves, and patients who have had surgical correction of congenital defects who are undergoing gastrointestinal (GI) or genitourinary (GU) procedures. Routine administration of prophylactic antibiotics is no longer recommended. However, if patients have active GU or GI infections, then the surgery should be delayed, if possible, to allow eradication of the infection with antibiotic treatment. Any antibiotic regimen should include agents that are active against enterococci, such as ampicillin or vancomycin, and should be administered 30 minutes before to 2 hours after the procedure (224,225). Antibiotic prophylaxis may be reasonable for patients with prosthetic cardiac valves if the valves have been placed within the previous 6 months; previous history of infective endocarditis; or certain congenital heart diseases (CHD) such as unrepaired cyanotic CHD, any repaired CHD with prosthetic material within the previous six months, and any repaired CHD with residual defect adjacent to a prosthetic patch or device (which prevents endothelialization) (226).

Arrhythmias

Postoperative arrhythmias are often secondary to noncardiac problems such as hypotension, electrolyte abnormalities, hypoxia, or infection. Whenever an arrhythmia occurs in the postoperative setting, myocardial ischemia must first be ruled out (227). If ECG and cardiac enzyme measurements are normal, the arrhythmia is not likely to be due to myocardial ischemia. Fortunately, most arrhythmias in the postoperative period are transient and self-resolving. Asymptomatic arrhythmias, except in the preoperative period (Table 11.2), are generally of little clinical significance.

Hypercapnia, hypoxemia, hypokalemia, acidosis, inadequate analgesia, and anemia can all promote cardiac arrhythmias. Supraventricular tachycardia is the most common rhythm disturbance seen in the postoperative period (228). Treatment with calcium channel blockers (such as diltiazem) or a β -blocker is usually effective after correction of the underlying etiology. Amiodarone as first-line treatment of acute-onset postoperative atrial fibrillation has been associated with a lower incidence of recurrent atrial fibrillation (229).

Pulmonary Issues

Ventilator Management

The ability to provide ventilatory support to the surgical patient has been a tremendous advance in postoperative care. Mechanical ventilators have enabled oncologic surgeons to perform major operations for aggressive control of lesions that were once considered to be unresectable. Although preemptive preoperative therapies attempt to avoid postoperative mechanical ventilation, some patients will require this therapy. Mechanical ventilation must be thought of as providing 2 functions: ventilation and oxygenation. However, these 2 functions must be separated and applied independently to each particular situation. A more difficult concept for residents and fellows to understand is that ventilation has nothing to do with oxygenation. Many patients decompensate on the ward despite supplemental oxygen and 100% oxygen saturation because tidal volumes were low and the patient was not ventilating.

When contemplating mechanical ventilation, one must ask 2 questions: is the patient able to oxygenate her tissues adequately, and can she ventilate adequately to maintain normal partial pressure of carbon dioxide (PCO_2) and acid-base function? Adequate oxygenation can be determined by measurement of oxygen saturation and arterial partial pressure of oxygen (PO_2). Targets are generally an O_2 saturation $>92\%$ or PO_2 greater than 65 mm Hg. Poor oxygenation may be caused by fluid overload, depressed mental status, underlying pulmonary disease, or shunt. Evaluation of the arterial blood gas will also give a pH and PCO_2 measurement. Patients may hypoventilate for a number of reasons. Postoperative pain may prohibit deep inspiration. Conversely, overuse of pain medication may depress the level of consciousness, leading to fewer and poorer respirations. Atelectasis, pneumonia, and poor pulmonary compliance all lead to difficulties in ventilation. Finally, a bronchial mucous plug or a pneumothorax will lead to life-threatening ventilatory compromise. A respiratory rate greater than 35 per minute or a PCO_2 greater than 55 mm Hg are accepted indications for intubation and mechanical ventilation.

When intubating patients, the size of the endotracheal tube must be considered, as this may impact removal of mechanical ventilation. The larger the tube, the less resistance and the easier it will be for the patient to participate in “weaning” trials to discontinue ventilatory support (230). Typical recommendations are an 8.5-mm tube for women and a 9.0-mm tube for men.

Traditionally, there are pressure-cycled ventilators and volume-cycled ventilators. Pressure-cycled ventilators are used routinely in neonatal ICU patients because overinflation can be dangerous to neonates. In the adult ICU, most ventilators are volume-cycled, meaning that the clinician sets the tidal volume, and regardless of the pressures necessary to give the volume, the volume will be delivered. In patients in whom pulmonary compliance is reduced (i.e., due to a stiff lung or acute respiratory distress syndrome [ARDS]), efforts at controlling pressure are important. When setting the ventilator, a number of decisions must be made. The mode of delivery, tidal volume, and rate will determine ventilation, whereas the fraction of inspired oxygen (FIO_2) and positive end-expiratory pressure (PEEP) will determine oxygenation.

Mode

There are a number of ventilator modes. The first developed was controlled mechanical ventilation (CMV), where the tidal volume and rate are set and that is exactly what the patient receives—no more and no less. This mode is very good for patients under general anesthesia or who are paralyzed. However, this mode is very disturbing to the patient who wishes to participate, however slightly, in her own ventilation. This mode has evolved into the current assist/control mode (A/C), whereby the patient is guaranteed the fixed rate and tidal volume but can also trigger breaths in between with a similar tidal volume. In addition, the machine will synchronize the breath when the patient triggers such a breath. This mode provides complete rest for the patient by performing all the work of breathing and is generally used for patients in the immediate postoperative period or for patients who have critical illnesses such as organ failure or sepsis.

Intermittent mandatory ventilation (IMV) is a mode whereby the clinician sets a rate and a tidal volume, which the machine delivers. Any breath initiated by the patient is delivered in relation to the amount of effort the patient puts forth, meaning a strong effort gives the patient a large breath and a meager effort a smaller one. This is sometimes called a weaning mode. The patient is given full support with rate and tidal volume until she is stronger. The rate is slowly turned down, allowing the patient more frequent, spontaneous breaths until extubation. Synchronized IMV (SIMV) ensures that a machine-delivered breath does not stack onto a patient-initiated breath.

Pressure support ventilation (PSV) is a mode where patient-initiated breaths are given support from the ventilator only during the beginning of ventilation (inspiratory phase). The support is meant to help the patient overcome the large amount of resistance present in the valves of the machine, the ventilator circuit, and the endotracheal tube. By titrating PSV to the spontaneous tidal volume produced by the patient, one can fully or partially support patient breathing and overcome the work of breathing. This mode of ventilation is important during the “weaning” process.

Work of Breathing

When conceptualizing the job of the ventilator, the different types of work must be defined (230). In addition to the physiologic work of breathing that all humans do on a daily basis, huge workloads are imposed from the resistance of the ventilator equipment (e.g., breathing through a straw analogy). Finally, there is the pathologic work of breathing from pneumonia, the incision, etc. The intent of mechanical ventilation during disease states is to assume the last two types of “work” so that the patient may convalesce. As a patient improves and the pathologic work has been removed, then the patient should be able to resume normal, physiologic work.

More Advanced Modes of Ventilation

With advanced circuitry and computer microprocessors, newer ventilator modes have been developed. Pressure-regulated volume control (PRVC) has largely replaced AC ventilation (ACV). PRVC provides the same function as AC while preventing overinflation. Recent data have shown that preventing overinflation (or stretch) of alveoli prevents trauma and decreases the incidence of ARDS (231). PRVC delivers the same tidal volume but changes the flow rate to prevent high pressures by measuring the pressure on a breath-to-breath basis. Volume control (VC) ventilation is a mode whereby a tidal volume target is set and the ventilator continually titrates the amount of PSV to provide this volume. This mode has been termed “autowean” or “weekend” mode because as the patient gets stronger, he or she will be able to meet the tidal volume setting. In situations where difficulties in ventilation

are encountered, such as ARDS, hypercarbia, and acidosis, pressure control (PC) is used. This mode is similar to the neonatal pressure-cycled ventilator where the maximum pressure is set and the flow rate is decreased but the inspiratory time is lengthened to achieve proper ventilation. Airway pressure release ventilation (APRV), high-frequency jet ventilation, and inverse ratio ventilation are other advanced modes, the discussion of which is beyond the scope of this chapter.

Setting the Ventilator

Initial ventilator settings require a rate of 12 to 14 breaths per minute with a tidal volume of 6 to 8 cc/kg. This is a departure from the traditional 12 cc/kg, which has been determined to result in greater alveolar trauma and increased risk for the development of ARDS (232). After initial setting of the ventilator, measurements of pH, PO₂, and PCO₂ from arterial blood gas are used to make further ventilator adjustments.

Oxygenation

Oxygenation is controlled by two settings: FIO₂ and PEEP. The inspired oxygen content can easily be controlled with the ventilator, to keep blood oxygen saturation greater than 92%. Inspired oxygen concentration greater than 60% is considered to be potentially toxic and may be the etiologic reason for pathologic changes similar to ARDS. In patients with normal lung function, studies have shown that higher concentrations of inspired oxygen can cause acute inflammation and fibroproliferative changes, resulting in toxic effects to lung tissue. Similar studies in patients with underlying lung disease are lacking (233,234). If it is necessary to have oxygen concentrations above 60%, the recommendation is to wean these levels as soon as possible. PEEP is another mechanism for improving oxygenation. In normal physiology, the glottis closes before full expiration, creating a PEEP of approximately 4 cm H₂O, and is termed physiologic PEEP. When ventilating patients, the addition of 5 cm H₂O PEEP is used as a baseline and is increased if added oxygen delivery is required. Increasing PEEP is the preferred method for improving oxygenation in post-surgical patients as opposed to increasing the FIO₂. Postsurgical patients have atelectasis and shunting secondary to operative pain and anesthesia. The addition of PEEP recruits collapsed alveoli, improving oxygenation and lung compliance. However, the use of PEEP must be balanced by potential adverse effects, which include decreased cardiac output and the risk for barotrauma.

Weaning From Ventilator

Multiple opinions exist on the techniques of weaning patients from mechanical ventilation. T-piece trials, spontaneous breathing trials (SBT), SIMV, and PSV are just a few. The best method of weaning is a pathway agreed upon by clinicians, nurses, and respiratory therapists. Before discontinuing mechanical ventilation, the disease process that required ventilation should have resolved and patients should have proper mental status and the ability to generate a cough. Copious secretions are often an initial reason not to consider weaning or extubation. Criteria for extubation, whether on T-piece or minimal PSV, have traditionally included a respiratory rate less than 35, a PCO₂ less than 50 mm Hg, and a negative inspiratory force (NIF) greater than -20 cm H₂O. Rapid shallow breathing, defined as the respiratory frequency divided by the tidal volume in liters over a minute, is the most accurate predictor of failure in weaning patients from mechanical ventilation (235).

Acute Respiratory Distress Syndrome

ARDS is a condition that has been well recognized and extensively studied (236–238). This disease is a form of refractory hypoxemia which is caused by a variety of insults, which incites

an inflammatory response consisting of increased production of cytokines, leukotrienes, endothelial adhesion molecules, and interleukins. These molecules, which are useful in the defense of the host organism, are particularly detrimental to pulmonary endothelium. ARDS is the result of some inciting cause and does not arise *de novo* as a primary problem. A study of patients who develop multiple organ dysfunction syndrome (MODS), a state where sequential organ failure leads to patient death, has shown that the lung may be the first organ system susceptible to these circulating inflammatory mediators (239). In addition to supportive treatment for ARDS, operative injuries or postoperative complications (e.g., intra-abdominal abscess, anastomotic leak) must be sought and ruled out.

In 1994, a consensus of American and European intensivists defined the criteria for ARDS and a lesser form of the disease described as acute lung injury (ALI) (237). Criteria include (a) acute onset after defined insult; (b) bilateral diffuse infiltrates on chest radiograph; (c) no evidence of left atrial hypertension, CHF, or a PAOP less than or equal to 18 mm Hg; and, most importantly, (d) impaired oxygenation. Impaired oxygenation was classified as ALI if the partial pressure of arterial oxygen (PaO₂)/FIO₂ ratio was ≥300 mm Hg and ARDS if the PaO₂/FIO₂ ratio was ≥200 mm Hg. Postmortem examination of lungs with ARDS shows atelectasis, edema, inflammation, hyaline membrane deposition, and fibrosis. The mortality of ARDS is 30% to 40%. Treatment of these severely hypoxemic patients consists of mechanical ventilatory support with FIO₂ and PEEP. Because of alveolar damage, ventilation/perfusion mismatch occurs, resulting in a worsening shunt fraction and increasing dead space. As ALI/ARDS progresses, ventilation, due to decreased pulmonary compliance, becomes difficult and oxygenation progressively worsens. The end result is a hypercapnic state and respiratory acidosis.

The recent ARDS NET trial comparing high tidal volume, in order to maintain normocapnia, to low tidal volumes, to prevent barotrauma, showed significantly improved survival among patients in the low tidal volume group (231). Current strategies employ tidal volumes of 6 cc/kg, while accepting elevated PCO₂ levels (permissive hypercapnea).

Pneumonia

Pneumonia is a significant complication in postsurgical patients. Patients requiring mechanical ventilation are particularly susceptible to pneumonia (ventilator-acquired pneumonia [VAP]), with rates as high as 30% after 72 hours of ventilation. The mortality rate from VAP ranges from 25% to 50%. The pathogens are often gram-negative bacteria and are resistant to multiple antibiotics. High clinical suspicion and aggressive treatment of VAP is crucial. An exhaustive review of this complicated and serious topic by Chastre and Fagon is recommended for further reading (240).

Pulmonary Embolism and Deep Venous Thrombosis Prophylaxis

The prevention of venous thromboembolism is an important component of perioperative management of the gynecologic oncology patient. The American College of Chest Physicians consensus statement published in 2012 reviews the data exhaustively and provides recommendations (241). Patients undergoing major gynecologic surgery without venous thromboembolism prophylaxis have a risk of deep vein thrombosis (DVT) between 17% and 40% (242). Surgery for cancer, advanced age, previous VTE, prior pelvic radiation therapy, and abdominal resection (in contrast to vaginal resection) appear to increase the thromboembolic risk after gynecologic surgery (243). The incidence of pulmonary embolism (PE) is 1.6% with rate of fatal PE being 0.9%. In trials comparing low-dose unfractionated heparin (LDUH) with no therapy in general surgical patients, the DVT rate was decreased

from 25% to 8%. These studies also produced a 50% decrease in the rate of fatal PE (244). Comparisons of low-molecular-weight heparin (LMWH) versus LDUH have shown equal efficacy. LMWH may have fewer complications (mostly wound hematomas) and greater ease of use with once daily dosing.

Sequential pneumatic compression devices (PCDs) are attractive for patients at risk for bleeding complications. In trials comparing PCD with LDUH, both have shown efficacy. Elastic stockings T.E.D. hose and aspirin usage are not currently recommended for DVT prophylaxis. Studies have shown that the presence of D-dimer positivity in the face of DVT and/or PE, but the presence of any released blood or hematoma (i.e., in any post-operative patient) makes the D-dimer positivity nonspecific. In the surgical patient, a negative D-dimer makes DVT or PE highly unlikely; however, a positive test is essentially useless.

Patients at low risk (age less than 40 years, no risk factors, and minor surgery) need no prophylaxis, but early ambulation is encouraged. Moderate-risk patients (minor surgery in a patient with risk factors, major surgery with no risk factors) should receive PCD, LMWH, or LDUH, with equal results. High-risk patients require LMWH in addition to PCD.

Diagnosis of DVT is performed by duplex ultrasonography, and treatment is with either heparinization to 1.5 times control prothrombin time or therapeutic doses of LMWH. Diagnosis of PE was traditionally made by pulmonary arteriogram. This practice has been abandoned because dynamic contrast-enhanced computerized tomography has better sensitivity. Once diagnosis is confirmed, the patient is anticoagulated with IV heparin or LMWH. Ultimately, the patient is converted to warfarin (Coumadin) therapy for at least 3 months in the case of DVT and PE (241).

Fluid and Electrolyte Issues

Understanding fluid and electrolyte physiology in gynecologic oncology is paramount because of the underlying disease processes that face the gynecologic oncologist and the ultimate, radical surgical interventions that are needed to treat them. These treatments result in great fluid shifts perioperatively, requiring careful attention to input of fluids (volume and content/type) as well as output from renal and gastrointestinal sources, insensible sources, and drains. Since extensive discussions of these topics can be found elsewhere, this section presents a brief review of normal fluid and electrolyte physiology and discusses strategies for fluid resuscitation and correction of electrolyte deficiencies.

Total body water (TBW) can be calculated by a variety of methods and varies directly with the amount of adipose or lean tissue present in an individual patient. TBW estimates, therefore, must be adjusted based on the adiposity of the patients. In women, TBW accounts for approximately 60% of a patient's weight. TBW is distributed into extracellular fluid (ECF) and intracellular fluid (ICF), with the ECF being further divided into intravascular (one-quarter of the ECF) and interstitial (three quarters of the ECF) compartments. The ECF accounts for approximately one-third of the TBW, whereas ICF accounts for two thirds (245,246). Direct measurement of the ECF and TBW are possible with the resulting difference being an estimated ICF. Table 8.13 describes the body fluid compartments and their contributions to body weight. Despite these arbitrary compartments (and electrolyte concentration differences between compartments, which are discussed in the paragraph below), water flows freely across all compartments. Thus, a derangement in one compartment will result in a compensatory change in another (247).

The electrolyte composition of the various compartments is different. Sodium is the predominant cation in the ECF and potassium is the predominant cation of the ICF. Table 8.14

Table 8.13 Body Fluid Compartments

Total Body Water	Body Weight (%)	Total Body Water (%)
Total	60	100
Intracellular	40	67
Extracellular	20	33
Intravascular	5	8
Interstitial	15	25

Source: From Wait RB, Kahng KU, Dresner LS. Fluid and electrolytes and acid-base balance. In: Greenfield LJ, Mulholland M, Oldham KT, et al., eds. *Surgery: Scientific Principles and Practice*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1997:242–266, with permission.

describes the various concentrations of electrolytes in the various fluid compartments. Because of the Donnan principle of equilibration, the content of cations and anions in the interstitial compartment is slightly higher than in the intravascular compartment. This principle describes the unique relation between solutions of permeable and impermeable complex anions when these anions are unevenly distributed across a semipermeable membrane. Water, on the other hand, as mentioned earlier, freely equilibrates between the compartments (247).

Effective circulating volume (ECV) is a term used to describe the portion of the ECF that perfuses the organs of the body and affects baroreceptors (see next paragraph). In healthy patients, the ECV equates to the intravascular volume/compartment. But in disease states that increase “third spacing” such as sepsis (leaky capillaries), ascites due to intra-abdominal metastasis, or bowel obstruction with resulting edema and transudation, the interstitial compartment increases at the expense of the intravascular compartment, decreasing the ECV (245).

The osmotic activity of a fluid compartment is affected by the component ions and is described in milliosmoles (mOsm). Normal serum osmolality (in the ECF, of course) averages 290 mOsm/kg of H₂O. Osmoreceptors in the hypothalamus

Table 8.14 Electrolyte Concentrations in the Various Fluid Compartments

	Extracellular Fluid		
	Plasma	Interstitial Fluid	Intracellular Fluid
Cations			
Na ⁺	140	146	12
K ⁺	4	4	150
Ca ²⁺	5	3	10 ⁻⁷
Mg ²⁺	2	1	7
Anions			
Cl ⁻	103	114	3
HCO ₃ ⁻	24	27	10
SO ₄ ²⁻	1	1	—
HPO ₄ ³⁻	2	2	116
Protein	16	5	40
Organic anions	5	5	—

Source: From Wait RB, Kahng KU, Dresner LS. Fluid and electrolytes and acid-base balance. In: Greenfield LJ, Mulholland M, Oldham KT, et al., eds. *Surgery: Scientific Principles and Practice*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1997:242–266, with permission.

respond to small changes in serum osmolality, increasing or decreasing secretion of antidiuretic hormone (ADH) and modifying the thirst response. These receptors are responsible for the day-to-day fine-tuning of fluid balance. Baroreceptors, on the other hand, in the intrathoracic vena cava, the atria, the aortic arch, the carotid arteries, and the renal parenchyma, sense volume changes by changes in pressure. These receptors begin a cascade of mediators such as aldosterone, atrial natriuretic peptide (ANP), prostaglandins, and the renin-angiotensin system, which ultimately result in changes of water and sodium balance mediated through the kidneys. These baroreceptors have little to do with the day-to-day fluid management and require intravascular losses of 10% to 20% to initiate activity (247).

The goal of fluid resuscitation is to maintain the ECV and return the patient to a homeopathic state. Many gynecologic oncology procedures are lengthy and can result in large blood losses requiring immediate intraoperative replacement. In addition, following procedures where evacuation of large amounts of ascites has occurred and/or “peritoneal stripping” has left denuded surfaces, these patients may have large fluid shifts into the interstitial compartment, requiring large volumes of fluid to maintain the ECV. Finally, losses are not water alone and include electrolytes and clotting factors, which may need repletion. Selecting fluids to administer to a given patient is akin to selecting the correct intravenous medication to give; not *all* fluids are for *all* patients. The physician should understand the amount of daily maintenance fluid and electrolytes required by patients, calculate losses (fluid and electrolytes), determine ongoing fluid and electrolyte losses, and replace them with the appropriate fluid and electrolyte combinations. It is easy to fall into the trap of giving all patients an 8-hour rate (125 mL/hour) of maintenance fluid. However, an octogenarian, even with normal cardiac and renal function, weighing 50 kg does not need that much maintenance fluid. “Formulas” for calculating appropriate maintenance fluid requirements exist (247), but calculating 30 to 40 mL/kg/day, depending upon body frame size, is a much simpler and quicker estimate of maintenance fluid requirements for patients.

In general, the normal maintenance requirement of sodium is 1 to 2 mEq/kg/day and for potassium 0.5 to 1.0 mEq/kg/day. Table 8.15 lists the various IV fluid preparations available for fluid resuscitation. Which fluid to be used is controversial and driven, in more instances, by “dogma,” varying from physician to physician and institution to institution; rather than by evidence. Controversy over which fluid type to use in fluid resuscitation continues to this day. Several meta-analyses have shown no advantage of colloid over crystalloid for resuscitation in surgical patients (248–255). Almost all studies have shown that administered colloid leaks from the intravascular compartment to the interstitial compartment in several hours, decreasing the ECV and requiring further administration of colloid (248–255). The use of colloid has been shown to be advantageous in conditions of hypoproteinemia, or in malnourished states where patients require plasma volume expansion and cannot tolerate large amounts of fluid (255).

Most of the time patients are given isotonic solutions, such as lactated Ringer’s solution, to cover perioperative losses. In the immediate postoperative course, patients are given their maintenance fluid requirements in addition to the immediate intraoperative losses. It is helpful to convert all losses to equivalents of crystalloid to determine fluid rates. For example, to replace 500 mL of blood loss, one would give 1,500 mL of isotonic fluid, a ratio of 3 mL of crystalloid to 1 mL of blood loss. It is traditional to replace one-half of the intraoperative losses in the first 24 hours, with the rest being replaced during the ensuing several days. Other intraoperative losses, which need to be accounted for, are the insensible losses that occur through evaporation from the incision (5 to 10 mL/kg/hour of operation) and from the anesthesia circuit and ascites.

Table 8.15 Electrolyte Content of Commonly Used Intravenous Electrolyte Solutions

Solution	Electrolyte Concentration (mEq/L)					
	Na ⁺	K ⁺	Ca ₂ ⁺	Mg ₂ ⁺	Cl ⁻	HCO ₃ ⁻
Lactated Ringer’s solution	130	4	4	—	109	28
0.2% NaCl	34	—	—	—	34	—
0.33% NaCl	56	—	—	—	56	—
0.45% NaCl	77	—	—	—	77	—
0.9% NaCl	154	—	—	—	154	—
3.0% NaCl	513	—	—	—	513	—
5.0% NaCl	855	—	—	—	855	—

Source: Adapted from Wait RB, Kahng KU, Dresner LS. Fluid and electrolytes and acid-base balance. In: Greenfield LJ, Mulholland M, Oldham KT, et al. eds. *Surgery: Scientific Principles and Practice*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1997:242–266, with permission.

Sodium Derangements

Hyponatremia is the most common electrolyte abnormality seen in postoperative patients and is caused by excess free water rather than a depletion of sodium. Increases in free water absorption are mediated by a self-limited, physiologic increase in the secretion of ADH in response to the stress of surgery. Serum sodium levels rarely fall below 130 mEq/L, but may be further exacerbated by intravenous administration of large volumes of hypotonic solutions (i.e., 0.2%, 0.33%, and 0.45% sodium solutions). Other disease states can result in a hyperosmolar condition, resulting in a hyperosmolar ECF, causing fluid to shift from the ICF and lowering the sodium levels. These conditions include hyperglycemia; mannitol, ethylene glycol, or ethanol ingestion; and uremia. For each increase of 180 mg/dL of glucose above 100 mg/dL, there is a concomitant decrease in the serum sodium of 5 mEq/L (254). In addition, during situations where potassium is low, there is a compensatory exchange of sodium for potassium, resulting in hyponatremia. In either of these prior cases, total body sodium does not change. Finally, patients with hyperproteinemia or hyperlipidemia may have falsely low sodium values, which result from errors in the laboratory measurement of sodium. This *pseudohyponatremia* does not result in any symptoms of hyponatremia (247).

The symptoms of hyponatremia are driven by cellular water intoxication and are related to the central nervous system (CNS) (e.g., lethargy, headaches, confusion, delirium, weakness, muscle cramps). The rate at which hyponatremia occurs also determines the symptoms. Chronic hyponatremia tends to be asymptomatic, whereas acute drops in the serum sodium (levels 120 to 130) result in the symptoms listed above. Correction of hyponatremia must be done carefully to avoid central pontine myelinolysis, which results in the “locked-in syndrome.”

Because most hyponatremia is related to dehydration (low ECV) simple correction of this state will increase the sodium plasma level. If the patient has a high ECV (such as the syndrome of inappropriate antidiuretic hormone [SIADH] secretion) or is in an edematous state, free water restriction should normalize the sodium level. However, if patients have symptoms of hyponatremia, aggressive replacement of sodium is prudent should the duration of the hyponatremia be determined to be no longer than 48 hours. Hyponatremic states lasting longer than 48 hours increase the risk of central pontine myelinolysis. Chronic cases need replacement at rates not to exceed 0.5 mEq/L/hour. Acute cases may be replaced at rates of 5 mEq/L/hour.

Hypernatremia is an uncommon finding and is related to large volumes of free water loss (through insensible routes such as breathing, sweating, and ventilation), diabetes insipidus, adrenal hyperfunction, or ingestion or administration of increased sodium solutions. Again, the symptoms are predominantly CNS oriented because of brain cell dehydration. Symptoms rarely occur until serum sodium levels exceed 160 mEq/L. In addition, the rapidity at which the derangement occurs determines the symptoms manifested. Treatment is carefully done with replacement of free water. Replacement too rapidly can cause cerebral edema and herniation. Patients with chronic hypernatremia need free water administration, which decreases the serum sodium no faster than 0.7 mEq/L.

Potassium Derangements

Whereas sodium is the major extracellular cation, potassium is the major intracellular cation by a ratio of 30:1. The intracellular potassium concentrations tend to be relatively constant, whereas the extracellular concentrations vary depending upon renal function/excretion. The majority of potassium secretion occurs in the distal tubule and the collecting duct of the nephron. Secretion is stimulated by increased urine flow, increased sodium delivery, high potassium levels, alkalosis, aldosterone, vasopressin, and β -adrenergic agonists. Insulin causes potassium to move into cells (as previously mentioned), reducing the extracellular concentration of potassium. Serum potassium levels are further affected by the acid-base status of patients. In alkalotic states, the potassium shifts into cells in exchange for hydrogen ions, whereas in acidotic states the exchange is opposite.

The predominant reason for hyperkalemia in a postoperative patient is renal dysfunction or failure. When these patients become critically ill, serum potassium concentrations can increase by 0.3 to 0.5 mEq/L/day in noncatabolic patients and 0.7 mEq/L/day in catabolic patients. It is important to rule out a spuriously elevated level secondary to hemolysis at the time of the blood draw either from too small a gauge of needle or simply from the application of the tourniquet and squeezing (247).

Hyperkalemia changes the membrane potential established by differences between the intracellular and extracellular milieu. This increased concentration has deleterious effects on cardiac muscle function, causing peaked T waves, flattened P waves, prolonged QRS complexes, and deep S waves on the ECG, and possibly resulting in ventricular fibrillation and cardiac arrest. Skeletal musculature is also affected with paresthesias and weakness, which can progress to a flaccid paralysis.

Treatment for hyperkalemia has been outlined in the section on renal risk factors. The mainstay is saline diuresis unless ECG changes are present, then infusion of calcium gluconate can be lifesaving. Utilization of 25 to 50 g of glucose and 10 to 20 units of regular insulin can drive potassium intracellularly and transiently lower plasma levels. Ultimately, definitive therapy relies upon increased excretion of potassium. For each gram of sodium polystyrene sulfonate (Kayexalate, given in the doses previously mentioned) used either orally or rectally, 0.5 mEq of potassium will be removed. Finally, in patients not responding to these therapies or patients with renal failure, hemodialysis may be indicated.

Hypokalemia is caused by decreased intake, increased gastrointestinal losses (vomiting, diarrhea, fistulae), excessive renal losses (metabolic alkalosis, magnesium deficiency, hyperaldosteronism), a shift of potassium into the intracellular space (acute or uncompensated metabolic alkalosis, glucose and insulin administration, catecholamines), or any combination thereof. A reduction of serum potassium by 1 mEq/L represents a total body deficiency of about 100 to 200 mEq. (Remember that total exchangeable potassium is approximately 3,000 mEq, with the majority being intracellular and thus the majority of the loss [247].) Symptoms of hypokalemia cause ECG changes with

flattening of the T waves, depression of S-T segments, prominent U waves, and prolongation of the Q-T interval. Treatment is accomplished by replacement of potassium either orally or intravenously, depending upon the severity of symptoms and whether or not the patient is able to take oral preparations. Intravenous replacement of potassium can be done at approximately 10 mEq/hour and should not be more concentrated than 40 mEq/L. If less fluid is desired, 20 mEq can be placed in 100 mL, but administration should not exceed 40 mEq/hour (247).

Magnesium Derangements

Most magnesium in the body is confined to the intracellular space and bone. Less than 1% of total body magnesium is in the serum. Of the magnesium in the serum, 60% is ionized, 25% is protein bound, and 15% is complexed with nonprotein anionic species (247). Magnesium is absorbed in the small intestine, directed by levels of vitamin D, and filtered by the kidney for excretion. Approximately 40% of renally excreted magnesium is reabsorbed in the ascending loop of Henle. Loop diuretics, hypermagnesemia, hypercalcemia, acidosis, and phosphate depletion result in increased excretion of magnesium.

Patients with renal failure and receiving magnesium-containing antacids or laxatives can become hypermagnesemic. In addition, patients with acidosis and dehydration may become hypermagnesemic. Patients present with CNS depression, loss of deep tendon reflexes, and ECG changes (prolonged P-R interval and QRS complex) in the face of elevated magnesium levels (greater than 8 mg/dL). As levels rise, patients will develop coma, respiratory failure, and/or cardiac arrest. Acute treatment of hypermagnesemia is slow IV infusion of 5 to 10 mEq of calcium. Because the etiology of this condition is usually renal failure, withholding magnesium-containing preparations may be all that is necessary. In severe instances, hemodialysis is required.

In gynecologic oncology patients, the overwhelming reason for hypomagnesemia is a history of cisplatin administration. However, other conditions such as hypoparathyroidism, malabsorptive states, chronic loop diuretic use, and the diuretic phase of acute renal failure can cause hypomagnesemia. Symptoms are similar to hypocalcemia, with muscle weakness, fasciculations, tetany, hypokalemia, and ECG changes (Q-T prolongation, torsade de pointes). Treatment can be accomplished with oral preparations in less acute situations. However, large doses may produce diarrhea, worsening the situation. Intravenous boluses of 2 to 3 g followed by infusions of 1 to 2 mEq/kg/day can be utilized for patients with severe symptoms.

Calcium Derangements

Almost all the calcium in the body is in bone, stored as hydroxyapatite crystals, and provides a supply that can be exchanged to the serum. Calcium homeostasis is controlled by parathyroid hormone (PTH), controlling intestinal absorption of calcium, renal excretion of calcium, and exchange of calcium from the bone. In the serum, calcium exists in three phases: 45% as an ionized form, which is responsible for most of the physiologic function of calcium; 40% in a protein bound form, bound mostly to albumin; and 15% in a nonionized form, complexed with nonprotein anions that do not easily dissociate. A serum total calcium level is usually obtained when assessing calcium homeostasis, as measurement of ionized calcium is cumbersome. The total calcium levels change by 0.8 g/dL for each 1 g/dL change of albumin (up or down) (247).

In gynecologic oncology patients with hypercalcemia, the underlying malignancy is usually the etiologic agent. Hypercalcemia may be caused by direct bony involvement or, more commonly, secretion of PTH-like peptides and/or other humoral factors, which increase serum calcium levels. Other reasons for hypercalcemia include primary, secondary, or tertiary hyperparathyroidism,

thiazide diuretic use, or lithium usage (247,256). Patients present with muscle fatigue, weakness, confusion, coma, ECG changes (shortening of the Q-T interval), nausea, and vomiting. The goal of treatment is to increase calcium excretion and stop bone turnover in order to decrease serum total calcium. Initial measures include vigorous hydration (200 mL/hour) with 0.9% or 0.45% saline solutions. Furosemide or other loop diuretics may be helpful in patients with borderline cardiac function or in patients with fluid overload. If the underlying malignancy is a breast carcinoma, patients may respond to high doses of steroids to reduce calcium levels. Other pharmacologic agents have been developed to stop bone resorption and reduce serum calcium levels. Calcitonin (4 IU/kg every 12 hours via subcutaneous or intramuscular injection) has a rapid onset of action and works by interfering with osteoclast maturation at several points (256). However, the duration of response is usually about 48 hours because of downregulation of calcitonin receptors by osteoclasts. Bisphosphonates have emerged as the drug of choice for treatment of hypercalcemia in malignancy. These agents work by inhibiting osteoclast activity and survival. The nitrogen-containing bisphosphonates are the most potent. Pamidronate (approved in 1991) and zoledronic acid (approved in 2001) are utilized in the United States. Another agent, ibandronate, is utilized in Europe but has not been approved for use in the United States. Zoledronic acid is the current drug of choice because of its proven superiority over pamidronate (257). The effective dose of zoledronic acid is 4 mg infused over 15 minutes and dosed every 3 to 4 weeks. Serum calcium levels return to normal in approximately 10 days and duration of response lasts approximately 40 days (258). Surgical resection is the treatment of choice for primary, secondary, or tertiary hyperparathyroidism (246,256).

Hypocalcemia is caused by hypoparathyroidism, hypomagnesemia, pancreatitis, and malnutrition. Patients present with tetany, hyperactive deep tendon reflexes, a positive Chvostek sign, positive Trousseau sign, and ECG changes (prolonged Q-T interval, prolonged S-T segment). Low levels of calcium may be present because of low albumin levels, but these levels do not affect the ionized portion of calcium and usually do not cause symptoms. Symptomatic hypocalcemia can be treated with intravenous infusion of either calcium gluconate or calcium chloride at a rate not to exceed 50 mg/minute. Calcium chloride dissociates into the ionized form of calcium more readily and is the treatment of choice to raise serum ionized calcium level.

Acid-Base Disturbances

Optimum cellular function requires a very narrow range of pH for chemical reactions to occur normally. Several buffering systems exist within the body to maintain this optimum pH. The predominant buffering system is the carbonic acid-bicarbonate buffering system. Derangements in the concentration of bicarbonate (HCO_3^-) or in concentrations of carbon dioxide (CO_2) result in acid-base disorders. Because the kidneys control excretion/generation of bicarbonate and the lungs exchange CO_2 , these organs play a central role in the compensation of any acid-base disorder. Therefore, 4 situations arise in acid-base balance: metabolic acidosis and alkalosis, and respiratory acidosis and alkalosis. Compensatory mechanisms exist in each situation in order to blunt the effect on pH (Table 8.16).

Metabolic Acidosis

Most clinically significant metabolic acidosis occurs with a net loss of bicarbonate either due to direct loss or when consumption is greater than generation. Situations where extra renal losses of bicarbonate occur include diarrhea, gastrointestinal fistulae, and urinary diversions (ureterosigmoidostomy or ureteroileostomy, which result in reabsorption of NH_4Cl from urine). Certain disease states result in the production of organic acids

Table 8.16 Concentrations of HCO_3^- and PCO_2 in Primary Acid-Base Derangements and the Compensatory Response

Disorder	Primary		Compensatory Response		
	pH	HCO_3^-	PCO_2	HCO_3^-	PCO_2
Metabolic acidosis	↓	↓			↓
Metabolic alkalosis	→	→			→
Respiratory acidosis	↓		→	→	
Respiratory alkalosis	→		↓	↓	

Source: Adapted from Wait RB, Kahng KU, Dresner LS. Fluid and electrolytes and acid-base balance. In: Greenfield LJ, Mulholland M, Oldham KT, et al., eds. *Surgery: Scientific Principles and Practice*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1997:242–266, with permission.

(ketoacidosis and lactic acidosis), which consume bicarbonate and outpace the renal compensatory mechanisms. Similarly, overdoses of certain drugs (e.g., aspirin) or ingestion of toxins (e.g., ethylene glycol, methanol) consume bicarbonate and outpace the renal compensatory mechanisms. Renal acidosis occurs when the intrinsic acid-excreting function of the kidney malfunctions, resulting in retention of acid and consumption of bicarbonate without concomitant regeneration of bicarbonate. These are classified as renal tubular acidosis (RTA I, distal tubule dysfunction; or RTA-II, proximal tubule dysfunction). Cardiac effects are the major findings in metabolic acidosis (peripheral arteriolar dilation, decreased cardiac contractility, and central venous constriction). Other manifestations of metabolic acidosis include gastric distention, abdominal pain, nausea, and vomiting. In surgical patients, lactic acidosis is the primary cause of metabolic acidosis and results from tissue hypoperfusion. Therefore, treatment should be aimed at increasing tissue perfusion with fluid and blood administration. The use of bicarbonate is best reserved for patients with other, not easily reversible causes of metabolic acidosis. Older patients and patients with CVD may benefit from administration of bicarbonate. Administration should be instituted when the pH is 7.1 to 7.2. One or 2 ampules of bicarbonate (approximately 55 mEq/amp) can be administered intravenously, with further administrations being dictated by the pH obtained from an arterial blood gas measurement. In diabetic ketoacidosis, treatment with insulin and glucose infusion should not only reverse the acidosis but also treat the hyperglycemia.

Metabolic Alkalosis

Sustained metabolic alkalosis is an uncommon clinical entity and is related to renal dysfunction. Loss of HCl is the most common reason for an increase in extracellular bicarbonate. This situation occurs with prolonged nausea and vomiting or prolonged nasogastric suctioning of gastric contents. As acid is removed from the gastrointestinal tract, a net gain of bicarbonate occurs. Other situations that can result in metabolic alkalosis include volume contraction, exogenous administration of bicarbonate or bicarbonate precursors (citrate, lactate, or calcium carbonate), hypokalemia, hypercalcemia, hypochloremia, excess mineralocorticoid usage, and high PCO_2 . Patients rarely present with symptoms, as metabolic alkalosis occurs gradually. However, in patients who develop this situation acutely, most symptoms are CNS oriented (e.g., confusion, stupor, coma, muscle fasciculations, tetany). Correction of the underlying disease state usually corrects the metabolic alkalosis. Repletion of electrolyte abnormalities and infusion of appropriate fluids (chloride containing) restore volume and result in normal renal excretion of excess bicarbonate.

Respiratory Acidosis

A depression of the pH occurs when there is hypoventilation. This occurs secondary to airway obstruction, COPD, depression of the respiratory center, impaired excursion of the thorax, or inappropriate ventilatory management in the mechanically ventilated patient. Development of symptoms depends upon the chronicity or acute nature of the event. If chronic, most patients have no symptoms. If it is an acute change, drowsiness, restlessness, headache, or development of a flapping tremor may occur. Treatment of this condition is aimed at the underlying cause of the hypoventilation. In chronic conditions, the hypoxemia, and subsequent hypercapnia, resulting from the hypoventilation may be the sole drive for the patient's respirations. Correction of the hypoxemia may further worsen the respiratory acidosis and must be considered. In general, correction of the PCO_2 must be done slowly because re-equilibration of cerebral bicarbonate concentration lags behind systemic changes (247).

Respiratory Alkalosis

Respiratory alkalosis occurs when the PCO_2 decreases with hyperventilation. Hyperventilation may occur because of hypoxia, drugs, decreased lung compliance, and mechanical ventilation. With drops in the arterial PO_2 , the peripheral chemoreceptors (in the carotid and aortic body) sense this change and result in hyperventilation to increase arterial PO_2 with a resulting decrease in PCO_2 . Because of renal compensatory mechanisms, this condition is usually asymptomatic. However, in acute situations, patients may have a sensation of breathlessness, dizziness, nervousness with altered levels of consciousness, and tetany. Treatment of underlying hypoxia should address the hyperventilation. If acute symptoms are present, having the patient rebreathe expired air should temporarily relieve the symptoms.

Postoperative Nutritional Issues

As mentioned earlier, the full consideration of nutrition in the gynecologic oncology patient is presented in Chapter 33. In this section, we will discuss early refeeding in the postoperative gynecologic oncology patient, indications for enteral nutrition, and total parenteral nutrition (TPN).

Although malnutrition has been shown to be prevalent among gynecologic oncology patients (126,127), many patients are adequately nourished, undergo surgery uneventfully, and have return of bowel function in 2 to 5 days while simultaneously resuming oral intake. Recently, several prospective randomized trials have been conducted that demonstrate the utility of early refeeding in the postoperative period. In these studies, patients in the early feeding group were fed on the first postoperative day, with 90% or more tolerating diets. The underlying malignancies, types of operations, and complications occurred at similar rates between the early refeeding and the "traditionally fed" patients in all the studies. The placement of nasogastric tubes (NGTs) for intolerance of diet was low among the studies (less than 10% incidence). Finally, length of hospital stay was shorter among the earlier fed patients (258–264).

The use of the enteral route is preferred in sustaining or repleting patients in the postoperative period after extensive procedures. Enteral nutrition utilizes normal physiologic absorptive mechanisms, maintains gut epithelial integrity, and reduces infectious morbidity (265,266). Studies on nutrition have found that the splanchnic circulation and support of the mucosal integrity of the small bowel may prevent progression to MODS (Multi-Organ Dysfunction Syndrome). Specifically, the intestinal mucosa will atrophy secondary to lack of luminal nutrients and intermittent activation of the destructive cytokine pathways, and/or intermittent translocation of bacteria into the blood stream will occur. These events result in "priming" neutrophils, which ultimately leads to a full-blown systemic inflammatory response,

causing organ damage. A number of well-designed randomized trials have compared early enteral feeds to TPN in patients with pancreatitis, major elective surgery, and trauma (265,266). All of these studies have shown a clear benefit for early enteral feeding, with a decrease in infectious complications (266).

Although considered a nonessential amino acid in nourished, healthy patients, glutamine has emerged as an essential amino acid in patients who are stressed and critically ill. This amino acid has been shown to be an important component in maintaining enterocyte integrity and has now been added to most enteral preparations (265,266).

Enteral feeds may be given in a variety of fashions, and each is associated with its own type and number of complications. Intra-gastric feeds may be accomplished with NGTs, oral-gastric tubes, or percutaneous endoscopic gastrostomy tubes (PEGs). Intra-gastric feeding has the advantage of utilizing the stomach as a reservoir for bolus feeding. In addition, stretching of the stomach stimulates the biliary-pancreatic axis, which may be trophic to the small bowel. Finally, the gastric secretions mix with the feeding material and decrease the osmolality, thus reducing the incidence of diarrhea. The main disadvantage of this route of enteral feeding is the increased risk of gastric overdistention with high residual amounts of feeding material and the increased risk of aspiration pneumonia (265). Enteral feeds may also be accomplished through the placement of nasal tubes, which are positioned into the pylorus, duodenum, or jejunum (such as Dobhoff tubes). These tubes have the advantage of being placed (or migrating) more distal in the upper gastrointestinal tract, greatly reducing the risk of aspiration. These types of tubes are preferred in patients who require long-term ventilation. Because of advances in endoscopic instrumentation, many of the tubes can be placed via this method. At the time of laparotomy, gastrostomy, or jejunostomy, tubes (such as a Stamm or Witzel tube) may be placed. These have the advantage of being placed at the time of major abdominal surgery under direct visualization/palpation. The techniques are described in other texts (265,267). Several enteral feeding preparations are available, but vary from hospital to hospital depending upon formulary makeup. The use of the enteral route is contraindicated in patients with mechanical intestinal obstructions, and for these patients nutritional support can be accomplished through the parenteral route.

TPN took the forefront in nutritional sustenance and replacement in the 1980s. The basic premise of TPN is to provide dietary precursors to maintain anabolic function. TPN can be broken into 3 components of replacement: glucose and lipid preparations for normal or increased energy expenditures, and amino acid preparations for protein synthesis. Because of the higher osmolar load presented by these preparations, central venous access is necessary for administration. Subclavian, internal jugular, or peripherally inserted central catheters (PICCs) will need to be placed, and they present the first of several potential complications associated with TPN administration. At the time of placement, pneumothorax, intubation of arterial structures, air embolism, or cardiac arrhythmias may occur. Later complications include the possibility of infection at the skin entrance site or line sepsis. Should these infectious complications occur, removal of the catheter and antibiotic administration will be necessary (266).

The Harris-Benedict equation is utilized to calculate basal energy expenditure (BEE) for patients and approximates the BEE of a sedentary, fasting, nonstressed individual (268):

$$BEE = 666 + (9.6 \times \text{weight [kg]}) + (1.7 \times \text{height [cm]}) - (4.7 \times \text{age [yr]})$$

Because stress of disease and surgical intervention need to be considered, "stress factors" have been developed and are multiplied by the BEE to arrive at kilocalories per day. Stress level multipliers are 1.2 for a resting individual, 1.3 for an ambulatory individual or moderate stress (e.g., systemic inflammatory response syndrome [SIRS], sepsis), and 1.5 for severe stress/burn patients.

After calculation of caloric requirements, the composition of the TPN solution to be administered should be determined. Because there are many different types of TPN preparations available, consultation with the nutrition team or pharmacists in an individual hospital is necessary to arrive at the desired solution.

In aerobic situations, glucose is the primary substrate for energy expenditure. It provides 3.4 kcal/g and is usually given in a concentrated form in order to provide 70% of the calculated calories. The remaining 30% of calories is provided by lipid preparations. Not only does this component have denser caloric content (it provides 9 kcal/g), but administration precludes the development of a fatty acid deficiency. Adjustment of the composition of TPN may be necessary depending upon the disease state (e.g., more contribution of kilocalories from fat vs. carbohydrate in a ventilated patient because of the respiratory quotient of fat vs. glucose).

Protein requirements are provided by amino acid solutions and are determined by the patient's age, sex, nutritional status, ongoing stress, and comorbid conditions. In general, 25% of protein requirements are obtained by normal oral intake. The remaining protein comes from breakdown of serum and organic proteins. Thus, periods of prolonged malnutrition, with decreased protein intake, and increased stress of disease will lead to breakdown of visceral protein. An estimate of maintenance protein requirements is 1 g nitrogen per kilogram of body weight. In situations of increased stress, the patient may need 1.2 to 1.5 g/kg in order to maintain and/or replace protein losses. Table 8.17 shows serum protein measurements and their respective half-lives, which are useful for determining anabolic versus catabolic response to TPN treatment. Another method to assess nitrogen balance (positive or negative) is (265):

$$\text{Nitrogen balance} = \text{protein intake} / 6.25 - (\text{urinary urea nitrogen} + 4)$$

The amount of protein intake is divided by 6.25 to give the grams of nitrogen taken in. The urinary urea nitrogen is expressed in grams based upon a 24-hour collection. The correction factor of 4 is meant to adjust for the grams of nitrogen lost in the stool or non-urea nitrogen losses.

In addition to these three main components of TPN, daily requirements of vitamins, trace elements, and insulin are necessary to maintain/regain nourishment. Again, these preparations vary by hospital formulary and need consultation with resident pharmacists.

The rate of infusion of TPN needs to be titrated upward to take into account the large glucose load that the patient will be receiving. This lower rate allows the pancreas time to increase insulin secretion in order to meet the glucose load being presented. Similarly, the rate of infusion needs to be decreased when TPN is being stopped to prevent hypoglycemia. During TPN

administration, blood glucose measurements by finger stick are required so that hyperglycemia is avoided. For the first several days, measurement of serum electrolytes, with adjustments being made daily, is necessary.

As previously mentioned, complications from venous access are some of the drawbacks of TPN administration. Other complications include metabolic derangements, which most often are mild but need correcting as soon as they are identified, abnormalities of liver function tests, the clinical significance of which is unclear (267), and cholelithiasis/cholecystitis secondary to gallbladder sludge.

Renal Issues

Acute renal failure (ARF) or hospital-acquired renal insufficiency (HARI) continues to be a common problem among postsurgical patients. Although the incidence of HARI is 1.5 patients per 1,000 admitted, the impact of HARI on morbidity and mortality is quite high (mortality averages 45% but may exceed 80% if dialysis is required). The best methods for preventing HARI are reducing risk factors and reversing the condition by early detection and intervention (269).

When HARI presents in the postoperative patient, causes can be divided into 3 parts: prerenal, renal, or postrenal (inflow, parenchymal, and outflow). The function of glomeruli to create the urinary filtrate depends upon adequate renal perfusion and represents the prerenal component. If the renal mean arterial pressure (MAP) falls below 80 mm Hg, perfusion of the glomeruli decreases (some disease states require the renal MAP to be higher for adequate perfusion). Many situations can decrease renal MAP and include anesthetics, atherosclerotic emboli, decreased vascular resistance, hypotension, intravascular volume contraction, mechanical ventilation, sepsis, and any form of shock. Autoregulation of the glomeruli can be disrupted by nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (diltiazem or verapamil), and endotoxins produced by gram-negative sepsis.

Renal parenchymal damage occurs most commonly in the postoperative patient because of prolonged hypotension or direct injury from inflammatory responses initiated by sepsis. In general, if the hypoperfusion is corrected quickly, reversible azotemia, creatinine elevation, and decreased urine output may be the only manifestations. However, prolonged hypoperfusion can cause acute tubular necrosis (ATN), which results in sloughing of renal tubular cells into the tubular lumen and obstruction. In addition, the production of Tamm-Horsfall proteins forms coarse granular casts, inciting an intense inflammatory response, further injuring the renal parenchyma (270,271). Other agents

Table 8.17 Visceral Proteins Utilized as Indicators for Nutritional Status during Nutritional Repletion

Protein	Normal Range	Half-Life (days)	Levels Low in	Levels High in
Albumin	3.5–5.4 g/dL	18	Liver disease, pregnancy, overhydration, nephrotic syndrome	Dehydration
Transferrin	200–400 mg/dL	8	Chronic infection, chronic inflammation, liver disease, iron overload, nephrotic syndrome	Iron deficiency, pregnancy
Prealbumin	20–40 mg/dL	2	Liver disease, inflammation, surgery, nephrotic syndrome	
Retinol-binding protein (RBP)	3–6 mg/dL	0.5	Liver disease, hyperthyroidism, zinc deficiency, nephrotic syndrome	Renal insufficiency

that can induce ATN include aminoglycoside antibiotics and iodinated contrast media. Approximately 15% of patients who receive aminoglycosides will have nephrotoxicity, and serum levels of these antibiotics need to be carefully monitored (272). Iodinated contrast media, used in multiple radiographic procedures, induces ATN by impairing nitric oxide production and increasing free radical formation (273,274). Diabetic patients with creatinine clearance rates less than 50 mL/minute are at particularly high risk (275).

The final reason for ARF in the postoperative gynecologic oncology patient is outflow obstruction. Because of the radical pelvic procedures performed by gynecologic oncologists, ureteral injury is possible and needs to be excluded early in the evaluation of patients with ARF. Prompt reversal of the obstruction can further limit renal damage.

In general, expected postoperative urinary output should be maintained at 0.5 mL/kg of weight per hour. Most oliguria can be treated with intravascular expansion in the first 24 to 48 hours postsurgery. Hypoperfusion of the renal parenchyma must be avoided to prevent ATN from occurring. The definition of ARF is not standardized, but includes rising serial creatinine measurements, urine output less than 400 mL/24 hours, or, in drastic situations, the initiation of dialysis (269). Once diagnosed, calculating the fractional excretion of sodium (FENa) or chloride can help to discern between prerenal causes or renal causes (hypoperfusions vs. ATN). The formula is presented below (269):

$$\text{FENa} = (\text{urine Na level} \times \text{serum Cr level}) / (\text{serum Na level} \times \text{urine Cr level}) \times 100\%$$

If the FENa is less than 1% and the urine specific gravity is greater than 1.025, the diagnosis is hypoperfusion. However, if ischemia has occurred, the FENa will be greater than 4% and the urine specific gravity will fall to 1.010 because of tubular damage and loss of renal concentrating mechanisms. One cannot calculate FENa in patients who have received diuretics or hyperosmotic agents (e.g., mannitol or contrast media). If prerenal and renal causes of low urine output have been excluded, ultrasonography may be useful in evaluating for outflow obstruction.

Once the underlying causes for HARI have been eliminated (e.g., hypoperfusion, obstruction, sepsis), only time can be offered as treatment. Therapies such as low-dose dopamine, furosemide, or mannitol administration, or atrial natriuretic peptide use have not demonstrated prevention of or improved recovery from HARI (276–281). Dialysis remains the only intervention that can support patients until return of renal function. Indications for dialysis include (a) hyperkalemia, metabolic acidosis, or volume expansion that cannot be controlled; (b) symptoms of uremia or encephalopathy; or (c) platelet dysfunction inducing a bleeding diathesis (269).

Shock

Definition

Shock is defined in its simplest terms as a decrease in tissue perfusion below the lowest metabolic needs of the tissue bed. This usually results in a depletion of stored energy and an increase in anaerobic metabolism with a buildup of lactic acid in addition to other toxic waste products. Hypotension is incorrectly thought of as a defining component of shock. Hypotension often leads to hypoperfusion, but the hypotensive patient is not in shock until evidence of hypoperfusion occurs. Various types of shock exist.

Hemorrhagic Shock

The first thought for a surgeon managing a postoperative patient who manifests signs and symptoms of shock is hemorrhage.

Hypovolemic shock secondary to inadequate preload can be the result of excessive or ongoing blood loss or inadequate replacement or both. Certainly, after radical debulking procedures or major extirpative procedures, the potential for postoperative hemorrhage exists. Tachycardia, hypotension, and oliguria are typical clinical signs. In the face of these clinical signs, the surgeon should have high suspicion for active bleeding and be preparing to return the patient to the operating room for correction. Measurement of hemoglobin or hematocrit can be normal in the setting of acute blood loss since a decrease in red cells is accompanied by a decrease in mass. Once fluid is given for resuscitation, dilution will occur and the hemoglobin/hematocrit will fall. With invasive monitoring, the CVP will be low, as will cardiac output and the PAOP. As the stroke volume decreases to inadequate amounts, the heart compensates by increasing the heart rate in order to maintain cardiac output. The treatment in these cases is aggressive volume resuscitation and control of ongoing blood loss. The controversy between resuscitation with colloid (albumin, plasma) or crystalloid (normal saline or lactated Ringer's solution) remains ongoing. The SAFE study is a large, randomized controlled double blind study that compared albumin to saline infusion in the intensive care unit. It failed to demonstrate a beneficial effect (282).

Endpoints of resuscitation include normalization of serum lactic acid and base deficit. Measurement of the base deficit via an arterial blood gas analysis has become an effective means for following response to resuscitation. Following large operations where patients are admitted to the ICU and where large, expected fluid shifts occur, the base deficit should be monitored serially until it has returned to normal. If a patient has a worsening base deficit (i.e., becomes more negative), then a search for other problems, such as ongoing hemorrhage, subacute anastomotic leak(s), or tissue ischemia, must be made and be addressed before the base deficit will normalize. The base deficit should normalize within the first 24 hours after surgery.

In the case of continued or rapid bleeding, the obvious course of treatment is reoperation. A number of options are now available intraoperatively in these situations. Obvious bleeders are controlled and ligated. Raw surfaces can be coagulated, treated with fibrin sealants or absorbable hemostatic powders. Damage-control packing has been shown to increase survival in the direst situations. Massive transfusion, defined as greater than 1.5 blood volumes, presents a number of additional problems. These patients will have a dilutional coagulopathy, hypocalcemia, and hyperkalemia. After 6 to 8 red blood cell transfusions have been given in rapid fashion for massive bleeding, some would advocate empiric fresh frozen plasma and platelets. Platelet transfusion is indicated for a platelet count <50,000 in the actively bleeding patient. The trauma literature supports the use of high product ratio during massive transfusion to improve mortality; however, this has yet to be demonstrated in the general surgical population (283). Attention to delivery of warm transfusions is critical as hypothermia and acidosis will promote coagulopathy and worsening in bleeding. Once any of the “lethal triad” (hypothermia, acidosis, and coagulopathy) is manifested then the operation needs to be quickly terminated even if this means damage-control packing and transport to an ICU setting.

Cardiogenic Shock

A patient with adequate preload who shows signs of poor perfusion secondary to poor cardiac output is categorized as being in cardiogenic shock. The etiology may be a decrease in contractility (secondary to myocardial infarction) or an increase in afterload (severe hypertension). Typically, “pump failure” results in decreased stroke volume and backup of fluid into the pulmonary circulation. This leads to pulmonary edema and decreased oxygen delivery. The most common provocation for pump failure is the over-administration of fluid in a patient with

compromised ventricular function. Treatment consists of diuresis and optimization of cardiac output without increasing myocardial oxygen demand (a difficult task). In the case where significant failure has led to hypotension, dopamine and dobutamine are usually the drugs of choice. The usage of these drugs was discussed previously. Digoxin is commonly used for increasing contractility, but its effects are minor in the acute setting. In addition to inotropic support, correction of electrolyte disturbances (particularly potassium, calcium, and magnesium), maintenance of proper systemic oxygen saturation, and analgesia are important factors in decreasing myocardial stress.

Septic Shock

Septic shock has commonly been defined as hypotension related to infection with eventual organ failure secondary to hypoperfusion despite adequate fluid resuscitation. This definition has changed with that of SIRS and is discussed in the section on “Sepsis and Systemic Inflammatory Response Syndrome” below. Sepsis is defined as a subset of patients with SIRS who have a documented infectious process. Resuscitation should be guided according to the recommendations in the Surviving Sepsis Campaign (284).

Infectious Disease Issues

Nosocomial Infections

Infections in the critically ill patient population are a significant cause of morbidity and mortality. Patients in the ICU are particularly vulnerable to infection because of decreased host defenses and the high incidence of resistant bacterial isolates found in ICU settings. In addition, the presence of indwelling catheters and intravenous lines lowers the inoculum needed to cause infection and provides portals of entry (285). Nosocomial infections are commonly associated with complications of medical or surgical therapy. Approximately 45% of ICU patients will have an infection and approximately half of those will have acquired the infection while in the ICU (285). Treatment includes identifying and eradicating the source of infection and promptly initiating empirical antibiotic therapy aimed at multi-drug-resistant gram-negative and gram-positive organisms. If an intra-abdominal or pelvic source is suspected, empiric antibiotic therapy should include anaerobic coverage. Appropriate antibiotic classes include carbapenems, extended-spectrum penicillins, fluoroquinolone-metronidazole, aminoglycoside-metronidazole, or clindamycin combinations (286). In Chapter 29, the management of infections in the gynecologic cancer patient is discussed; therefore, information here is limited to infections pertaining to the critically ill patient.

Fungal Infections

Systemic fungal infections are of great concern for severely ill patients and are linked to an increased risk of morbidity and mortality. Diagnosis of a systemic candidal infection is not based on a unique presentation and therefore can be difficult to definitively pronounce at onset. Although a positive blood culture is the gold standard for diagnosis, blood culture techniques are relatively insensitive and clinicians frequently must rely on clinical judgment about the probability that candidemia is responsible for a patient's symptoms. Patients who have persistent fever, hypothermia, or unexplained hypotension, despite broad spectrum antibiotic coverage, may have candidemia. Risk factors that have been associated with candidemia and invasive candidiasis include treatment with multiple antibiotics for extended periods, the presence of central venous catheters, the use of TPN, abdominal surgery, prolonged ICU stay, and compromised immune status (287). The initial choice of therapeutic

agents depends on the epidemiologic characteristics of the particular ICU and host factors such as the severity of illness, infection site(s), neutropenia, and organ dysfunction. Fluconazole has excellent activity against *Candida albicans*, but infections caused by *Candida glabrata* or *Candida krusei* must be treated with amphotericin B or caspofungin. Amphotericin B should not be used in patients with renal failure, and azoles and echinocandins (caspofungin) should be used with caution in patients with hepatic dysfunction. Antifungal therapy should be continued for 14 days past the first negative blood culture for candidemia or until clinical microbiological or radiographical resolution of the infection (288). In addition to antifungal therapy, it is generally recommended that all patients with candidemia have a dilated eye exam by an ophthalmologist and that all catheters be removed if possible (although tunneled catheters are at less risk) (287).

Abdominal Infections

The diagnosis of an intra-abdominal source of infection can be challenging in critically ill patients. Not all patients exhibit the same classic symptoms, as they may be masked by other disease processes or medical interventions. For example, abdominal pain and peritoneal signs may not be apparent in patients who are obtunded or sedated and ventilated. Fever and leukocytosis may be absent in 35% and 55% of patients with peritoneal infections (289). Ultrasonography is a useful diagnostic test that can be performed in the ICU and may assist with therapeutic intervention as well. It is extremely sensitive for evaluations of the pelvis and right upper quadrant, but evaluation of the entire abdomen can be limited by bowel gas, surgical dressings, and operator experience. For many of these reasons, a computed tomographic (CT) scan is the preferred study for the evaluation of patients with suspected intra-abdominal infection. To avoid misdiagnosing fluid-filled bowel as a possible abnormal fluid collection, it is essential that contrast agents be used when performing these studies. CT also has limitations, especially when used in the critically ill population. The presence of renal insufficiency precludes the use of intravenous contrast, and ileus or bowel obstruction may prevent complete opacification of the gastrointestinal tract. Diagnostic laparoscopy can be performed in the ICU with minimal anesthesia and is a safe, accurate, and cost-effective alternative to laparotomy when managing suspected intra-abdominal processes (290).

Once identified, an intra-abdominal abscess must be fully evacuated and the source controlled. Radiologically assisted percutaneous drainage has become the preferred method for treating most abscesses located in the abdomen and pelvis. For well-delineated unilocular fluid collections, percutaneous drainage has a success rate better than 80% (291). Percutaneous drainage of complex abscesses or those with an enteric communication has a lower success rate, but remains a reasonable alternative treatment for the high-risk patient (292).

In some cases, surgery may be the only appropriate lifesaving intervention. Timely laparotomy in the critically ill patient with diffuse peritonitis allows for peritoneal toilet, debridement of infected and necrotic tissue, and control or repair of the source. Laparoscopic drainage of complex intra-abdominal abscess has also been reported with good success rates (293). Complex intra-abdominal infections that cannot be effectively controlled by a single laparotomy may be managed best with an open-abdomen approach with temporary wound closure utilizing a composite, negative pressure (vacuum-pack) dressing (294). Potential advantages of the open-abdomen approach include facilitation of repeated debridement, effective drainage, repeat exploration of the peritoneal cavity (at the ICU bedside if necessary), and reduction in intra-abdominal pressure. In general, the intervention that accomplishes the source control objective with the least physiologic upset should be employed (295).

Sepsis and Systemic Inflammatory Response Syndrome

Inflammation is the body's initial response to tissue injury produced by chemical, mechanical, or microbial stimuli. Inflammation is an exceedingly complex cellular and humoral response involving interaction between the complement, kinin, coagulation, and fibrolytic cascades. The goal of inflammation is to enhance the movement of nutrients and phagocytic cells to the injury site in order to prevent invasion of microbes and limit the extension of injury. As a local response, this is beneficial, but appropriate regulation is necessary to prevent a pathologic, exaggerated systemic response, which is clinically identified as SIRS. Sepsis is the clinical syndrome of SIRS that is due to severe infection. The mediator response in SIRS can be divided into 4 phases based on the cytokine/cellular response: induction, triggering of cytokine synthesis, evolution of cytokine and coagulation cascade, and elaboration of secondary mediators leading to cellular injury. The three most important mediators operating in SIRS appear to be tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6). The microcirculation endothelium is the key target for injury in the sepsis syndrome (296).

In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine published definitions for SIRS and sepsis (Table 8.18) with the goal of standardizing terminology to aid clinicians in the diagnosis and treatment and to aid in the interpretation of research in this field (297). Many have criticized the 1992 consensus definitions as too nonspecific to be of use. In 2001, a group of experts reconvened and expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience. In addition to the original criteria, altered mental status, oliguria, skin mottling, coagulopathy, hypoxemia, hyperglycemia in the absence of diabetes, thrombocytopenia, and altered liver function tests can also be used to establish the diagnosis of sepsis (298).

The host response, more than the pathogen, is the primary determinant of patient outcome. Failure to develop a fever, leukopenia, and hypothermia are associated with increased fatality rates in patients with sepsis and are thought to represent abnormalities in the host's inflammatory response. Other risk factors for mortality from sepsis include age greater than 40, underlying medical conditions, malnutrition, immune suppression, and cancer. The presence or absence of a positive blood culture does not influence outcomes; however, sepsis due to a nosocomial infection has a higher mortality than community-acquired infection (299).

Sepsis with acute organ dysfunction (severe sepsis) is a complex condition that represents a major challenge to the critical care team and carries a crude mortality rate of 28% to 50% (300).

Table 8.18	Definitions for Systemic Inflammatory Response and Sepsis (SIRS)
SIRS	Two or more of the following in the setting of a known cause of inflammation: Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$ Pulse >90 Respirations $>20/\text{min}$ or $\text{Paco}_2 <32 \text{ mm Hg}$ WBC count $>12,000$ or $<4000 \text{ cells}/\text{mm}^3$ or $>10\%$ band forms
Sepsis	SIRS due to known infection
Severe sepsis	Sepsis with evidence of organ dysfunction, hypoperfusion, or hypotension
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation

Source: Adapted from 1991 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions, with permission.

Gram-negative and gram-positive organisms as well as fungi cause systemic sepsis and septic shock. Early recognition is crucial to patient survival because mortality rates are exceedingly high if the full clinical picture of shock and organ dysfunction develops. Septic shock is divided into an early hyperdynamic state and a late hypodynamic state.

Low systemic vascular resistance, splanchnic vasoconstriction, and increased cardiac output characterize the hyperdynamic phase of shock. Venous capacitance is increased and results in diminished effectiveness of the circulating blood volume. Aggressive volume resuscitation must be provided to restore cardiac preload and ventricular filling. These patients are best managed in an ICU with the placement of an arterial line, a PA catheter, and a bladder catheter. Appropriate cultures should be obtained and intravenous broad-spectrum antibiotics should be started within the first hour of recognition of severe sepsis. Laboratory tests of immediate concern include arterial blood gas determinations, creatinine, electrolytes, lactate, coagulation panel, and a complete blood count. Oxygenation and ventilation should be optimized with mechanical ventilation if indicated. If hypotension persists after optimization of the PCWP, the use of norepinephrine or dopamine may be necessary. Surgical debridement or manipulation of infected material should not be performed until the patient has been stabilized.

Early goal-directed therapy of the septic patient has been shown to improve survival. During the first 6 hours of resuscitation, the goals of therapy as outlined by the Surviving Sepsis Campaign guidelines include CVP of 8 to 12 mm Hg, mean arterial pressure ≥ 65 mm Hg, urine output $\geq 0.5 \text{ mL}/\text{kg}/\text{hour}$, and central venous or mixed venous oxygen saturation $\geq 70\%$. If during the first 6 hours oxygen saturation goals are not achieved despite appropriate CVP, then transfusion of red blood cells to achieve a HCT $>30\%$ and/or initiation of a dobutamine infusion is the next step (301).

In the hypodynamic phase of septic shock, hypotension results from cardiac output deterioration. The patient is often cool, mottled, oliguric, diaphoretic, and confused. The etiology of the hypodynamic cardiovascular response to sepsis may be inadequate volume resuscitation, underlying cardiac disease, or myocardial dysfunction associated with sepsis. This is a state of gross decompensation with global tissue hypoxia and is associated with greater mortality.

Numerous clinical trials have attempted to find specific agents that could modulate the underlying disease process in sepsis. Candidate therapies included agents that target mediators of inflammatory response, agents that boost the immune system, and prostaglandin inhibitors, but none was shown to be beneficial. One such agent, drotrecogin alfa (activated-Xgris[®]), is a recombinant form of human activated protein C, an endogenous protein with antithrombotic, pro-fibrinolytic, and anti-inflammatory properties that is frequently deficient in sepsis. Although initial studies (The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis-PROWESS) showed a clinically significant reduction in the 28-day all-cause mortality rate due to severe sepsis (302), results from a subsequent trial, the PROWESS-SHOCK trial, failed to demonstrate any significant benefit in 28-day all-cause mortality. The drug was subsequently withdrawn from the market in October 2011 (303).

In addition to early goal-directed therapy with hemodynamic interventions that balance systemic oxygen delivery with oxygen demand, other management strategies have shown in randomized, controlled trials to reduce mortality associated with severe sepsis. These include limiting the tidal volume to 6 to 7 mL/kg ideal body weight for patients requiring mechanical ventilation for ARDS, the use of moderate-dose corticosteroids (hydrocortisone 200 to 300 mg and fludrocortisone 50 μg daily) for 7 days in patients with refractory septic shock, and maintaining serum glucose levels $<180 \text{ mg}/\text{dL}$ (301). These therapies are not mutually exclusive,

and optimal patient management may require a combination of approaches. Some of these strategies vary dramatically from traditional approaches and will require education and established protocols to safely incorporate them into practice.

Multiple Organ Dysfunction Syndrome

Multiple organ dysfunction syndrome (MODS) is defined as the development of progressive physiologic dysfunction of two or more organ systems after an acute threat to systemic homeostasis (297). An acute threat can include SIRS, sepsis, massive trauma, burns, ischemia, or reperfusion injury. Patients usually present with pulmonary dysfunction, which typically develops early in the course of SIRS or sepsis. Renal dysfunction will present as a prerenal azotemia unless the initial insult stimulated a sudden oliguric acute tubular necrosis. Hyperbilirubinemia is the earliest indication of hepatic dysfunction. Gastrointestinal abnormalities include ileus, stress ulcers, diarrhea, and mucosal atrophy. The platelet count has been used as a surrogate marker of the hematologic system. Cardiac function is often measured by the severity of hypotension or the need for vasopressors. Deterioration of the nervous system is manifested by encephalopathy and peripheral neuropathies. The treatment of MODS is support of individual organ function and aggressive therapies aimed at correcting the underlying process. Mortality is related to the number of dysfunctional systems and is greater than 80% once four organ systems fail (304).

The Acute Physiology and Chronic Health Evaluation (APACHE) provided population-based estimates of mortality for the day of ICU admission (305). Several versions of the APACHE scoring system have been utilized, most recently APACHE IV. Organ failure scores, such as the Sequential Organ Failure Assessment (SOFA), can help assess organ dysfunction over time and are useful to evaluate morbidity. Independent of the initial value, an increase of the SOFA score (Table 8.19) during the first 48 hours of an ICU admission predicts a mortality rate of 50% or greater, and improvement of cardiovascular, renal, or respiratory SOFA score from baseline through day 1 of ICU admission is significantly related to greater survival (306). It is important to note that these and other outcome

prediction models were designed as tools to be used in critical care research in order to stratify patients by severity of illness. They have not been validated for making decisions relating to individual patients.

Abdominal compartment syndrome (ACS) is an important but often unrecognized cause of acute deterioration of a patient after massive fluid resuscitation for septic or hypovolemic shock. Although ACS can impair the function of every organ system, it is generally manifested as hypotension, reduced urine output, and decreased pulmonary compliance. Most commonly associated with trauma patients, it has also been observed in patients with massive ascites, bowel obstruction or ileus, peritonitis, pancreatitis, and intraperitoneal blood. Intra-abdominal pressure (IAP) is usually measured indirectly by a balloon-tipped catheter in the bladder. Intra-abdominal hypertension is defined as an IAP of 12 mm Hg or greater recorded by a minimum of 3 standard measurements conducted 4 to 6 hours apart (307). ACS is defined by an IAP of 20 mm Hg or greater and single or multiple organ failure that was not previously present. Operative decompression of the abdominal cavity with maintenance of an open abdomen via use of temporary closure techniques such as a vacuum pack is the only treatment that reverses the physiological abnormalities resulting from ACS.

NEUROLOGIC ISSUES

Emotional and mental health of critically ill patients can affect their physical well-being, pain tolerance, and recovery. Stress and strain can be exacerbated by the unknown, pain, wounds, pre-existing disease, infection, invasive medical interventions, and routine nursing care such as airway suctioning, repositioning, or dressing changes. The restlessness and distress often associated with critical illness must be quelled with analgesia, sedation, and neuromuscular blockade as a last resort. The Society of Critical Care Medicine and American Society of Health-System Pharmacists (ASHP) clinical practice guidelines for sedation, analgesia, and neuromuscular blockade of the critically ill adult were revised in 2002. This comprehensive document is available online at www.ashp.org (308,309).

Table 8.19 The Sequential Organ Failure Assessment (SOFA) Score

Variables	SOFA score				
	0	1	2	3	4
Respiratory: PaO ₂ /FIO ₂ , mm Hg	>400	≤400	≤300	≤200 ^a	≤100 ^a
Coagulation: platelets × 10 ³ /μL ^b	>150	150	100	50	20
Liver bilirubin, mg/dL ^b	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or Dob (any dose) ^c	Dop >5, Epi 0.1, or Norepi 0.1 ^c	Dop >15, Epi >0.1, or Norepi >0.1 ^c
Central nervous system, Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal creatinine, mg/dL or urine output, mL/d	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

Norepi, norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; FIO₂, fraction of inspired oxygen; PaO₂, partial pressure oxygen.

^aValues are with respiratory support.

^bTo convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

^cAdrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).

Source: From Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286:1754–1758, with permission.

Analgesia

Pain management for critically ill patients is a universal goal for all involved in their care. Patients who are not satisfied with the treatment they receive for pain may become more stressed and irritable, sleep less, and have a poor opinion of the care they are receiving on the whole. Pain may contribute to pulmonary dysfunction through localized guarding and generalized muscle rigidity that restricts movement of the chest wall and diaphragm. Unrelieved pain also evokes a stress response characterized by tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism (310). The combined use of effective analgesia and sedation may ameliorate the stress response and diminish pulmonary complications in postoperative critically ill patients. A comprehensive overview of pain management is covered in Chapter 32; therefore, only key aspects of pain management applicable to patients in the ICU will be addressed.

Pharmacologic therapies include opioids, NSAIDs, and acetaminophen. ASHP guidelines recommend fentanyl, hydromorphone, and morphine given as a continuous infusion or scheduled doses rather than “as needed.” Fentanyl has the most rapid onset and shortest duration, but repeated dosing may cause accumulation and prolonged effects. Fentanyl may also be administered via a transdermal patch to hemodynamically stable patients with more chronic analgesic needs, but it is not recommended for the management of acute pain. Morphine has a quick onset but longer duration of action, so intermittent doses may be given. However, morphine causes histamine release, which contributes to hypotension, especially in a hemodynamically unstable patient. Hydromorphone’s duration of action is similar to morphine but lacks an active metabolite or histamine release, making it an ideal drug for continuous infusion and for use in patients who cannot tolerate hypotension. Meperidine has an active metabolite that causes neuroexcitation including apprehension, tremors, delirium, and seizures, so its use is not recommended in critically ill patients who may need repeated doses. The characteristics of analgesics and sedatives commonly used in ICU patients are summarized in Table 8.20.

Sedation

To further combat anxiety and agitation associated with hospitalization and pain, sedatives are commonly added to routine medication administration. The physical environment of the ICU, limited ability to communicate, sleep deprivation, and medical circumstances precipitating the ICU admission are contributing factors creating anxiety in critically ill patients. Efforts to reduce anxiety, including frequent reorientation, provision of adequate analgesia, and optimization of the environment, may be supplemented with sedatives. Agitation is also common in ICU patients; however, not all patients with anxiety will exhibit agitation. Sedatives reduce the stress response and improve tolerance to routine ICU procedures. For example, the use of sedation medication may be necessary to facilitate mechanical ventilation. Generally, sedatives should be administered intermittently to determine the dose needed to achieve the sedation goal, but they may be given as a continuous infusion if necessary. Daily interruption of sedative infusion is associated with shorter duration of mechanical ventilation, shorter ICU stays, and fewer instances of posttraumatic stress disorder (311,312). Benzodiazepines are sedatives and hypnotics that cause anterograde amnesia but lack analgesic properties. Midazolam has a rapid onset and short duration of effect with single doses, making it ideal for treating acutely agitated patients or for brief sedation with invasive procedures. Lorazepam has a slower onset but fewer potential drug interactions because of its metabolism via glucuronidation (Table 8.20).

Propofol is an intravenous general anesthetic that has sedative and hypnotic properties at lower doses. Like the benzodiazepines, propofol has no analgesic properties. Propofol has a rapid onset and short duration of sedation once discontinued. Propofol is a phospholipid emulsion that provides 1.1 kcal/mL from fat and should be counted as a caloric source. Long-term infusions may result in hypertriglyceridemia and monitoring is recommended after 2 days of use (308). Physiologic dependence and potential withdrawal symptoms have been described in ICU patients who have been exposed to more than 1 week of sedative or narcotic therapy, including the use of propofol (313).

Table 8.20 Characteristics of Selected Analgesics and Sedatives Frequently Used in Critically Ill Patients

Agent	Indication	Active Metabolites (Effect)	Adverse Effects	Intermittent Dose (IV) ^a	Infusion Dose Range
Fentanyl	Pain	No metabolite, patient accumulates	Rigidity with high doses	0.35–1.5 µg/kg q 0.5–1 h	0.7–10 µg/kg/h
Hydromorphone	Pain	None	—	10–30 µg/kg q 1–2 h	7–15 µg/kg/h
Morphine	Pain	Yes (sedation)	Histamine release	0.01–0.15 mg/kg q 1–2 h	0.07–0.5 mg/kg/h
Ketorolac	Pain	None	GI bleeding, renal	15–30 mg q 6 h; decrease if >65 yr; avoid >5 day use	—
Midazolam	Acute agitation	Yes (prolonged sedation)	—	0.02–0.08 mg/kg q 0.5–2 h	0.04–0.2 mg/kg/h
Lorazepam	Sedation	None	Solvent-related acidosis/renal failure in high doses	0.02–0.06 mg/kg q 2–6 h	0.01–0.1 mg/kg/h
Propofol	Sedation	None	Elevated triglycerides	—	5–80 µg/kg/min
Haloperidol	Delirium	Yes (EPS)	QT interval prolongation	0.03–0.15 mg/kg q 0.5–6 h	0.04–0.15 mg/kg/h

EPS, extrapyramidal symptoms; GI, gastrointestinal; IV, intravenous.

^aMore frequent doses may be needed for acute management in mechanically ventilated patients.

Neuromuscular Blockade

Neuromuscular blocking agents (NMBAs) can be used in conjunction with sedatives to facilitate mechanical ventilation, to manage intracranial pressure in head trauma, to ablate muscle spasms, and to decrease oxygen consumption only when all other means to accomplish these aims have failed (309). Pancuronium is a long-acting NMBA that is effective for up to 90 minutes after intravenous bolus dose of 0.06 to 0.1 mg/kg. It can be used as a continuous infusion by adjusting the dose to the degree of neuromuscular blockade that is desired. Since pancuronium is vagolytic, 90% of patients will have an increase in heart rate of greater than 10 beats per minute. For patients who cannot tolerate an increase in heart rate, vecuronium can be used. If neuromuscular blockade is necessary for patients with significant hepatic or renal failure, cisatracurium or atracurium should be used. Patients receiving any NMBA should be assessed using electronic twitch monitoring with a goal of adjusting the blockade to achieve 1 or 2 twitches. Before initiating neuromuscular blockade, patients should be adequately medicated with sedative and analgesic drugs, as it is difficult to assess pain and anxiety after NMBAs are given. Furthermore, neuromuscular paralysis without sedation is an extremely frightening and unpleasant experience.

Acute quadriplegic myopathy syndrome, also referred to as postparalytic quadriplegia, is a clinical triad of acute paresis, myonecrosis with increased creatine phosphokinase concentration, and abnormal electromyography that is related to prolonged exposure to NMBAs. This is a devastating complication of NMBA therapy and one of the reasons that indiscriminate use of these agents is discouraged. Increased risk of acute quadriplegic myopathy is associated with the concurrent use of corticosteroids; drug “holidays” may decrease the risk (314).

ICU Syndrome/Delirium

First reported in the 1960s, the term ICU syndrome, or psychosis, refers to a multitude of psychological disturbances exhibited by many critically ill patients (315). It has also been labeled postoperative delirium. The ICU syndrome has been defined as an altered emotional state occurring in a highly stressful environment that may manifest itself in a variety of psychological reactions including fear, memory disturbance, anxiety, confusion, withdrawal, despair, agitation, and disorientation. Factors such as sleep deprivation, noise, constant light exposure, restriction of movement, limited ability to communicate, as well as the patient's preadmission mental state and coping ability have all been reported as contributing causes of ICU syndrome. Current medical literature challenges this concept and argues that what is being called ICU syndrome or psychosis is diagnostic of delirium and not due to the ICU environment per se. Concerns have been raised that using the term *ICU syndrome* implies that confusion can be expected in the ICU setting and may reduce the vigilance necessary to recognize delirium and identify and treat the physiologic disturbances leading to it (316). Delirium is found in as many as 80% of critically ill patients and is associated with longer ICU admissions and increased mortality (317,318).

Delirium in the ICU setting is commonly caused by metabolic disturbances, hypoxia, electrolyte imbalances, alcohol or drug withdrawal, acute infection, and medications (Table 8.21) (316,318). Many drugs have anticholinergic properties that can exert an additive effect, causing neurotoxicity, especially in elderly patients. Anticholinergic-related delirium can be differentiated from other causes of delirium if the mental status clears after administration of the cholinesterase inhibitor physostigmine. Delirium presents in both a hypoactive and hyperactive form. Hypoactive delirium, which is associated with the worst prognosis, is characterized by psychomotor retardation, represents more global cerebral dysfunction, and is

Table 8.21 Commonly Used ICU Drugs Associated with Delirium^a

Anesthetics	Anticonvulsants	Atropine ^b
Lidocaine	Carbamazepine	Cimetidine ^b
Propofol	Phenobarbital	Corticosteroids ^b
	Phenytoin	Digoxin ^b
Antibiotics		
Amphotericin B	Antihypertensives	Narcotic analgesics
Aztreonam	Diltiazem	Fentanyl
Cephalosporins	Enalapril	Meperidine ^b
Ciprofloxacin	Hydralazine	Morphine
Doxycycline	Methyldopa	
Imipenem	Propranolol	Nitroprusside
Metronidazole	Verapamil	Phenylephrine
Penicillins		Procainamide ^b
Tobramycin		Scopolamine ^b
		Tricyclic antidepressants ^b

^a Listing is not intended to be all inclusive.

^b Drugs known to have significant anticholinergic properties.

manifested by a calm appearance, inattention, and obtundation in extreme cases. Hyperactive delirium is more easily recognized by agitation and combative behaviors. Elderly patients may pose a particular diagnostic challenge when delirium is superimposed on baseline dementia.

The medical management of delirium consists of finding and treating underlying medical conditions and then controlling any behavioral disturbances if necessary. Neuroleptic drugs are the first-line agents for the treatment of delirium. When causes are related to alcohol withdrawal syndrome, management is with benzodiazepines. Haloperidol is the neuroleptic of choice because it has minimal anticholinergic or hypotensive effects. A dose of 2 to 10 mg intravenously can be given every 20 to 30 minutes until agitation resolves. Once the delirium is controlled, scheduled doses every 4 to 6 hours consisting of 25% of necessary loading doses can be used and tapered off over several days. A continuous infusion can also be used (Table 8.20). Patients receiving repeat doses of haloperidol should be monitored for electrocardiographic changes. Extrapyrimal side effects such as rigidity, tremor, or facial tics can be managed with diphenhydramine hydrochloride (308).

End of Life Considerations

Despite valiant efforts and adherence to best practices of care, patients, families, and health care professionals are often faced with the difficult decision to withdraw life-sustaining treatment and care. The ethical aspect of foregoing treatment resides in the legal and ethical right of the patient to self-determination. Unfortunately, the majority of critically ill patients are unable to speak for themselves when decisions need to be made to withhold treatment. Living wills, power of attorney status, and advance directives must be acknowledged and honored regarding end of life considerations. If a medical power of attorney is not in place, some states stipulate who the surrogate will be by a legal hierarchy. The ethical basis for identification of an appropriate surrogate is primary if none of the preceding legal bases apply. In this situation, the physician and other health care providers

have the responsibility to help identify the person or persons who have knowledge of the patient's values and preferences in order to assist with medical decisions on the patient's behalf. This process can become difficult in circumstances when family members or others close to the patient are in disagreement as to who should be the surrogate or what the patient would prefer. In these cases, health care providers should be knowledgeable of applicable legal directives and their ethical responsibility to act in their patient's best interest. Consultation with the institution's ethics committee may be helpful in trying to reach consensus (319). Although not responsible for the patient's death, those close to the patient often are left with feelings of guilt and anxiety in addition to their bereavement. It is important that the health care providers support the family both before and after the decision to withhold or withdraw life-sustaining treatment has been made, not imparting any personal bias.

End-of-life care of patients in the ICU requires a dramatic paradigm shift in attitude and interventions from intensive rescue-type care to intensive palliative care. When considering the array of interventions that may be discontinued or held, physicians and surrogates should focus on clearly articulating the

goals of care. For example, a goal for survival until the patient's important loved ones can gather to say their good-byes may justify short-term continuation of ventilator support. If the only goal is patient comfort, then such treatment should be stopped. The withdrawal of life-sustaining treatment is a clinical procedure that deserves the same preparation and expectation of quality as other medical procedures. Honest, caring, and culturally sensitive communication with the patient's loved ones and the patient, if competent, should include explanations of how therapies will be withdrawn, what symptoms are expected, strategies to assess and ensure the patient's comfort, and information about the expected survival after interventions are withdrawn. Informed consent should be documented along with a formulated plan for withdrawing care (320). Adequate analgesia and sedation should be prescribed to relieve symptoms of pain, dyspnea, and anxiety during the dying process. Intravenous opioids and shorter acting benzodiazepines are the drugs of choice. The clinician's primary goal should be to prevent suffering and ensure the patient's comfort even if doing so unintentionally hastens the patient's death. For this reason, palliative care teams might be useful (320).

REFERENCES

- Dean MM, Finan MA, Kline RC. Predictors of complications and hospital stay in gynecologic cancer surgery. *Obstet Gynecol*. 2001;97:721-724.
- Wijesundera DN, Beattie WS, Austin PC, et al. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. *Lancet*. 2008;372:562-569.
- Auerbach AD, Rasic MA, Sehgal N, et al. Opportunity missed: medical consultation, resource use and quality of care of patients undergoing major surgery. *Arch Intern Med*. 2007;167:2338-2344.
- Macpherson DS, Lofgren RP. Outpatient internal medicine preoperative evaluation: a randomized clinical trial. *Med Care*. 1994;32:498-507.
- Fisher SP. Cost-effective preoperative evaluation and testing. *Chest*. 1999;115:96S-100S.
- Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Preoperative Evaluation. http://www.icsi.org/preoperative_evaluation/preoperative_evaluation_2328.html. Retrieved April 25, 2012.
- National Institute for Clinical Excellence (NICE). *The Use of Routine Preoperative Tests for Elective Surgery*. NICE Clinical Guidance No. 3. London, England: National Institute for Clinical Excellence; 2003.
- St Clair CM, Shah M, Diver EJ, et al. Adherence to evidence-based guidelines for preoperative testing in women undergoing gynecologic surgery. *Obstet Gynecol*. 2010;116:694-700.
- National Institutes of Health, National Heart, Lung, and Blood Institute. *Women's Heart Health: Developing a National Health Education Action Plan*. NIH Publication No. 01-2963, Sep. 2001.
- Pregler J, et al. The heart truth professional education Campaign on women and heart disease: needs assessment and evaluation results. *J Womens Health*. 2009;18(10):1541-1547.
- Poon S, et al. Bridging the gender gap: insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. *Am Heart J*. 2012;163(1):66-73.
- Hollenberg SM. Preoperative cardiac risk assessment. *Chest*. 1999;115(suppl. 5):51-57.
- Freeman WK, Gibbons RJ. Perioperative assessment of cardiac patients undergoing noncardiac surgery. *Mayo Clin Proc*. 2009;84:79-90.
- Fleisher LA, et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. *J Am Coll Cardiol*. 2007;50:1707-1732.
- Eagle KA, Boucher CA. Cardiac risk of noncardiac surgery. *N Engl J Med*. 1989;321:1330-1332.
- Blaustein AS. Preoperative and perioperative management of cardiac patients undergoing noncardiac surgery. *Cardiol Clin*. 1995;13:149-161.
- Cohn SL, Goldman L. Preoperative risk evaluation and perioperative management of patients with coronary artery disease. *Med Clin N Am*. 2003;87(1):111-136.
- Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977;297:845-850.
- Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481-1501.
- Shammash JB, Ghali WA. Preoperative assessment and perioperative management of the patient with nonischemic heart disease. *Med Clin N Am*. 2003;87:137-152.
- Kertai MD, et al. Aortic stenosis: an underestimated risk factor for perioperative complications in patients undergoing noncardiac surgery. *Am J Med*. 2004;116:8-13.
- Halm EA, Browner WS, Tubau JF, et al. Echocardiography for assessing cardiac risk in patients having noncardiac surgery. *Ann Intern Med*. 1996;125:433-441.
- Karthikeyan G, Moncur RA, Levine O, et al. Is a preoperative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systemic review and meta-analysis of observational studies. *J Am Coll Cardiol*. 2009;54(17):1599-1606.
- Ferreira MJ. The role of nuclear cardiology for preoperative risk assessment prior to noncardiac surgery. *Rev Port Cardiol*. 2001;19(suppl. 1):163-169.
- Ashton CM, Petersen NJ, Wray NP, et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med*. 1993;118:504-510.
- Mangano DT, Layug EL, Wallace A, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med*. 1996;335:1713-1720.
- POISE Study Group, Devereaux PJ, Yang H, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomized controlled trial. *Lancet*. 2008;371(9627):1839-1847.
- Fisher BW, Majumdar SR, McAlister FA. Predicting pulmonary complications after nonthoracic surgery: a systematic review of blinded studies. *Am J Med*. 2002;112:219-225.
- Mitchell CK, Smoger SH, Pfeifer MP, et al. Multivariate analysis of factors associated with postoperative pulmonary complications following general elective surgery. *Arch Surg*. 1998;133:194-198.
- Beecher HK. Effect of laparotomy on lung volumes: demonstration of a new type of pulmonary collapse. *J Clin Invest*. 1933;12:651-666.
- The VA Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med*. 1991;325:525-532.
- Arozullah AM, Khuri SF, Henderson WG, et al. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. *Ann Intern Med*. 2001;135:847-857.
- Smetana GW. Preoperative pulmonary evaluation. *N Engl J Med*. 1999;340:937-944.
- Qaseem A, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. *Ann Intern Med*. 2006;144(8):575-578.

35. Latimer RG, Dickman M, Day WC, et al. Ventilatory patterns and pulmonary complications after upper abdominal surgery determined by preoperative and postoperative computerized spirometry and blood gas analysis. *Am J Surg.* 1971;122:622–632.
36. Gibbs J. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg.* 1999;134:36–42.
37. Restrepo RD, Wettstein R, et al. Incentive Spirometry: 2011. *Respir Care.* 2011;56(10):1600–1604.
38. Hawn MT, Houston TK, et al. The attributable risk of smoking on surgical complications. *Ann Surg.* 2011;254(6):914–920.
39. Bluman LG, Mosca L, Newman N, et al. Preoperative smoking habits and postoperative pulmonary complications. *Chest.* 1998;113:883–889.
40. Moller AM, Villebro N, Pedersen P, et al. Effect of preoperative smoking intervention on postoperative complications: a randomized clinical trial. *Lancet.* 2002;359:114–117.
41. Nakagawa M, Tanaka H, Tsukuma H, et al. Relationship between the duration of the preoperative smoke-free period and the incidence of postoperative pulmonary complications after pulmonary surgery. *Chest.* 2001;120:705–710.
42. Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States.* Atlanta, GA: U.S. Department of Health and Human Services; 2011.
43. Elixhauser A, Yu K, Steiner C, et al. *Hospitalization in the United States, 1997. Healthcare Costs and Utilization.* Project Fact Book No. 1. AHRQ Publication No. 00-0031. Rockville, MD: Agency for Healthcare Research and Quality; 2000.
44. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care.* 2004;27:553–591.
45. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. *Diabetes Care.* 2009;32:287–294.
46. Sheehy AM, Gabbay RA. An overview of preoperative glucose evaluation, management and perioperative impact. *J Diabetes Sci Technol.* 2009;3:1261–1269.
47. Kohl BA, Schwartz S. How to manage perioperative endocrine insufficiency. *Anesthesiol Clin.* 2010;28:139–155.
48. Meneghini LF. Perioperative management of diabetes: translating evidence into practice. *Cleveland Clin J Med.* 2009;76:S53–S59.
49. Dronge AS, Perkal ME, Kancir S, et al. Long-term glycemic control and postoperative infectious complications. *Arch Surg.* 2006;141:375–380.
50. Raju TA, Torjman MC, Goldberg ME. Perioperative blood glucose monitoring in the general surgical population. *J Diabetes Sci Technol.* 2009;3:1282–1287.
51. The International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care.* 2009;32:1327–1334.
52. American Diabetes Association. Standards of medical care in diabetes-2009. *Diabetes Care.* 2009;32(suppl. 1):S13–S61.
53. Fahy BG, Sheehy AM, Coursin MD. Glucose control in the intensive care unit. *Crit Care Med.* 2009;37:1769–1776.
54. Egi M, Bellomo R, Stachowski E, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med.* 2008;3:2249–2255.
55. Rady MY, Johnson DJ, Patel BM, et al. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc.* 2005;80:1558–1567.
56. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal/bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 Surgery). *Diabetes Care.* 2011;34:256–261.
57. Khan NA, Ghali WA, Spratt SE, et al. *Perioperative Management of Diabetes Mellitus. Physicians' Information and Education Resources.* American College of Physicians, 31 Aug. 2009. Web. 26 Apr. 2012. <http://pier.acponline.org/physicians/public/periopr879/tables/periopr879-tl.html>.
58. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2012;97:16–38.
59. Pomposelli JJ, Baxter JK, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN.* 1998;22:77–81.
60. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in non-cardiac surgery. *Diabetes Care.* 2010;33:1783–1788.
61. Noordzij PG, Boersma E, Schreiner F, et al. Increased preoperative glucose levels are associated with perioperative mortality in patients undergoing non-cardiac, non-vascular surgery. *Eur J Endocrinol.* 2007;156:137–142.
62. Ramos M, Khalpey Z, Lipsitz S, et al. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. *Ann Surg.* 2008;248:585–591.
63. Sato H, Carvalho G, Sato T, et al. The association of preoperative glycemic control, intraoperative insulin sensitivity and outcomes after cardiac surgery. *J Clin Endocrinol Metab.* 2010;95:4338–4344.
64. Gallacher SJ, Thomason F, Fraser WD, et al. Neutrophil bactericidal function in diabetes mellitus: evidence for association with blood glucose control. *Diabet Med.* 1995;12:916–920.
65. Van Den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359–1367.
66. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360(13):1283–1297.
67. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Pract.* 2009;15:353–369.
68. Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care.* 2007;30:2181–2186.
69. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal/bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 Surgery). *Diabetes Care.* 2011;34:256–261.
70. Ringle MD. Management of hypothyroidism and hyperthyroidism in the intensive care unit. *Crit Care Clin.* 2001;17:59–74.
71. Schiff RL, Welsh GA. Perioperative evaluation and management of the patient with endocrine dysfunction. *Med Clin N Am.* 2003;87:175–192.
72. Weinberg AD, Brennan MD, Gorman CA. Outcome of anesthesia and surgery in hypothyroid patients. *Arch Intern Med.* 1983;143:893–897.
73. Ladenson PW, Levin AA, Ridgway EC, et al. Complications of surgery in hypothyroid patients. *Am J Med.* 1984;77(2):261–266.
74. Bennett-Guerrero E, Kramer DC, Schwinn DA. Effect of chronic and acute thyroid reduction on perioperative outcome. *Anesth Analg.* 1997;85:30–36.
75. Klubo-Gwiedzinska J, Wartofsky L. Thyroid emergencies. *Med Clin N Am.* 2012;96:385–403.
76. Conner LE, Coursin DB. Assessment and therapy of selected endocrine disorders. *Anesthesiol Clin N Am.* 2004;22:93–123.
77. Warofsky L. Myxedema coma. *Endocrinol Metab Clin North Am.* 2006;35:687–698, vii–viii.
78. Dutta P, Bhanasali A, Masoodi SR, et al. Predictors of outcome in myxedema coma: a study from a tertiary care centre. *Crit Care.* 2008;12(1):R1.
79. Forfar JC, Muir AL, Sawyers SA, et al. Abnormal left ventricular function in hyperthyroidism. *N Engl J Med.* 1982;307:1165–1170.
80. Klein I, Ojamaa K. Mechanisms of disease: thyroid hormone and the cardiovascular system. *N Engl J Med.* 2001;344:501–509.
81. Sawin CT, Geller A, Wolf PA. Low serum thyrotropin concentration as a risk factor for atrial fibrillation in older patients. *N Engl J Med.* 1994;331:1249–1252.
82. Woebler KA. Thyrotoxicosis and the heart. *N Engl J Med.* 1992;327:94–97.
83. Furlong D, Ahmed I, Jabbour S. Perioperative management of endocrine disorders. In: Merli GJ, Weitz HH, eds. *Medical Management of the Surgical Patient.* 3rd ed. Philadelphia, PA: Elsevier Saunders; 2007. Chapter 12.
84. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin N Am.* 2006;35:663–686, vii.
85. Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid.* 2011;21(6):593–646.
86. Nicholson G, Burrin JM, Hall GM. Perioperative steroid supplementation. *Anaesthesia.* 1998;53:1091–1104.
87. Henzen C, Suter A, Lerch E, et al. Suppression and recovery of adrenal response after short-term, high dose glucocorticoid treatment. *Lancet.* 2000;355:542–545.
88. Hopkins RL, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. *Endocrinol Metab Clin N Am.* 2005;34:371–384.
89. Axelrod L. Perioperative management of patients treated with glucocorticoids. *Endocrinol Metab Clin N Am.* 2003;32:367–383.
90. Kehlet H, Binder C. Value of an ACTH test in assessing hypothalamic-pituitary-adrenocortical function in glucocorticoid-treated patients. *Br Med J.* 1973;2:147–149.
91. Knudsen L, Christiansen LA, Lorentzen JE. Hypotension during and after operation in glucocorticoid-treated patients. *Br J Anaesth.* 1981;53:295–301.
92. Plumpton FS, Besser GM, Cole PV. Corticosteroid treatment and surgery. 1. An investigation of the indications for steroid cover. *Anaesthesia.* 1969;24:3–11.
93. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids. *Arch Surg.* 2008;143(12):1222–1226.
94. U.S. Renal Data System, *USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2011.
95. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003;139(2):137–147.

96. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
97. Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: effects on the cardiovascular system. *Circulation*. 2007;116:85–97.
98. Weir MR. Recognizing the link between chronic kidney disease and cardiovascular disease. *Am J Manag Care*. 2011;17:S396–S402.
99. Conlon PJ, Krucoff MW, Minda S, et al. Incidence and long-term significance of transient S-T segment deviation in hemodialysis patients. *Clin Nephrol*. 1998;49(4):236–239.
100. Pochmalicki G, Jan F, Fouchard I. Frequency of painless myocardial ischemia during hemodialysis in 50 patients with chronic kidney failure. *Arch Mal Coeur Vaiss*. 1990;83:1671–1675.
101. Pun PH, Smarz TR, Honeycutt EF, et al. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney Int*. 2009;76:653–658.
102. De Bie MK, Maurits SB, Ton JR, et al. How to reduce sudden cardiac death in patients with renal failure. *Heart*. 2012;98:335–341.
103. Wallia R, Greenberg A, Piraino B, et al. Serum electrolyte patterns in end stage renal disease. *Am J Kidney Dis*. 1986;8:98–104.
104. Palevsky PM. Perioperative management of patients with chronic kidney disease or ESRD. *Best Pract Res Clin Anaesthesiol*. 2004;18(1):129–144.
105. Greenberg A. Hyperkalemia: treatment options. *Semin Nephrol*. 1998;18:46–57.
106. Joseph AJ, Cohn SL. Perioperative care of the patient with renal failure. *Med Clin North Am*. 2003;87:193–210.
107. Clement FM, Klarenbach S, Tonelli M, et al. An economic evaluation of erythropoiesis-stimulating agents in CKD. *Am J Kidney Dis*. 2010;56:1050–1061.
108. Esbach JW, Kelly MR, Haley NR, et al. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med*. 1989;321:158–163.
109. Rabelink TJ, Zwaginga JJ, Koomans HA, et al. Thrombosis and hemostasis in renal disease. *Kidney Int*. 1994;46:287–296.
110. Mannucci PM, Remuzzi G, Pusineri F, et al. Deamino-8-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med*. 1983;308:8–12.
111. Livio M, Mannucci PM, Vigano G, et al. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med*. 1986;315:731–735.
112. Aronoff GR, Bennett WM, Berns JS, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*. 5th ed. Philadelphia, PA: American College of Physicians; 2007.
113. Matzke GR, Aronoff GR, Atkinson AJ, et al. Dug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80:1122–1137.
114. Hanje AJ, Patel T. Preoperative evaluation of patients with liver disease. *Nat Clin Pract Gastroenterol Hepatol*. 2007;4:266–276.
115. Hoetzel A, Ryan H, Schmidt R. Anesthetic considerations for the patient with liver disease. *Curr Opin Anesthesiol*. 2012;25(3):340–347.
116. Mulenburgh DJ, Singh A, Torzilli G, et al. Surgery in the patient with liver disease. *Med Clin N Am*. 2009;93:1065–1081.
117. Friedman LS. Surgery in the patient with liver disease. *Trans Am Clin Climatol Assoc*. 2010;121:192–204.
118. Runyon BA. Surgical procedures are well tolerated by patients with asymptomatic chronic hepatitis. *J Clin Gastroenterol*. 1986;8:542–544.
119. O'Sullivan MJ, Envoy D, O'Donnell C, et al. Gallstones and laparoscopic cholecystectomy in hepatitis C patients. *Ir Med J*. 2001;94:114–117.
120. Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg*. 1964;1:1–85.
121. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646–649.
122. Muir AJ. Surgical clearance for the patient with chronic liver disease. *Clin Liver Dis*. 2012;16:421–433.
123. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864–871.
124. Amarapurkar DM. Prescribing medications in patients with decompensated liver cirrhosis. *Int J Hepatol*. 2011;519526, doi:10.4061/2011/519526.
125. Huhmann MB, August DA. Nutrition support in surgical oncology. *Nutr Clin Pract*. 2009;24:520–526.
126. Laky B, Janda M, Bauer J, et al. Malnutrition among gynecological cancer patients. *Eur J Clin Nutr*. 2007;61:642–646.
127. Gupta D, Vashi PG, Lammersfeld, et al. Role of nutritional status in predicting the length of stay in cancer: a systematic review of the epidemiological literature. *Ann Nutr Metab*. 2011;59:96–106.
128. Kathiresan AS, Brookfield KF, Schuman SI, et al. Malnutrition as a predictor of poor postoperative outcomes in gynecologic cancer patients. *Arch Gynecol Obstet*. 2011;284:445–451.
129. Obermair A, Hagenauer S, Tamandl D, et al. Safety and efficacy of low anterior en bloc resection as part of cytoreductive surgery for patients with ovarian cancer. *Gynecol Oncol*. 2001;83:115–120.
130. Laky B, Janda M, Cleghorn G, et al. Comparison of different nutritional assessments and body composition measurements in detecting malnutrition among gynecologic cancer patients. *Am J Clin Nutr*. 2008;87:1678–1685.
131. Huhmann MB, August DA. Review of American Society for Parenteral and Enteral Nutrition (ASPEN) Clinical Guidelines for Nutrition Support in Cancer Patients: nutrition screening and assessment. *Nutr Clin Pract*. 2008;23:182–188.
132. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *JPEN*. 1987;11:8–13.
133. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition*. 1996;12:S15–S19.
134. MacCallum PD, Polisena CG. *The Clinical Guide to Oncology Nutrition*. The American Dietetic Association: Chicago, IL; 2000.
135. Donato D, Angelides A, Irani H, et al. Infectious complications after gastrointestinal surgery in patients with ovarian carcinoma and malignant ascites. *Gynecol Oncol*. 1992;44:40–47.
136. Buzby GP, Mullen JL, Matthews DC, et al. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg*. 1980;139:160–167.
137. Santoso JT, Cannada T, O'Farrell B, et al. Subjective versus objective nutritional assessment study in women with gynecological cancer: a prospective cohort trial. *Int J Gynecol Cancer*. 2004;14:220–223.
138. Anthony PS. Nutrition screening tools for hospitalized patients. *Nutr Clin Pract*. 2008;23:373–382.
139. Braga M, Ljungqvist O, Soeters P, et al. ESPEN guidelines on parenteral nutrition: surgery. *Clin Nutr*. 2009;28:378–386.
140. Meijerink WJ, von Meyenfeldt ME, Rouffart MM, et al. Efficacy of perioperative nutritional support. *Lancet*. 1992;340:187–188.
141. Bozzetti F, Gavazzi C, Miceli R, et al. Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. *JPEN*. 2000;24:7–14.
142. Wu GH, Liu ZH, Wu ZH, et al. Perioperative artificial nutrition in malnourished gastrointestinal cancer patients. *World J Gastroenterol*. 2006;12:2441–2444.
143. Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. *Blood*. 2011;117:5044.
144. Destro MW, Speranzini MB, Cavalheiro Filho C, et al. Bilateral haematoma after rhytidoplasty and blepharoplasty following chronic use of Ginkgo biloba. *Br J Plast Surg*. 2005;58:100.
145. Cheema P, El-Mefty O, Jazieh AR. Intraoperative haemorrhage associated with the use of extract of Saw Palmetto herb: a case report and review of literature. *J Intern Med*. 2001;250:167.
146. Crosby E. Perioperative use of erythropoietin. *Am J Ther*. 2002;9:371–376.
147. Feringa HH, Bax JJ, Poldermans D. Perioperative medical management of ischemic heart disease in patients undergoing noncardiac surgery. *Curr Opin Anaesthesiol*. 2007;20:254–260.
148. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;50:e159–e241.
149. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery – executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation*. 2002;105:1257–1267.
150. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med*. 2005;353:349–361.
151. Howard-Alpe GM, Sear JW, Foex P. Methods of detecting atherosclerosis in non-cardiac surgical patients: the role of biochemical markers. *Br J Anaesth*. 2006;97:758–769.
152. O'Neil-Callahan K, Katsimaglis G, Tepper MR, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery: the statins for risk reduction in surgery (StaRRS) study. *J Am Coll Cardiol*. 2005;45:336–342.
153. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth*. 2007;99:316–328.
154. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411–2420.

155. Thachil J, Gatt A, Martlew V. Management of surgical patients receiving anticoagulation and antiplatelet agents. *Br J Surg*. 2008;95:1437–1448.
156. Korte W, Cattaneo M, Chassot PG, et al. Perioperative management of antiplatelet therapy in patients with coronary artery disease: joint position paper by members of the working group on Perioperative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Perioperative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (OGARI) and the Working Group Thrombosis of the European Society for Cardiology (ESC). *Thromb Haemost*. 2011;105:743–749.
157. Patrono C, Baigent C, Hirsh J, et al. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008;133(suppl. 6):199–233.
158. Cortés J, Caralt M, Delalage S, et al. Safety of bevacizumab in metastatic breast cancer patients undergoing surgery. *Eur J Cancer*. 2012;48(4):475–481.
159. Erinjeri JP, Fong AJ, Kemeny NE, et al. Timing of administration of bevacizumab chemotherapy affects wound healing after chest wall port placement. *Cancer*. 2011;117(6):1296–1301.
160. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol*. 2005;91(3):173–180.
161. Ng SP. Blood transfusion requirements for abdominal hysterectomy: 3-year experience in a district hospital (1993–1995). *Aust N Z J Obstet Gynaecol*. 1997;37:452–457.
162. Lentz SS, Shelton BJ, Toy NJ. Effects of perioperative blood transfusion on prognosis in early-stage cervical cancer. *Ann Surg Oncol*. 1998;5:216–219.
163. Dodd RY, Notari EP, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion*. 2002;42:975–979.
164. Dunne JR, Malone D, Tracy JK, et al. Perioperative anemia: an independent risk factor for infection, mortality, and resource utilization in surgery. *J Surg Res*. 2002;102:237–244.
165. Taylor RW, Manganaro L, O'Brien J, et al. Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. *Crit Care Med*. 2002;30:2249–2254.
166. Vanderlinde ES, Heal JM, Blumberg N. Autologous transfusion. *BMJ*. 2002;324:772–775.
167. Popovsky MA, Whitaker B, Arnold NL. Severe outcomes of allogeneic and autologous blood donation: frequency and characterization. *Transfusion*. 1995;35:734–737.
168. Goldman M, Savard R, Long A, et al. Declining value of preoperative autologous donation. *Transfusion*. 2002;42:819–823.
169. Horowitz NS, Gibb RK, Menegakis NE, et al. Utility and cost effectiveness of preoperative autologous blood donation in gynecologic and gynecologic oncology patients. *Obstet Gynecol*. 2002;5:771–776.
170. Shander A, Rijhwani TS. Acute normovolemic hemodilution. *Transfusion*. 2004;44:265–345.
171. Monk TG, Goodnough LT, Brecher ME, et al. A prospective randomized comparison of three blood conservation strategies for radical prostatectomy. *Anesthesiology*. 1999;91:24–33.
172. Goodnough LT, Despotis GJ, Merkel K, et al. A randomized trial comparing acute normovolemic hemodilution and preoperative autologous blood donation in total hip arthroplasty. *Transfusion*. 2000;40:1054–1057.
173. Naunheim KS, Bridges CR, Sade RM. Should a Jehovah's Witness patient who faces imminent exsanguination be transfused? *Ann Thorac Surg*. 2011;92(5):1559–1564.
174. Aapro M, Jelkmann W, Constantinescu SN, et al. Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer. *Br J Cancer*. 2012;106(7):1249–1258.
175. Rovera F, Dionigi G, Boni L, et al. Mechanical bowel preparation for colorectal surgery. *Surg Infect (Larchmt)*. 2006;7(suppl. 2):S61.
176. Frazee RC, Roberts J, Symmonds R, et al. Prospective, randomized trial of inpatient vs. outpatient bowel preparation for elective colorectal surgery. *Dis Colon Rectum*. 1992;35:223–226.
177. Curran MP, Plosker GL. Oral sodium phosphate solution: a review of its use as a colorectal cleanser. *Drugs*. 2004;64:1697–1714.
178. Oliveira L, Wexner SD, Daniel N, et al. Mechanical bowel preparation for elective colorectal surgery. A prospective, randomized, surgeon-blinded trial comparing sodium phosphate and polyethylene glycol-based oral lavage solutions. *Dis Colon Rectum*. 1997;40:585–591.
179. Barclay RL, Depew WT, Vanner SJ. Carbohydrate-electrolyte rehydration protects against intravascular volume contraction during colonic cleansing with orally administered sodium phosphate. *Gastrointest Endosc*. 2002;56:633–638.
180. Hsu CW, Imperiale TF. Meta-analysis and cost comparison of polyethylene glycol lavage versus sodium phosphate for colonoscopy preparation. *Gastrointest Endosc*. 1998;48:276–282.
181. Itani K, Wilson S, Awad S. Polyethylene glycol versus sodium phosphate mechanical bowel preparation in elective colorectal surgery. *Am J Surg*. 2007;193:190–194.
182. Valantas M, Beck D, DiPalma J. Mechanical bowel preparation in the older surgical patient. *Curr Surg*. 2004;61:320–324.
183. Belosoesky Y, Grinblat J, Weiss A, et al. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. *Arch Intern Med*. 2003;163:803–808.
184. Tan HL, Liew QY, Loo S, et al. Severe hypophosphatemia and associated electrolyte and metabolic derangement following the administration of sodium phosphate for bowel preparation. *Anaesthesia*. 2002;57:478–483.
185. Pitcher DE, Ford RS, Nelson MT, et al. Fatal hypocalcemic, hyper-phosphatemic, metabolic acidosis following sequential sodium phosphate-based enema administration. *Gastrointest Endosc*. 1997;46:266–268.
186. Rex DK, Di Palma JA, Rodriguez R, et al. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. *Gastrointest Endosc*. 2010;72:328–336.
187. Platell C, Hall J. What is the role of mechanical bowel preparation in patients undergoing colorectal surgery? *Dis Colon Rectum*. 1998;41:875–882; discussion 882–883.
188. Zmora O, Pikarsky AJ, Wexner SD. Bowel preparation for colorectal surgery. *Dis Colon Rectum*. 2001;44:1537–1549.
189. Bucher P, Gervaz P, Egger JF, et al. Morphologic alterations associated with mechanical bowel preparation before elective colorectal surgery: a randomized trial. *Dis Colon Rectum*. 2006;49:109.
190. Guenaga K, Atallah AN, Castro AA, et al. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev*. 2005;(1):CD001544. doi: 10.1002/14651858.CD001544.pub2.
191. Zmora O, Wexner SD, Hajjar L, et al. Trends in preparation for colorectal surgery: survey of the members of the American Society of Colon and Rectal Surgeons. *Am Surg*. 2003;69:150–154.
192. Lewis RT. Oral versus systemic antibiotic prophylaxis in elective colon surgery: a randomized study and meta-analysis send a message from the 1990s. *Can J Surg*. 2002;45:173–180.
193. Espin-Basany E, Sanchez-Garcia JL, Lopez-Cano M, et al. Prospective, randomized study on antibiotic prophylaxis in colorectal surgery. Is it really necessary to use oral antibiotics? *Int J Colorectal Dis*. 2005;20:542–546.
194. Nichols R, Choe EU, Weldon CB. Mechanical and antibiotic bowel preparation in colon and rectal surgery. *Chemotherapy*. 2005;51(suppl. 1):115–121.
195. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control*. 1999;27:97–132.
196. Malone DL, Genuit T, Tracy JK, et al. Surgical site infections: reanalysis of risk factors. *J Surg Res*. 2002;103:89–95.
197. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Am J Surg*. 2005;189:395–404.
198. ASHP therapeutic guidelines on antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 1999;56:1839–1888.
199. ACOG Practice Bulletin No.74: antibiotic prophylaxis for gynecologic procedures. *Obstet Gynecol*. 2006;108:225–234.
200. Antimicrobial prophylaxis for surgery. *Treat Guidel Med Lett*. 2006;4:83–88.
201. Itani K, Wilson S, Awad S, et al. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. *N Engl J Med*. 2006;355:2640–2651.
202. Ingraham AM, Cohen ME, Bilimoria KY, et al. Association of surgical care improvement project infection-related process measure compliance with risk-adjusted outcomes: implications for quality measurement. *J Am Coll Surg*. 2010;211(6):705–714.
203. Kirkland KB, Briggs JP, Trivette L, et al. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infect Control Hosp Epidemiol*. 1999;20:725–730.
204. Perencevich EN, Sands KE, Cosgrove SE, et al. Health and economic impact of surgical site infections diagnosed after hospital discharge. *Emerg Infect Dis*. 2003;9:196–203.
205. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database Syst Rev*. 2007;(2):CD004985. doi:10.1002/14651858.CD004985.pub3.
206. Tanner J, Woodings D, Moncaster K. Preoperative hair removal to reduce surgical site infection. *Cochrane Database Syst Rev*. 2006;(3):CD004122. doi:10.1002/14651858.CD004122.pub3.
207. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes of patients having surgery. *Clin Infect Dis*. 2006;43:322–330.
208. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci*. 2001;321:249–279.
209. Haslam DW, James WP. Obesity. *Lancet*. 2005;366:1197–1209.
210. Gaszynski T. Anesthetic complications of gross obesity. *Curr Opin Anaesthesiol*. 2004;17:271–276.

211. Hopkins MP, Shriner AM, Parker MG, et al. Panniculectomy at the time of gynecologic surgery in morbidly obese patients. *Am J Obstet Gynecol.* 2000;182:1502–1505.
212. Pearl ML, Valea FA, Disilvestro PA, et al. Panniculectomy in morbidly obese gynecologic oncology patients. *Int J Surg Invest.* 2000;2:59–64.
213. Tillmanns TD, Kamelle SA, Abudayyeh I, et al. Panniculectomy with simultaneous gynecologic oncology surgery. *Gynecol Oncol.* 2001;83:518–522.
214. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care.* 2011;1(1):1. <http://www.annal-sofintensivecare.com/content/1/1/1>.
215. Eisner RF, Montz FJ, Berek JS. Cytoreductive surgery for advanced ovarian cancer: cardiovascular evaluation with pulmonary artery catheter. *Gynecol Oncol.* 1990;37:11.
216. Weitz HH. Perioperative cardiac complications. *Med Clin North Am.* 2001;85:1151–1169.
217. Adesanya AO, Lemos JA, et al. Management of perioperative myocardial infarction in noncardiac surgical patients. *Chest.* 2006;130(2):584–596.
218. Ho K, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol.* 1993;22:6A–13A.
219. Zaloga GP, Prielipp RC, Butterworth JF, et al. Pharmacologic cardiovascular support. *Crit Care Clin.* 1993;9:335–362.
220. Overgaard CB, Dzavik V. Inotropes and vasopressors. Review of physiology and clinical use in cardiovascular disease. *Circulation.* 2008;118:1047–1056.
221. Chiolerio R, Flatt J-P, Revelly J-P, et al. Effects of catecholamines on oxygen consumption and oxygen delivery in critically ill patients. *Chest.* 1991;100:1676–1684.
222. Raymer K, Yang H. Patients with aortic stenosis: cardiac complications in non-cardiac surgery. *Can J Anaesth.* 1998;45:855–859.
223. Torsher LC, Shub C, Rettke SR, et al. Risk of patients with severe aortic stenosis undergoing noncardiac surgery. *Am J Cardiol.* 1998;81:448–452.
224. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation.* 2007;116(15):1736–1754.
225. Nishimura RA, Clase A, Carabello DP, et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis. *Circulation.* 2008;118:887–896.
226. Allen U. Infective endocarditis: updated guidelines. *Can J Infect Dis Med Microbiol.* 2010;21(2):74–77.
227. Christians KK, Wu B, Quebbeman EJ, et al. Postoperative atrial fibrillation in noncardiothoracic surgical patients. *Am J Surg.* 2001;182:713–715.
228. Balser JR, Martinez EA, Winters BD, et al. Beta-adrenergic blockade accelerates conversion of postoperative supraventricular tachyarrhythmias. *Anesthesiology.* 1998;89:1052–1059.
229. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med.* 2000;342:913–920.
230. Mehta S, Heffer MJ, Maham N, et al. Impact of endotracheal tube size on preextubation respiratory variables. *J Crit Care.* 2010;25(3):483–488.
231. Banner MJ, Jaeger MJ, Kirby RR. Components of the work of breathing and implications for monitoring ventilator-dependent patients. *Crit Care Med.* 1994;22:515–518.
232. Stewart T, Meade M, Cook D, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med.* 1998;338:356–361.
233. Amato M, Barbas C, Medeiros D, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med.* 1998;338:347–354.
234. Lodat R. Oxygen toxicity. *Crit Care Clin.* 1990;6:749–765.
235. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med.* 1991;324:1445–1450.
236. Rosenberg AL, Dechert RE, et al. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med.* 2009;24(1):35–46.
237. Bernard G, Artigas A, Brigham KL, et al. Report of the American-European Consensus Conference on Acute Respiratory Distress Syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. *J Crit Care.* 1994;9:72–81.
238. Luce J. Acute lung injury and the acute respiratory distress syndrome. *Crit Care Med.* 1998;26:369–376.
239. Marshall J, Cook D, Christou N, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med.* 1995;23:1638–1652.
240. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165:867–903.
241. Guyatt GH, Crowther M, et al. Executive summary. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2):7s–47s.
242. Clarke-Pearson DL, Synan IS, et al. The natural history of postoperative venous thromboemboli in gynecologic oncology: a prospective study of 382 patients. *Am J Obstet Gynecol.* 1984;148:1051–1054.
243. Clarke-Pearson DL, Dodge RK, et al. Venous thromboembolism prophylaxis: patients at high risk to fail intermittent pneumatic compression. *Obstet Gynecol.* 2003;101:157–163.
244. Collins R, Scrimgeour A, Yusuf S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med.* 1988;318:1162.
245. Pestana C. *Fluids and Electrolytes in the Surgical Patient.* 4th ed. Baltimore, MD: Williams & Wilkins; 1989.
246. Vanatta JC, Fogelman MJ, eds. *Moyer's Fluid Balance: A Clinical Manual.* 2nd ed. Chicago, IL: Year Book; 1976.
247. Wait RB, Kahng KU, Dresner LS. Fluids and electrolytes and acid-base balance. In: Greenfield LJ, Mulholland M, Oldham KT, et al. eds. *Surgery: Scientific Principles and Practice.* 2nd ed. Philadelphia, PA: Lippincott–Raven Publishers; 1997:242–266.
248. Lowe RJ, Moss GS, Jilek J, et al. Crystalloid versus colloid in the etiology of pulmonary failure after trauma. A randomized trial in man. *Surgery.* 1977;81:676–683.
249. Virgilio RW, Rice CL, Smith DE, et al. Crystalloid versus colloid resuscitation: is one better? A randomized clinical study. *Surgery.* 1979;85:129–139.
250. Weinstein PD, Doerfler ME. Systemic complications of fluid resuscitation. *Crit Care Clin.* 1992;8:439–448.
251. Metildi LA, Shackford SR, Virgilio RW, et al. Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. *Surg Gynecol Obstet.* 1984;158:207–212.
252. Rizoli SB. Crystalloids and colloids in trauma resuscitation: a brief overview of the current debate. *J Trauma.* 2003;54(suppl. 5):S82–S88.
253. Alderson P, Schierhout G, Roberts I, et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev.* 2000;(2):CD000567.
254. Choi PT, Yip G, Quinonez LG, et al. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med.* 1999;27:200–210.
255. Roberts JS, Bratton SL. Colloid volume expanders. Problems, pitfalls and possibilities. *Drugs.* 1998;55:621–630.
256. Berenson JR. Treatment of hypercalcemia of malignancy with bisphosphonates. *Semin Oncol.* 2002;29(suppl. 21):12–18.
257. Mundy GR. Hypercalcemia. In: *Bone Remodeling and Its Disorders.* 2nd ed. London, England: Martin Dunitz; 1999:107–122.
258. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol.* 2001;19:558–567.
259. Pearl ML, Frandina M, Mahler L, et al. A randomized controlled trial of a regular diet as the first meal in gynecologic oncology patients undergoing intraabdominal surgery. *Obstet Gynecol.* 2002;100:230–234.
260. Pearl ML, Valea FA, Fischer M, et al. A randomized controlled trial of early postoperative feeding in gynecologic oncology patients undergoing intra-abdominal surgery. *Obstet Gynecol.* 1998;92:94–97.
261. Cuttillo G, Maneschi F, Franchi M, et al. Early feeding compared with nasogastric decompression after major oncologic gynecologic surgery: a randomized study. *Obstet Gynecol.* 1999;93:41–45.
262. MacMillan SL, Kammerer-Doak D, Rogers RG, et al. Early feeding and the incidence of gastrointestinal symptoms after major gynecologic surgery. *Obstet Gynecol.* 2000;96:604–608.
263. Steed HL, Capstick V, Flood C, et al. A randomized controlled trial of early versus “traditional” postoperative oral intake after major abdominal gynecologic surgery. *Am J Obstet Gynecol.* 2002;186:861–865.
264. Schilder JM, Hurteau JA, Look KY, et al. A prospective controlled trial of early postoperative oral intake following major abdominal gynecologic surgery. *Gynecol Oncol.* 1997;67:235–240.
265. Souba WW, Austen WG Jr. Nutrition and metabolism. In: Greenfield LJ, Mulholland M, Oldham KT, et al. eds. *Surgery: Scientific Principles and Practice.* 2nd ed. Philadelphia, PA: Lippincott–Raven Publishers; 1997:42–67.
266. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med.* 2001;29:2264–2270.
267. Morrow CP, Curtin JP. *Gynecologic Cancer Surgery.* New York, NY: Churchill Livingstone; 1996:194–205.
268. Blackburn GL, Bistrian BR, Moyni BS, et al. Nutritional and metabolic assessment of the hospitalized patient. *JPN.* 1977;1:11–22.
269. Edwards BF. Postoperative renal insufficiency. *Med Clin North Am.* 2001;85:1241–1254.

270. Klausner JM, Paterson IS, Goldman G, et al. Postischemic renal injury is mediated by neutrophils and leukotrienes. *Am J Physiol*. 1989;256 (5 Pt 2):F794-F802.
271. Kribben A, Edelstein CL, Schrier RW. Pathophysiology of acute renal failure. *J Nephrol*. 1999;12(suppl. 2):S142-S151.
272. Prins JM, Buller HR, Kuijper EJ, et al. Once versus thrice daily gentamicin in patients with serious infections. *Lancet*. 1993;341:335-339.
273. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. *J Am Soc Nephrol*. 2000;11:177-182.
274. Rudnick MR, Berns JS, Cohen RM, et al. Contrast media-associated nephrotoxicity. *Semin Nephrol*. 1997;17:15-26.
275. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors and relationship to mortality. *Am J Med*. 1997;103:368-375.
276. Baldwin L, Henderson A, Hickman P. Effect of postoperative low-dose dopamine on renal function after elective major vascular surgery. *Ann Intern Med*. 1994;120:744-747.
277. Dishart MK, Kellum JA. An evaluation of pharmacological strategies for the prevention and treatment of acute renal failure. *Drugs*. 2000;59:79-91.
278. Lassnigg A, Donner E, Grubhofer G, et al. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol*. 2000;11:97-104.
279. Marik PE, Iglesias J. Low-dose dopamine does not prevent acute renal failure in patients with septic shock and oliguria. NORASEPT II Study Investigators. *Am J Med*. 1999;107:387-390.
280. Sirivella S, Gielchinsky I, Parsonnet V. Mannitol, furosemide and dopamine infusion in postoperative renal failure complicating cardiac surgery. *Ann Thorac Surg*. 2000;69:501-506.
281. Allgren RL, Marbury TC, Rahman SM, et al. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. *N Engl J Med*. 1997;336:828-834.
282. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247-2256.
283. Roswell SE, Barbosa RR, et al. Effect of high product ratio massive transfusion on mortality in blunt and penetrating trauma patients. *J Trauma*. 2011;71(2 suppl. 3):S353-S357.
284. Dellinger RP, Levy MM, et al. Surviving sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:1394-1396.
285. National Nosocomial Infections Surveillance (NNIS). System report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control*. 2004;32:470-485.
286. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323.
287. Ostrosky-Zeichner L, Pappas PG. Invasive candidiasis in the intensive care unit. *Crit Care Med*. 2006;34:857-863.
288. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis*. 2004;38:161-189.
289. Crabtree TD, Pelletier SJ, Antevil JL, et al. Cohort study of fever and leukocytosis as diagnostic and prognostic indicators in infected surgical patients. *World J Surg*. 2001;25:739-744.
290. Jaramillo EJ, Trevino JM, Berghoff KR, et al. Bedside diagnostic laparoscopy in the intensive care unit: a 13-year experience. *JSLs*. 2006;10:155-159.
291. Cinat ME, Wilson SE, Din AM. Determinants of successful percutaneous image-guided drainage of intra-abdominal abscess. *Arch Surg*. 2002;137:845-849.
292. Garvais DA, Ho CH, O'Neill MJ, et al. Recurrent abdominal and pelvic abscesses: incidence, results of repeated percutaneous drainage, and underlying causes in 956 drainages. *Am J Roentgenol*. 2004;182:463-466.
293. Kok KY, Yapp SK. Laparoscopic drainage of postoperative complicated intra-abdominal abscess. *Surg Laparosc Endosc Percutan Tech*. 2000;10:311-313.
294. Schechter WP, Ivatury RR, Rotondo MF, et al. Open abdomen after trauma and abdominal sepsis: a strategy for management. *J Am Coll Surg*. 2006;203:390-396.
295. Marshall JC, Maier RV, Jimenez M, et al. Source control in the management of severe sepsis and septic shock: an evidence-based review. *Crit Care Med*. 2004;32(suppl. 11):S513-S526.
296. Aird WC. The role of endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood*. 2003;101:3765-3777.
297. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20:864-874.
298. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31:1250-1256.
299. Shorr AF, Tabak YP, Killian AD, et al. Healthcare-associated bloodstream infection: a distinct entity? Insights from a large U.S. database. *Crit Care Med*. 2006;34:2588-2595.
300. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303-1310.
301. Martí-Carvajal AJ, Solà I, Lathyrus D, et al. Human recombinant activated protein C for severe sepsis. *Cochrane Database Sys Rev*. 2012;(3):CD004388.
302. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344:699-709.
303. Xigris [drotrecogin alfa (activated)]: market withdrawal-failure to show survival benefit. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm277143.htm>. Posted October 25, 2011. Accessed April 25, 2012.
304. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26:1793-1800.
305. Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med*. 2006;34:1297-1310.
306. Levy MM, Macias WL, Vincent JL, et al. Early changes in organ function predict eventual survival in severe sepsis. *Crit Care Med*. 2005;33:2194-2201.
307. Vidal MG, Ruiz Weisser J, Gonzalez F, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. *Crit Care Med*. 2008;36(6):1823.
308. Society of Critical Care Medicine and American Society of Health-System Pharmacists. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Am J Health Syst Pharm*. 2002;59:150-178.
309. Society of Critical Care Medicine and American Society of Health-System Pharmacists. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Am J Health Syst Pharm*. 2002;59:179-195.
310. Epstein J, Breslow MJ. The stress response of critical illness. *Crit Care Clin*. 1999;15:17-33.
311. Kress JP, Gehlbach B, Lacy M, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med*. 2003;168:1457-1461.
312. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342:1471-1477.
313. Cammarano WB, Pittet JE, Weitz S, et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med*. 1998;26:676-684.
314. Bird SJ. Diagnosis and management of critical illness polyneuropathy and critical illness myopathy. *Curr Treat Options Neurol*. 2007;9:85-92.
315. McKegney FP. The intensive care syndrome. The definition, treatment and prevention of a new "disease of medical progress." *Comm Med*. 1966;30:633-636.
316. McGuire BE, Basten CJ, Ryan CJ, et al. Intensive care unit syndrome: a dangerous misnomer. *Arch Intern Med*. 2000;160:906-909.
317. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286:2703-2710.
318. Thomason J, Shintani A, Peterson J, et al. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective study of 261 nonventilated patients. *Crit Care*. 2005;9:R375-R381.
319. Way J, Back AL, Curtis JR. Withdrawing life support and resolution of conflict with families. *BMJ*. 2002;325:1342-1345.
320. Nelson JE, Azoulay E, Curtis JR, et al. Palliative care in the ICU. *J Palliat Med*. 2012;15(2):168-174.

Surgical Principles in Gynecologic Oncology

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The management of most human cancers involves multimodal therapy, and this is especially true for female genital malignancies. Although some early gynecologic cancers can be eradicated by surgery alone, and chemotherapy as a single modality can often cure gestational trophoblastic malignancies, the optimal treatment for the majority of gynecologic malignancies requires surgery combined with chemotherapy and/or irradiation.

In this chapter, surgery is discussed both as a separate discipline and as an integral part of multimodal therapeutic planning. Although specific operations and relatively new surgical techniques are described for some disease sites, many procedures are addressed more completely in surgical texts and atlases to which the reader is referred (1–3). The role of surgical intervention in the treatment of gynecologic cancers is addressed herein with a more philosophic approach than would be taken in a surgical atlas. However, select illustrations and tips are included that have enabled us to approach various radical procedures more confidently and safely. The major goal of this chapter is to give the reader an appreciation and understanding of the surgical principles of the subspecialty of gynecologic oncology.

TECHNICAL ASPECTS OF SURGERY

Many physicians who practice the art and science of surgery tend to focus on the technical craft of the specialty only when teaching young surgeons. At other times, we are acutely aware that the most difficult part of our practice is the decision of whether or not to utilize surgical therapy. Preoperative and postoperative management is also demanding since therapy must be tailored for individual patients depending not only on their specific disease but also on their overall medical status. Owing to the significance of these pressing issues, we often take for granted the many years of preparation and experience in the craft of surgery.

Mastering the skills of surgery involves a thorough understanding of proper technique. It also requires frequent and consistent practice to keep surgical maneuvers well honed. For the student, this means actual practice in tying knots, manipulating instruments, and suturing. For the accomplished surgeon, it means that a sufficient case load must be maintained to ensure adequate practice of the technical art of the specialty. The surgeon should also keep abreast of new suture materials, instruments, and technical developments.

Anatomy

There is no substitute for a detailed knowledge of the anatomy of the pelvis and abdomen. The physician who pursues gynecologic

oncology as a career must be completely familiar with the pelvis, abdomen, retroperitoneum, and the lymphatic drainage of the female genital tract. No amount of surgical skill or knowledge of cancer therapy can compensate for the lack of this knowledge.

Lymphatic drainage from the cervix follows the uterine arteries and cardinal ligaments to the pelvic lymph nodes that include the external iliac, internal iliac (hypogastric), and obturator node groups (Fig. 9.1). From these pelvic lymph nodes, the drainage proceeds superiorly through the common iliac and presacral lymph nodes and then up to the paraaortic nodes.

The lymphatic drainage from both the uterine corpus and the ovaries follows one of three routes (Fig. 9.1): (a) along the uterine arteries in the broad ligaments to the pelvic nodes, (b) in channels following the round ligaments to the inguinal lymph nodes, or (c) along the ovarian lymphatics in the infundibulopelvic ligaments directly up to the paraaortic nodes.

The anatomy of the paraaortic lymph nodes has been well described by Fowler and Johnson (4). The paraaortic lymph nodes are part of the lumbar lymph node group. Usually, six subgroups of retroperitoneal nodes in the paraaortic region are recognized: paracaval, retrocaval, interaorto-caval, preaortic, paraaortic (left side), and retroaortic. The preaortic group drains the abdominal part of the gastrointestinal tract down to the mid rectum, whereas the retrocaval and retroaortic groups have no special area of drainage. The paracaval, interaorto-caval, and paraaortic (left side) nodes receive lymphatic drainage from the iliac lymph nodes, ovaries, and other pelvic viscera (apart from the alimentary tract), and therefore it is these groups of nodes that are sampled in the surgical staging of gynecologic malignancies. However, systematic paraaortic lymphadenectomy should address all major regions, including paracaval, retrocaval, interaorto-caval, preaortic, paraaortic, and retroaortic nodes.

There are typically 15 to 20 paracaval and paraaortic nodes per side. They are located adjacent to the inferior vena cava (IVC) and aorta, anterior to the lumbar spine, extending bilaterally to the medial margins of the psoas major muscles, and up to the diaphragmatic crura (4). The paracaval and paraaortic nodes usually dissected in gynecologic oncology span the region from the aortic bifurcation up to either the inferior mesenteric artery (IMA) or the renal veins.

The first major blood vessel encountered during a caudad-to-cephalad paraaortic node dissection is the IMA (Fig. 9.1). The IMA originates from the anterior surface of the aorta, approximately 3 to 4 cm above the aortic bifurcation. Next, the right and left ovarian arteries arise from their respective sides of the aorta, about 5 to 6 cm above the bifurcation (Fig. 9.1). The right ovarian vein inserts into the right side of the inferior vena cava (IVC), approximately 1 cm below the right renal vein. The left ovarian vein does not insert directly into the IVC, rather follows a path close to the left ureter inserting into the left renal vein lateral to

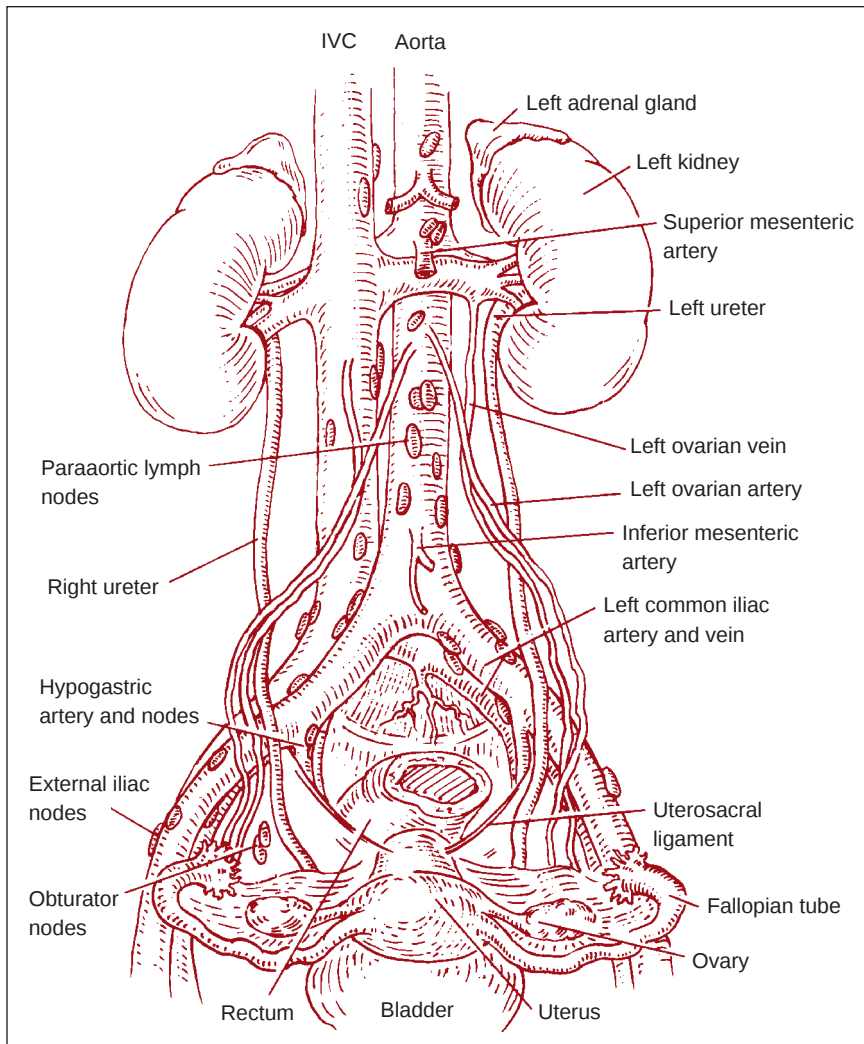


FIGURE 9.1. The pelvic and paraaortic lymph nodes and their relationship to the major retroperitoneal vessels.

the left border of the aorta. Three to four pairs of lumbar arteries and veins arise from the posterior surfaces of the aorta and IVC, respectively.

The gynecologic oncologist who operates on patients with advanced ovarian carcinoma often encounters disease being spread across upper abdominal structures such as the diaphragm, liver, pancreas, and spleen. Debulking of tumor from these areas has been demonstrated to improve the rate of optimal cytoreduction and subsequent survival (5,6). Anatomic considerations for diaphragm surgery include the relevant hepatic attachments and the underlying central vasculature (7,8) (Fig. 9.2). The anterior hepatic attachment is the falciform ligament, which contains the ligamentum teres in its infrahepatic portion, and attaches the liver to the anterior abdominal wall in its membranous hepatic portion. As the falciform ligament continues superiorly, its peritoneal surface divides laterally on each side to form the anterior right and left coronary ligaments. These coronary ligaments reflect off the liver capsule and delineate the posterior extent of peritoneum covering the superior diaphragm. The IVC lies to the right side of this falciform ligament division. The right and left hepatic veins drain into the anterior surface of the IVC at the level of this peritoneal reflection. The anterior coronary ligaments continue laterally and inferiorly along the posterior liver edge, where they join the posterior right and left coronary ligaments to form the right and left triangular ligaments, respectively. The right triangular ligament reflects from the liver to the diaphragm, right kidney, and right adrenal gland. The left triangular ligament

reflects primarily to the diaphragm; the posterior left coronary ligament lies higher than the esophageal hiatus and the esophagus is generally not encountered. The coronary ligaments on each side delineate the larger “bare area” of the liver on the right and a smaller “bare area” on the left, which underlie the central tendon of the diaphragm. The right phrenic nerve penetrates this central tendon lateral to the vena caval foramen on the right and is usually not encountered until the “bare area” is exposed. The left phrenic nerve may penetrate the left diaphragm muscle above the central tendon and is a consideration during left-sided anterior diaphragm surgery.

In the left upper quadrant of the abdomen, the spleen lies under the 9th, 10th, and 11th ribs. It is situated adjacent and slightly deep to the stomach and colon, lateral to the pancreas, and sits on the superior aspect of the left kidney. The posterior aspect of the spleen is in contact with the adrenal gland as well as Gerota’s fascia of the kidney. The tail of the pancreas often approaches the splenic hilum and sometimes contacts the spleen. The spleen varies in size between individuals, but in general measures 12 cm in length, 7 cm in width, and 3 to 4 cm in depth. The peritoneum creates folds that form the suspensory ligaments of the spleen. The four main “suspensory” ligaments are gastrosplenic, splenorenal, splenophrenic, and splenocolic ligaments. The splenophrenic and splenocolic ligaments are avascular. The gastrosplenic ligament contains the short gastric vessels. The splenorenal ligament has an anterior and posterior aspect and surrounds the splenic hilum. The splenic hilum contains the splenic artery, splenic vein, and

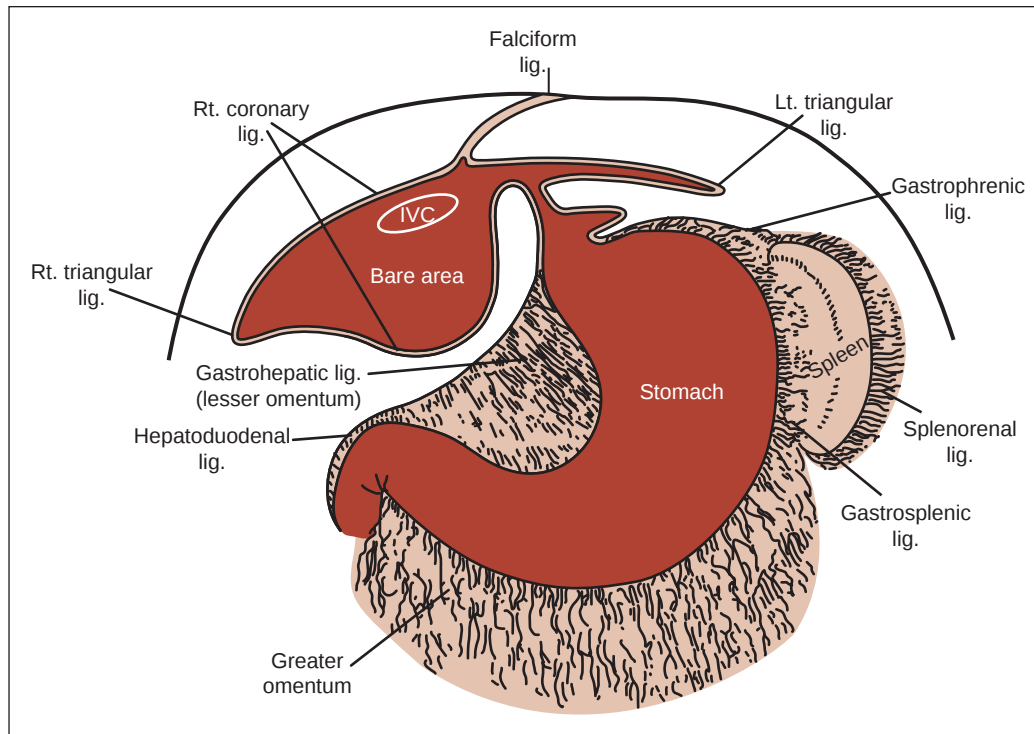


FIGURE 9.2. Peritoneal reflections of the liver: the lesser omentum (hepatogastric and hepatoduodenal ligaments) and its relation to the coronary ligament of the liver and diaphragm.

Source: Reprinted with permission from Skandalakis JE, Gray SW, Rowe JR, eds. *Anatomical Complications in General Surgery*. New York, NY: McGraw-Hill; 1983.

sometimes the tail of the pancreas. The splenic vessels sometimes branch before entering the spleen. The splenic artery is tortuous and is one of the three branches of the celiac trunk. It runs along the superior aspect of the pancreas and gives rise to the short gastric arteries prior to entering the spleen, which course in the gastrosplenic ligament and supply the portion of the greater curvature of the stomach, superior to the splenic artery (Fig. 9.3) (9). The splenic artery also gives rise to the left gastroepiploic artery, which supplies the remainder of the greater curvature of the stomach and the gastrocolic omentum. The splenic vein is slightly inferior and follows the course and branching of the artery.

Patient Positioning

Patient positioning for radical gynecologic oncology procedures is often critical in improving exposure, particularly in obese patients. For most women undergoing radical hysterectomy, ovarian cancer cytoreduction, or pelvic exenterative procedures, we prefer the low lithotomy position using Allen stirrups (Fig. 9.4) (1). The buttocks should extend 2 to 3 cm over the end of the table. This position allows simultaneous access to the perineum and abdomen. The weight of the leg should be on the foot with the legs well padded and attention paid to prevent pressure on the calf and the peroneal nerve. To further improve pelvic exposure, a blanket or pad can be placed under the small of the back.

Abdominal Incisions

Abdominal incisions in gynecologic oncology vary with the indication for the procedure, associated preoperative conditions (such as the presence of ascites or bowel obstruction), suspicion of upper abdominal pathology, and the presence of a previous abdominal scar. Incisions for surgery for gynecologic oncology patients should be highly individualized. Three basic incisions are used for

intraoperative exposure (Fig. 9.5) (2). Additionally, extraperitoneal access to the pelvic and paraaortic nodes can be achieved through a J-shaped incision (10) or a “sunrise” incision (11).

Transverse incisions offer the advantages of being the best cosmetic incisions for pelvic surgery while also being the least painful, resulting in less interference with postoperative pulmonary function. In addition, compared to vertical incisions, transverse incisions are allegedly stronger and allow better exposure to the pelvic sidewalls. Many gynecologic oncologists use transverse incisions when performing a radical hysterectomy or pelvic exenteration.

In performing the Maylard incision, it is recommended that the deep inferior epigastric vessels be isolated, sectioned, and ligated prior to dividing the rectus muscle (Fig. 9.6) (2). Occasionally, the pelvic surgeon will make a Pfannenstiel incision and find it inadequate. When more exposure is needed, the appropriate maneuver is to convert the Pfannenstiel to a Cherney-type incision. This conversion can be accomplished by dissecting the rectus muscles from the pyramidalis muscles and the anterior rectus sheath, and then transecting the rectus tendons at their insertion into the pubic bone.

Lymph Node Dissection

The surgical technique used to dissect the pelvic and paraaortic lymph nodes involves either a transperitoneal or extraperitoneal approach. The approach utilized is generally dictated by the primary site of disease and the planned accompanying procedure. In cases of endometrial and ovarian carcinoma where the anticipated procedure includes a hysterectomy and/or surgical debulking, the approach is invariably transperitoneal. However, in the pretreatment surgical staging of patients with advanced-stage cervical cancer, the transperitoneal approach has been associated with significant radiation-induced intestinal morbidity due to postoperative adhesion formation (12). Therefore, current clinical trials that require pretreatment surgical staging recommend that

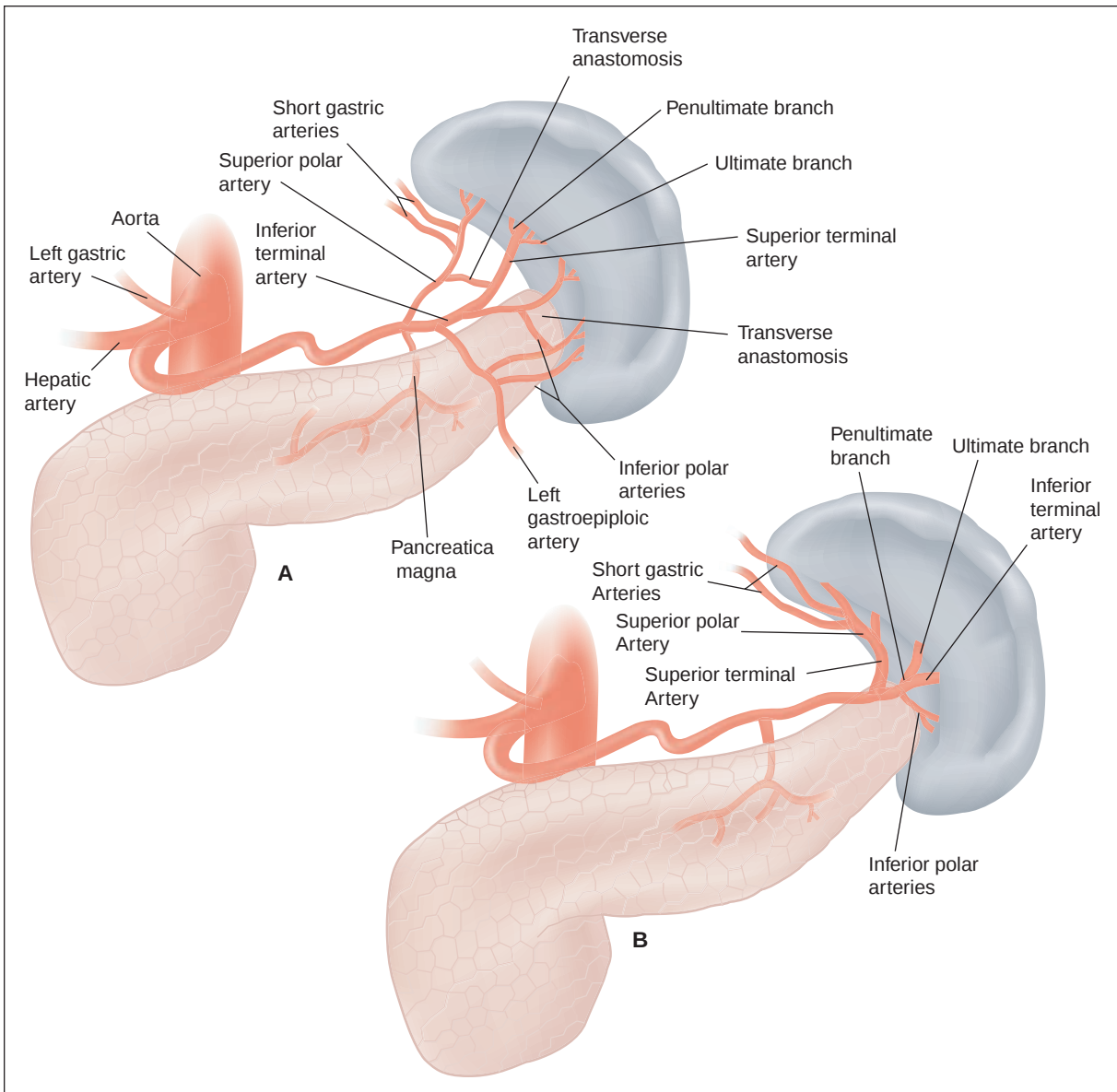


FIGURE 9.3. A, B. Variations of splenic vascularization.

Source: Reprinted with permission from Poulin EC, Schlachta DM, Maazza J. Splenectomy. *Gastrointestinal tract and abdomen*. In: Souba WW, Fink MJ, Jurkovich GJ, et al, eds. *ACS Surgery*. New York, NY:WebMd; 2005.



FIGURE 9.4. Low lithotomy position using Allen stirrups.

Source: Reprinted with permission from Morrow CP, Curtin JP, eds. *Gynecologic Cancer Surgery*. New York, NY: Churchill Livingstone; 1996.

the lymph node sampling be performed via the extraperitoneal approach or by operative laparoscopy (13).

Pelvic Lymph Node Dissection

Whether a transperitoneal or extraperitoneal approach is used, the pelvic lymphatic basin can be divided into 5 specific anatomical regions. Most surgeons initially remove pelvic nodes from the *external iliac region*. Lymphatic-fatty tissue is removed cranially, laterally, and medially from both external iliac vessels and between them. The medial border is formed by the paravesical space. The lateral border is the psoas muscle, the ventral is commonly indicated as the origin of the deep circumflex iliac vein, and the cranial border is the level of the common iliac artery bifurcation, where the lymphatic trunk continues as the superficial common iliac region (Fig. 9.7) (2). The genitofemoral nerve courses laterally to the external iliac artery and should be identified and preserved prior to excising the lymphatic tissue. It usually forms two branches, one running on the surface of the

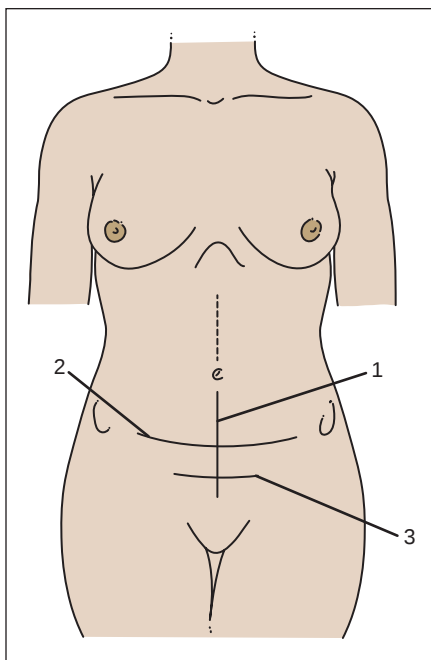


FIGURE 9.5. Entry into the abdominal cavity can be made by three basic incisions: (1) the midline incision; (2) the transverse Maylard-type incision from anterior–superior iliac spine to anterior–superior iliac spine; and (3) the Pfannenstiel incision. The latter is not an incision for radical pelvic surgery, but it can be converted to a Cherney-type incision for improved exposure. For the patient who has some type of transverse incision, and for whom later exposure of the upper abdominal cavity is necessary, a midline upper abdominal incision can be separately used.

Source: Reprinted with permission from Gallup DG, Talleo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:44.

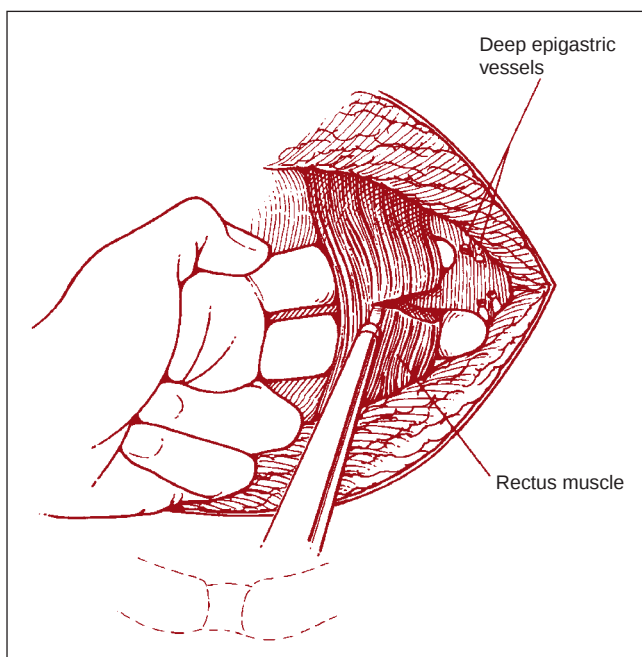


FIGURE 9.6. The Maylard incision. A transverse incision has been made from the anterior-superior iliac spine to the opposite anterior-superior iliac spine. The fascia has been incised transversely. The deep inferior epigastric vessels are located on the lateral and posterior borders of the rectus muscle. They are bluntly dissected from this position by the finger of the operator; isolated, clamped, sectioned, and tied. Only after they are tied should the rectus muscle be incised. This can be done with the Bovie.

Source: Reprinted with permission from Gallup DG, Talleo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:45.

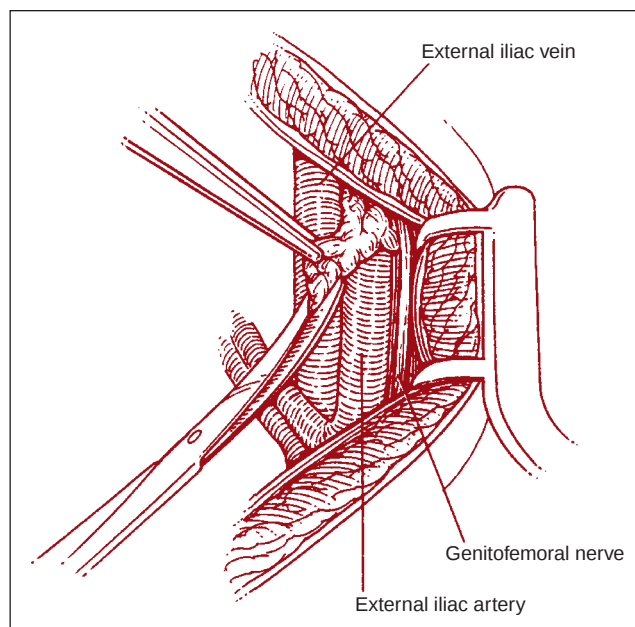


FIGURE 9.7. Starting at the bifurcation of the common iliac vessels, the loose areolar tissue over the vein is excised from cephalad to caudad. Clips should be used at the bifurcation of the common iliac to avoid troublesome bleeding.

Source: Reprinted with permission from Gallup DG, Talleo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:57.

psoas muscle and another through the lymphatic tissue on the external iliac vessels, where it can be easily cut or injured.

Mobilization and retraction of the external iliac vessels allows access to the *obturator region*. The cranial border is formed by the common iliac vessels bifurcation, where the lymphatic trunk continues cranially as the deep common iliac region. The medial anatomical border is the paravesical space and the ventral border is formed by the pubic bone together with levator ani and obturator muscles, where the obturator nerve leaves the pelvis through the obturator canal. The lateral border is formed by the obturator internal muscle and the caudal anatomical landmarks are the obturator vessels. The obturator nodes are most easily teased away from the nerve and vessels if one begins the dissection caudally (Fig. 9.8) (2). Usually the last dissected area is the *internal iliac region*, where the tissue is removed medially from the internal iliac vein.

The dissection continues cranially to the *common iliac region*. Tissue is removed ventrally and laterally from both common iliac vessels. The lymphatic tissue can be anatomically divided into two parts, the superficial one, which continues mostly from the external iliac region, and the deep one, which runs deeply between the common iliac vein and psoas muscle, continuing from the obturator region. The cranial border is the level of the aorta bifurcation. The genitofemoral nerve should be preserved as it lies on the surface of the psoas muscle. Deeply below the common iliac vessels and the psoas muscle, on the sacral bone, can be identified two nerve structures—the cranial part of the lumbosacral trunk (L4 + L5) (medially) and the obturator nerve (laterally), which enters the region from under the psoas muscle.

If presacral nodes are to be removed, the fatty-lymphatic tissue is removed above the sacral bone, below and between both common iliac veins. The caudal border is indicated by the level of right common iliac vessels bifurcation, where it continues caudally as the internal iliac region. Major branches of the inferior nerve hypogastric plexus should be preserved, as the plexus runs medially on both sides, below the ureters, inside of the mesoureter, which forms a thin layer of tissue between the medial pararectal fossa and large vessels.

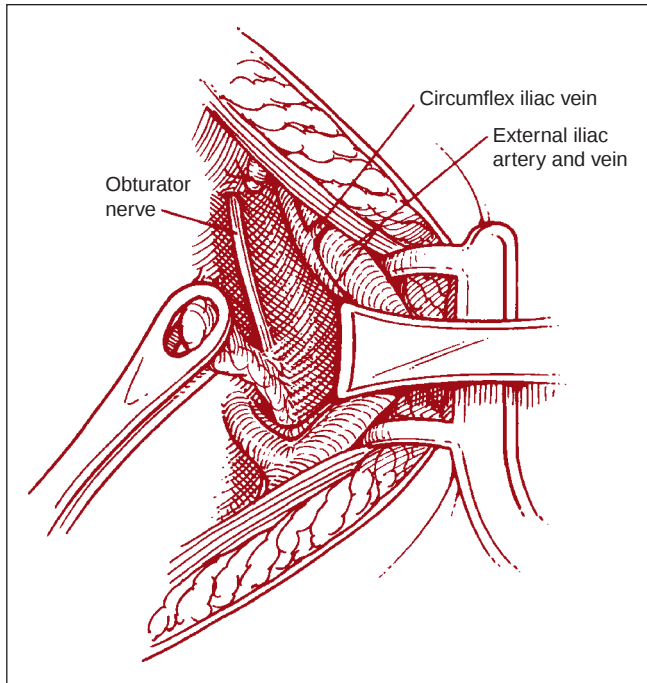


FIGURE 9.8. A vein retractor is used to retract the external iliac veins anterior and lateral to expose the obturator space. Lymphatic tissue is gently teased from the psoas muscle. The entire lymphatic bundle is clamped, sectioned at its caudal end, and ligated at the pelvic sidewall. With the use of the Singley forceps, the lymphatic bundle is bluntly dissected from the obturator nerve and mobilized superiorly. Often, the obturator vein and artery must be sacrificed to obtain access to tissue posterior and lateral to the nerve. Once the tissue is mobilized superiorly, all areolar tissue is cleaned off the hypogastric vessels to the level of the bifurcation of the common iliac artery. The large tissue bundle is clamped and removed en bloc. A tie or clips may be used at the level of the bifurcation.

Source: Reprinted with permission from Gallup DG, Talleo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA: WB Saunders Co.; 1994:58.

Transperitoneal Approach to the Paraaortic Nodes

The transperitoneal approach to the paraaortic lymph nodes can be accomplished by either the direct or the lateral approach. With the direct approach, the dissection begins with an incision in the peritoneum directly over the common iliac arteries and aorta. The lateral approach starts with an incision in the lateral paracolic gutters with subsequent medial reflection of the right and/or left colon. The advantage of the direct approach is that it involves less dissection of the intestine and ureter, whereas one of its main disadvantages is that it is associated with a greater degree of difficulty in exposing the left paraaortic nodes. Consequently, many surgeons sample the right paraaortic (paracaval) lymph nodes via the direct approach and use the lateral approach for the left-sided nodes.

With the direct approach to the right paraaortic nodes, an incision is made in the peritoneum overlying the right common iliac artery (Fig. 9.9). The incision is carried up over the aorta to the level of the duodenum. If the nodal dissection is to be carried out only to the level of the IMA, the duodenum may not need to be mobilized. Using blunt dissection, the ureter and ovarian vessels are identified and mobilized laterally. The lymphatic tissue lateral to the right common iliac artery is elevated and the caudal end is clipped and divided. The dissection then proceeds in a caudad-to-cephalad direction. A plane is created between the IVC and the lymphatic pedicle. The majority of the right paraaortic nodes overlie the IVC and they are generally easily dissected off the vessel. However, there is a fairly constant small

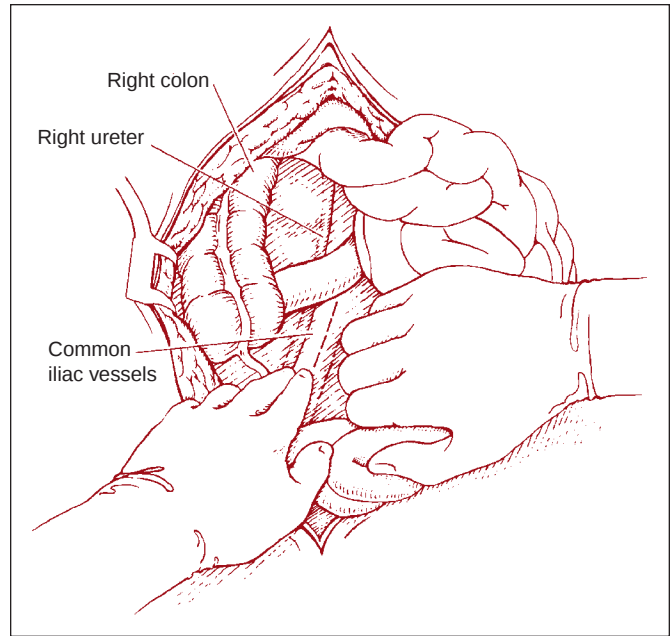


FIGURE 9.9. The small bowel is elevated out of the pelvis placing the mesentery on gentle traction. The right ureter and common iliac artery are identified and the peritoneum overlying the artery is incised.

vein within the lymphatics anterior to the IVC that inserts just above its bifurcation. If care is not taken to identify and ligate this so-called “fellow’s” vein early in the dissection, it can easily be torn with resultant heavy bleeding (1). When the most cephalad extent of the dissection is reached, the pedicle is clipped or coagulated and divided (Fig. 9.10).

If the nodes above the IMA need to be sampled, the third portion of the duodenum is mobilized by bilaterally incising the peritoneum around it and then sharply dissecting the areolar tissue underneath (4). The superior portion of the peritoneal incision can be carried up as high as the ligament of Treitz, which can also be divided if needed. Inferiorly, the peritoneal incision is extended over the right ureter around the cecum and up along the right paracolic gutter to mobilize the small bowel mesentery and part

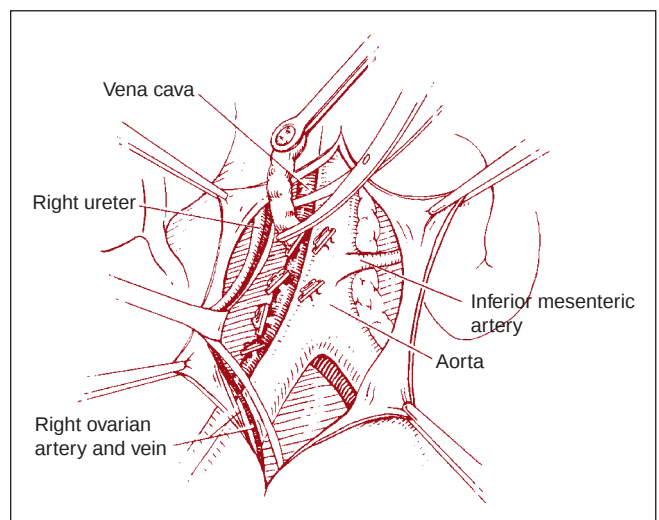


FIGURE 9.10. The specimen is dissected in a cephalad direction. Hemostatic clips are used on either side of the developing pedicle as it is mobilized and divided, and also at the most cephalad extent of the dissection before the specimen is removed.

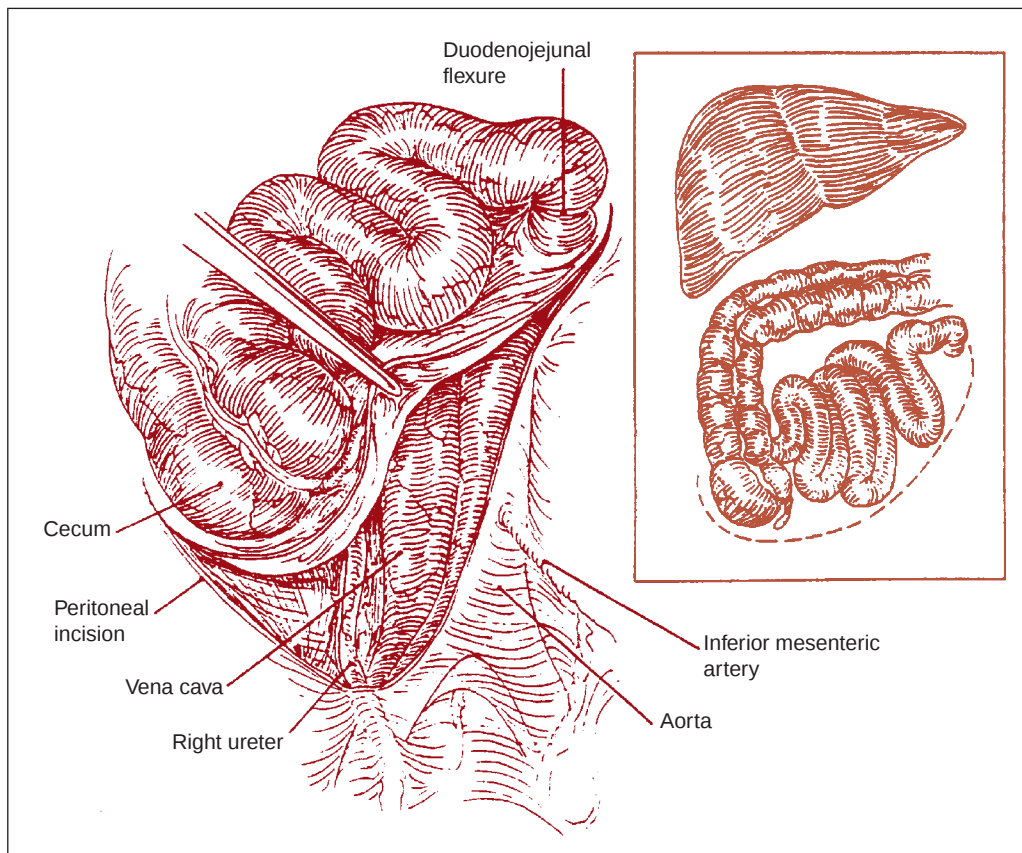


FIGURE 9.11. Extended peritoneal incision. The peritoneal incision is extended over the right ureter around the cecum and cephalad along the right paracolic gutter. This allows for mobilization of the small bowel mesentery as well as the ascending colon. Source: Reprinted with permission from Fowler JM, Johnson PR. Transperitoneal para-aortic lymphadenectomy. *Oper Tech Gynecol Surg* 1996;1:9.

of the right colon (Fig. 9.11) (4). The small bowel can then be packed into the upper abdomen or completely removed from the peritoneal cavity and stabilized outside of the abdominal cavity or put into a bowel bag outside the abdomen. The duodenum is retracted superiorly, allowing identification and ligation of the right ovarian artery and vein. The lymphatic tissue can then be safely dissected off of the right side of the aorta and the anterior surface of the IVC up to the level of the renal veins.

The left paraaortic lymph nodes may be removed through the same peritoneal incision. Sharp dissection is used to identify the left common iliac artery, left side of the aorta, IMA, left ureter, and left psoas muscle (Fig. 9.12). The ureter is again mobilized laterally. The lymphatic tissue lateral to the left common iliac artery and aorta is then removed in a caudad-to-cephalad direction. The left paraaortic lymph nodes lie lateral and partially behind the aorta. In dissecting these nodes, judicious use of vascular clips or the use of electrocautery will help prevent troublesome bleeding from the lumbar vessels. Safe removal of the lymph nodes above the IMA frequently requires identification and division of the left ovarian artery and vein, and occasionally ligation of the inferior mesenteric artery.

To remove right-sided paraaortic nodes via the lateral approach, the right paracolic gutter is incised along the line of Toldt (Fig. 9.13). The peritoneum is elevated off the psoas muscle and the incision is extended up to the hepatic flexure of the colon. Using sharp and blunt dissection, the right colon is reflected medially. The ureter and ovarian vessels can be identified attached to the undersurface of the reflected peritoneum. They may be left attached or mobilized laterally for better exposure. Further medial mobilization of the colon exposes the IVC and aorta. With the essential structures identified, the lymphatic tissue can then be dissected as previously described

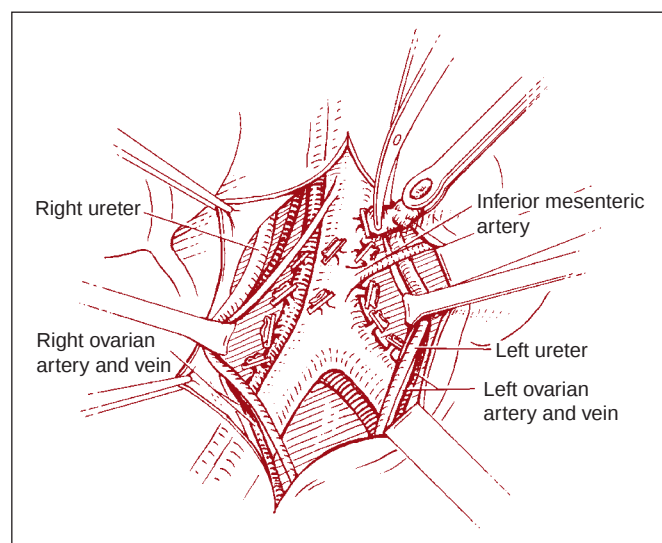


FIGURE 9.12. Removal of the left paraaortic nodes through the same peritoneal incision. The dissection also proceeds in a cephalad direction, again using hemostatic clips on the lateral and medial margins. Care should be taken to avoid injury to the inferior mesenteric artery that arises approximately 3 to 4 cm above the aortic bifurcation.

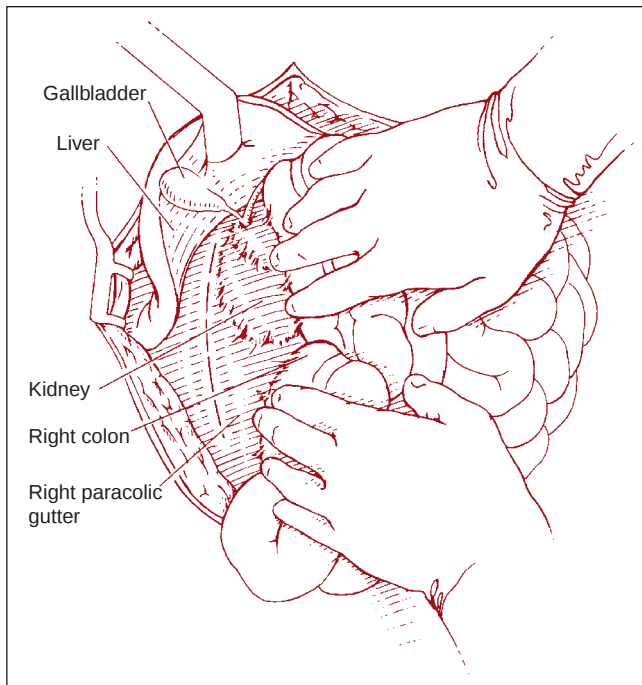


FIGURE 9.13. The right paracolic gutter is exposed by medial traction on the ascending colon. The gutter is incised along the line of Toldt.

in a caudad-to-cephalad direction up to the third portion of the duodenum (Fig. 9.14).

If the lymph nodes above the IMA need to be sampled, the Kocher maneuver is used to reflect the duodenum medially. The peritoneum lateral to the convexity of the C-curve of the duodenum is incised and the second portion of the duodenum is then dissected off of the IVC. For further exposure, the peritoneal incision along the line of Toldt may need to be extended cephalad to mobilize completely the hepatic flexure of the colon (Fig. 9.15). The right ovarian artery and vein are identified and divided. The right-sided paraaortic lymph nodes are then able

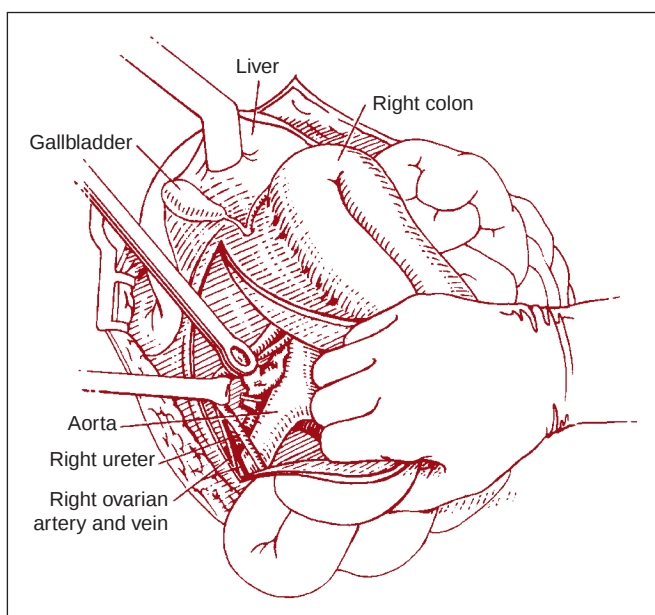


FIGURE 9.14. With the ureter and ovarian vessels identified, the dissection begins at the right common iliac artery and proceeds cephalad up to the third portion of the duodenum.

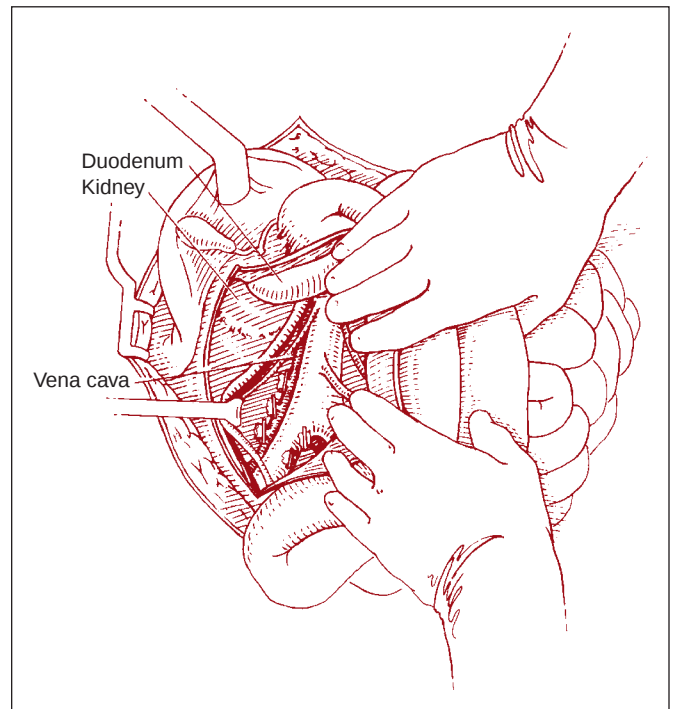


FIGURE 9.15. The Kocher maneuver can be used to gain access to the lymph nodes above the IMA. The peritoneum lateral to the convexity of the C-curve of the duodenum is incised and the second portion of the duodenum is then dissected off of the IVC. The common bile duct and pancreatic duct enter the second portion of the duodenum posteromedially. For further exposure, the incision along the line of Toldt can be extended cephalad to mobilize completely the hepatic flexure of the colon.

to be dissected off of the IVC and right aorta up to the level of the renal vessels.

The lateral approach to the left paraaortic lymph nodes is accomplished in a similar fashion by incising along the line of Toldt and mobilization of the left colon medially (Fig. 9.16).

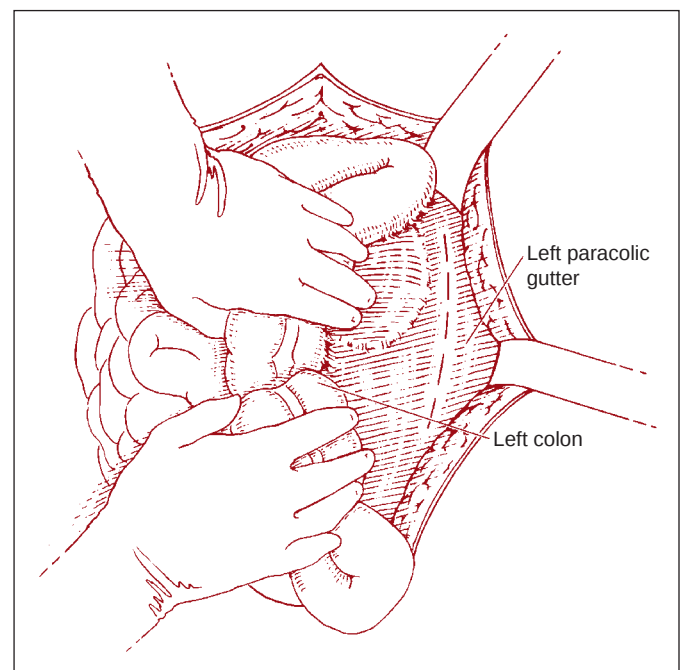


FIGURE 9.16. The lateral approach to the left paraaortic nodes is accomplished by retracting the descending colon medially and incising along the line of Toldt.

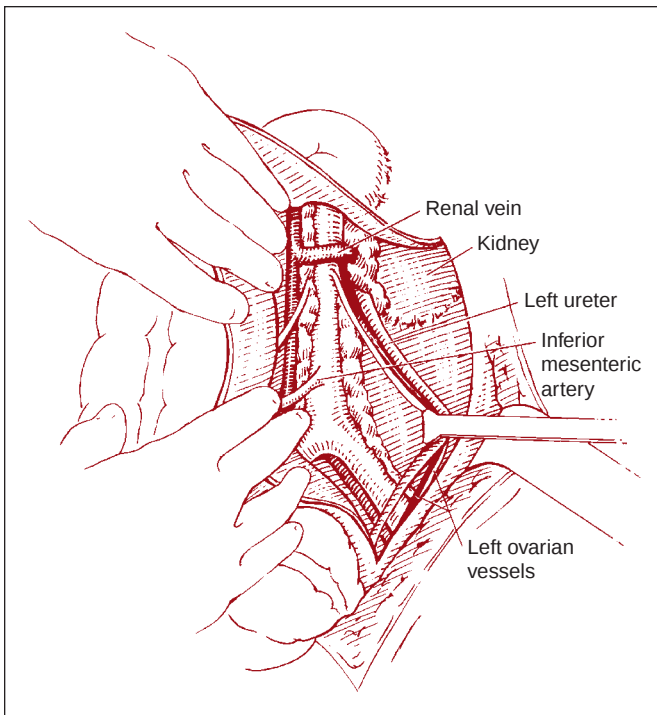


FIGURE 9.17. Using sharp and blunt dissection, the left colon can be mobilized medially, exposing the left ureter, ovarian vessels, and aorta.

Again, the ureter and ovarian vessels are identified on the undersurface of the reflected peritoneum, and they may be left attached or mobilized laterally for better exposure (Fig. 9.17). After further mobilization of the left colon and identification of the aorta and the IMA, the left-sided nodes are removed in a caudad-to-cephalad direction (Fig. 9.18). Dissection of the nodes

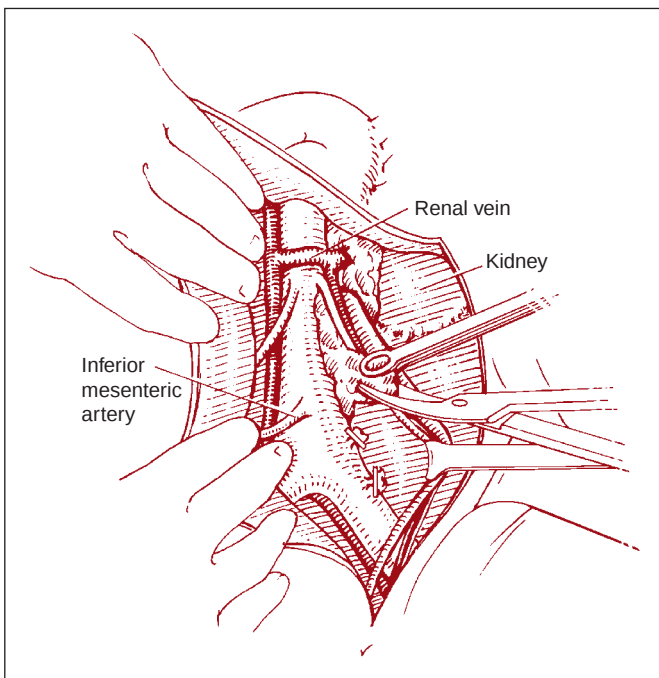


FIGURE 9.18. Dissection begins at the left common iliac artery and proceeds cephalad using hemostatic clips. Care should be taken to avoid injury to the inferior mesenteric artery that arises approximately 3 to 4 cm above the aortic bifurcation.

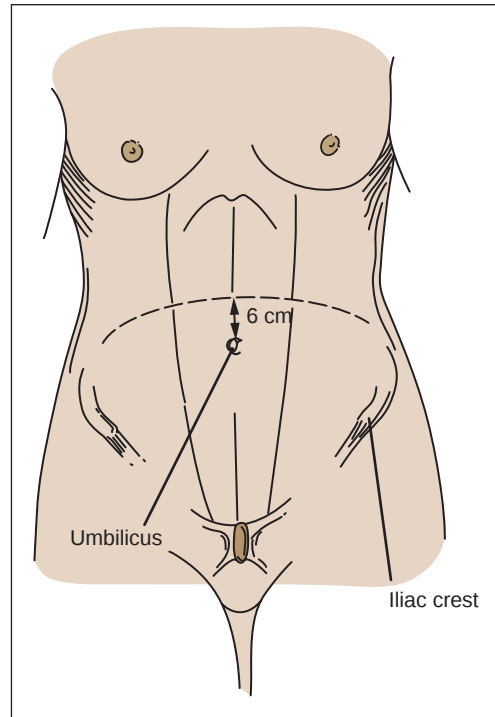


FIGURE 9.19. The “sunrise” incision. In the center, the incision is approximately 6 cm above the umbilicus. The incision is carried laterally in a downward fashion to the level of the iliac crests.

Source: Reprinted with permission from Gallup DG, Talleo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:118.

above the IMA requires mobilization of the splenic flexure of the colon, division of the left ovarian artery and vein, and occasionally ligation of the inferior mesenteric artery.

Extraperitoneal Approach to the Paraaortic Nodes

The extraperitoneal approach to the paraaortic lymph nodes by means of a supraumbilical transverse sunrise incision was initially described by Gallup et al. (11). The skin incision is made 6 cm above the umbilicus in the midline and is carried laterally and caudad to the level of the iliac crests bilaterally (Fig. 9.19) (2).

The fascia is incised transversely. The rectus muscles are dissected off of the anterior-lying fascia cephalad and caudad. The right rectus muscle is transected. The right transversus muscle is then identified and transected caudally and laterally. The hand of the operator is inserted deep into the incision until the right psoas muscle and external iliac vessels are palpated. The peritoneum is then bluntly dissected from caudad and lateral to cephalad and medial, separating it from the underlying common iliac vessels until the great vessels are exposed (Fig. 9.20) (2). If the peritoneum is inadvertently entered, it must be closed immediately.

After identification of the right ureter and ovarian vessels, the right paraaortic nodes can be removed. In thin patients, the left paraaortic nodes may be able to be removed through a right abdominal approach. However, if exposure is difficult, the left rectus and transversus muscles can be transected and the peritoneum mobilized medially in a similar fashion to gain access to the left paraaortic nodes.

Radical Hysterectomy

Although radical hysterectomy is a traditional procedure in gynecologic oncology, with a history of almost 100 years, its performance is still poorly standardized. Different terminology and

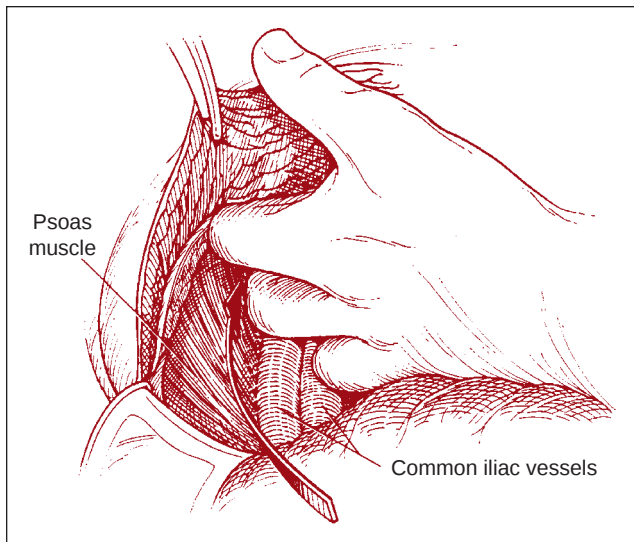


FIGURE 9.20. With the rectus and transversus muscles transected, the operator's hand is inserted caudad until the psoas muscle and external iliac vessels are palpated. The peritoneum is then bluntly dissected from caudad and lateral to cephalad and medial, separating it from the underlying common iliac vessels until the aorta and vena cava are exposed.
Source: Reprinted with permission from Gallup DG, Talledo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:121.

classifications are currently used to describe individual types of the procedure. As a consequence, the extent of the parametria resection may vary substantially between institutions and surgeons, even if the same terminology is used.

There are several key principles for the classification of radical hysterectomies. First, the key and sole parameter for differentiation between types of radical hysterectomy should be the extent of parametria resection. The resection or removal of other organs or structures should not determine the type of the procedure, including the size of vagina resection. Second, the extent of resection should be precisely defined for all three parts of the parametria (ventral, lateral, dorsal) and in three planes (sagittal, frontal, and transverse) (Fig. 9.21). Mainly surgical margins in vertical (deep parametrial) dimension determine long-term morbidity due to the localization of vegetative nerves

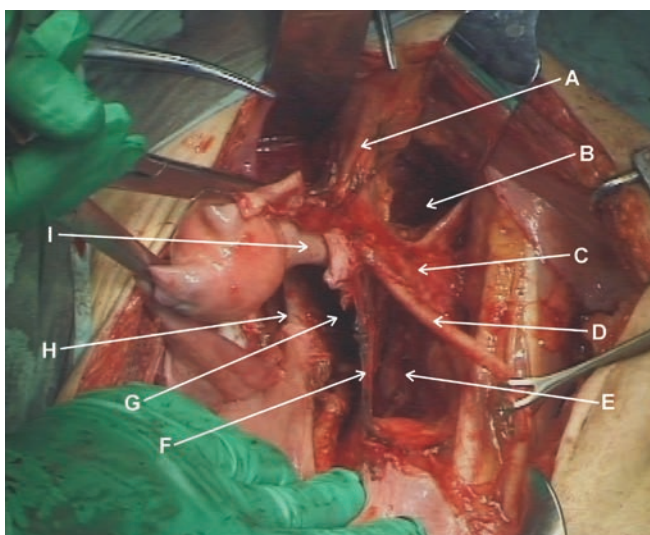


FIGURE 9.21. Three parts of the parametria. **A.** ventral parametrium; **B.** paravesical space; **C.** lateral parametrium; **D.** ureter; **E.** pararectal fossa; **F.** dorsal parametrium; **G.** sacro-uterine space; **H.** rectum; **I.** cervix.

Table 9.1 Proposed Classification System and Corresponding Historical Types of Radical Hysterectomy

New Classification System	Corresponding Types
A	Extrafascial hysterectomy
B	Modified radical hysterectomy Type II radical hysterectomy
C1	Nerve sparing radical hysterectomy
C2	Type III radical hysterectomy Classical/standard radical hysterectomy
D	Laterally extended parametrectomy

in the caudal part of all 3 parts of the parametria. Third, the extent of the procedure and its classification may be different on each side of the cervix if the tumor growth is asymmetrical. Fourth, although the classification system is usually proposed for radical hysterectomy, it is applicable to the radical trachelectomy and the radical parametrectomy.

Two classification systems are most frequently used in the current literature. The classical one published by Piver, Rutledge, and Smith in 1974 classified radical hysterectomy into five types, but the type II and III procedures, which are the most clinically relevant, are the best described (14). Recently, a new system has been proposed by Querleu and Morrow (15) and later extended into three dimensions (16).

Five types of the procedure (A, B, C1, C2, and D) correspond well to other common historical types of radical hysterectomy (Table 9.1). Several aspects make the new classification system unique: the system a) recognizes the size and type of parametrial resection as crucial and the sole parameter for classification, b) includes new type of nerve sparing procedure, c) uses stable anatomic landmarks for the description of surgical resection margins, and d) identifies surgical landmarks in three planes—frontal, sagittal, and horizontal.

The type B radical hysterectomy corresponds mostly to the type II or modified radical hysterectomy. The aim of the procedure is to remove limited parts of the lateral and dorsal parametria (Figs. 9.22, 9.23, and 9.24). The ureter must be identified in the parametrium, unroofed, dissected from the cervix and displaced laterally. The resection margin is indicated by the ureteral bed. The ureteral artery, branching from the uterine artery at its crossing of the ureter, can serve as a helpful lateral landmark. Dorsally, type B aims at the resection of 1 to 2 cm of the dorsal parametria. Identification of autonomic nerves is not required, as it remains preserved in the parametria deeply below the resection margins.

A major intention of the nerve sparing (C1) radical hysterectomy is to remove corresponding parts of ventral, lateral, and dorsal parametria but, at the same time, preserve major autonomic nerve supply to urinary bladder, upper vagina, and rectum (Figs. 9.22, 9.23, 9.24). Two types of vegetative nerves can be identified and spared: (a) the inferior hypogastric plexus, running in the lateral part of the dorsal parametrium, laterally to the cervix below the ureter at the level of the vaginal fornix and ventrally in the infraureteral part of the ventral parametrium towards the urinary bladder; and (b) the splanchnic nerves localized at the bottom of the lateral pararectal space and in the caudal part of the lateral parametrium below the parametrial veins. Surgical margins for the nerve sparing procedure must be kept above the course of the nerve structures in the ventral, lateral and dorsal parametrium. Dorsally, the nerve sparing procedure requires a dissection of two parts of the dorsal parametrium. The mesoureter (fine structure stretched

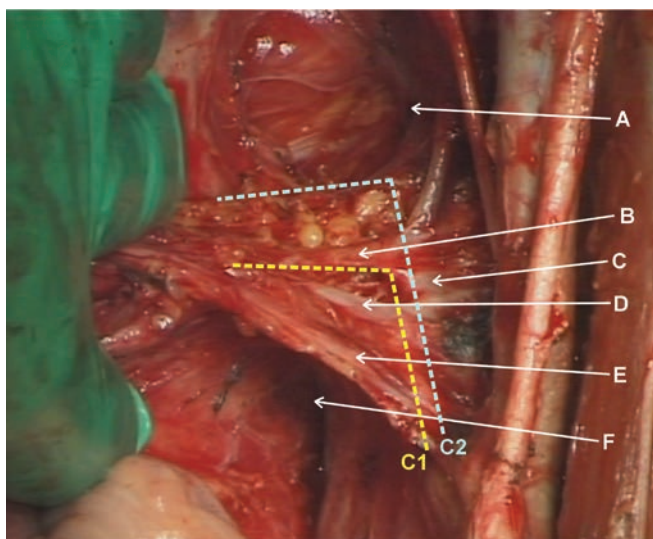


FIGURE 9.22. Resection lines for types B, C1, and C2 radical hysterectomy on the lateral parametrium. **A.** paravesical space; **B.** vaginal vein; **C.** internal iliac vein; **D.** uterine vein; **E.** uterine artery; **F.** pararectal fossa.

between the ureter and the sacral bone), containing major branches of the hypogastric plexus, is separated laterally from the uterosacral ligament, which allows for an adequate resection of the latter. On the lateral parametrium, the caudal resection margin is indicated by the vaginal vein, the largest parametrial vein, which guarantees the preservation of splanchnic nerves in the caudal part of the lateral parametrium. Ventrally, the ureter is only partially dissected from the ventral parametrium, allowing for limited resection of the proximal supraureteral part of the ventral parametrium.

The radicality of the C2 procedure, which corresponds to the type III radical hysterectomy, is different from the nerve sparing procedure, aiming at removal of the majority of all three parametrial parts (Figs. 9.22, 9.23, and 9.24). The C2 procedure requires complete dissection of the ureter from the lateral and ventral parametria and deeper dissection of the rectum from the dorsal parametria. The resection line on the dorsal parametria is deep below the former rectal attachment, causing unavoidable damage of the hypogastric plexus, so the dissection of the nerve from the uterosacral ligament is not required. The lateral

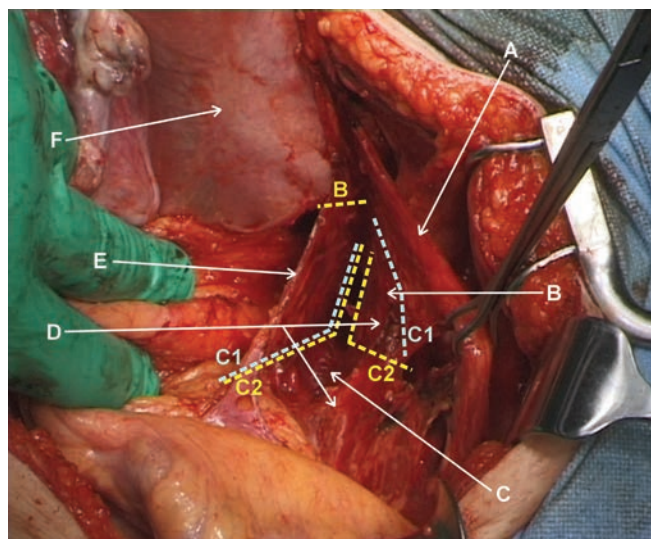


FIGURE 9.24. Resection lines for types B, C1, and C2 radical hysterectomy on the dorsal parametrium after dissection of the mesoureter from the sacrouterine ligament. **A.** ureter; **B.** mesoureter; **C.** space between the sacrouterine ligament and mesoureter; **D.** branches of the hypogastric plexus (white strips); **E.** sacrouterine ligament; **F.** cervix.

parametrium is completely separated from the pelvic side wall until the sacral bone is reached. On the ventral parametrium the ventral resection margin is formed by the urinary bladder. As a consequence, major branches of vegetative nerves are sacrificed during the C2 type procedure.

Ovarian Cancer Debulking

The goal of ovarian cancer debulking or cytoreduction is to remove all or as close as possible to all grossly visible and palpable tumor (17). The surgeon operating on patients with advanced ovarian cancer should be familiar with the techniques used to clear tumor from the pelvis and the upper abdomen.

Removal of Pelvic Disease

Ovarian malignancy often presents with large pelvic masses filling the pelvis. An initial incision over the lateral pelvic sidewall just anterior to the external iliac artery will allow adequate visualization of the ureter and the ovarian vessels (Fig. 9.25). The paracolic gutters can be incised cephalad along the avascular line of Toldt for more adequate exposure of the retroperitoneal space. To avoid further troublesome hemorrhage with large adnexal masses, if a hysterectomy is part of the planned procedure, the uterine vessels can be separately isolated and divided similar to a modified radical hysterectomy. When the anatomy is distorted by peritoneal implants, the ureters may need to be followed down to the tunnel and retracted laterally prior to removal of the uterus.

In cases where the pouch of Douglas is deeply infiltrated by disease, especially if it involves the rectosigmoid colon, a reverse hysterectomy can facilitate complete removal of the infiltrated peritoneum and help identify the rectovaginal plane sparing a larger part of the rectum for further anastomosis. The term modified posterior exenteration is commonly used for the above procedure, as it aims at en bloc removal of the uterus, adnexa, infiltrated peritoneum, and the rectum. The procedure starts with the incision of the vesical peritoneal plica and dissection of the urinary bladder down to the level of the vaginal fornix. In cases of carcinomatosis on the peritoneal plica, a ventral peritonectomy—complete dissection of the infiltrated peritoneum

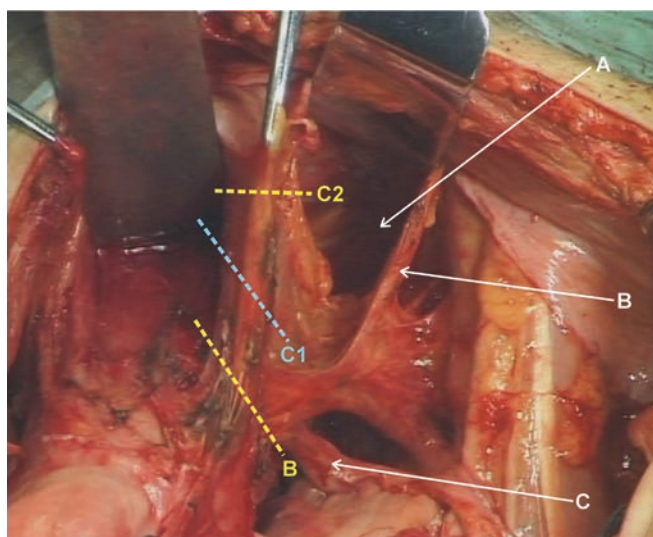


FIGURE 9.23. Resection lines for types B, C1, and C2 radical hysterectomy on the ventral parametrium. **A.** paravesical space; **B.** umbilical ligament; **C.** ureter.

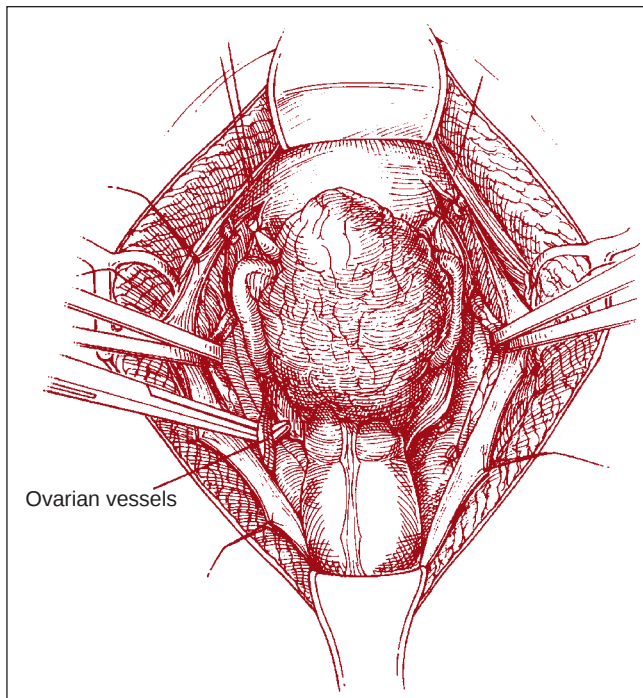


FIGURE 9.25. The ovarian vessels are skeletonized and divided at the pelvic brim. Early control of these vessels will help reduce blood loss during the later dissection. The ureter can be mobilized off the medial leaf of the broad ligament and retracted laterally on a Penrose drain or vessel loop.

Source: Reprinted with permission from Gallup DG, Talledo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:92.

from the urinary bladder—is part of the procedure. The retroperitoneum is opened laterally above the large vessels, both round ligaments are cut, the ureters are identified, and then the ovarian vessels are ligated and cut. The peritoneum is dissected from both ureters and the sigmoid colon is divided above the level of tumor infiltration. In some cases the infiltrated peritoneum is densely adherent to the ureter in the lateral parametria, so the complete removal of the tumor requires unroofing of the ureter in its parametrial part, and its dissection from the cervix and infiltrated parametria, identical to that performed during a radical hysterectomy. Once the uterine vessels are ligated bilaterally, the rectovaginal space between the vagina and the infiltrated pouch of Douglas is opened, the uterosacral ligaments are cut, and a reverse hysterectomy is completed by the incision of the vagina at the level of the vaginal fornix (Fig. 9.26). The vagina is sutured. At this stage, the specimen is fixed in the pelvis only by the rectum and pararectal ligaments. It allows for the retraction of the specimen cephalad, and in most cases partial cranial dissection of the infiltrated pouch of Douglas from the rectum, aiming at preservation of a larger part of the rectum for further anastomosis. After cutting pararectal ligaments, the exenterative part of the procedure is completed by the incision of the rectum below the level of tumor involvement. Low rectal anastomosis in this setting is generally performed and, in well-trained hands, is associated with a low rate of complications (18,19).

Upper Abdominal Disease

A recent meta-analysis by Bristow et al. demonstrated that expert centers with primary optimal cytoreduction rates of 75% or greater provided their patients with a 50% improvement in overall survival when compared to less experienced centers with primary optimal cytoreduction rates of 25% or less (20). A subsequent study by Chi et al. illustrated that in order to achieve primary optimal cytoreduction rates of 75% or more in

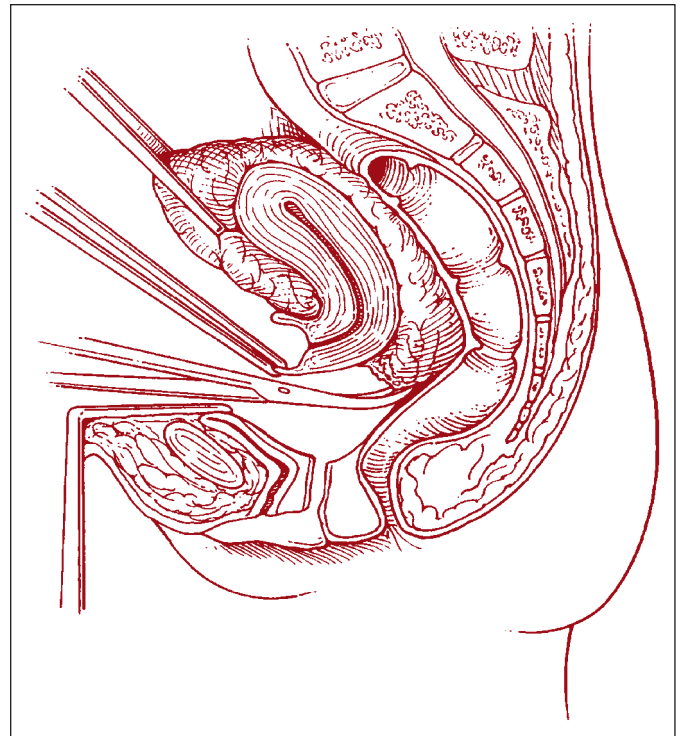


FIGURE 9.26. The posterior vaginal wall is grasped and retracted cephalad. The uterus can now be sharply dissected off of the rectosigmoid.

Source: Reprinted with permission from Gallup DG, Talledo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:103.

advanced-stage ovarian cancer patients, the surgeon's armamentarium should include the ability to remove disease involving upper abdominal structures such as the liver, diaphragm, spleen, and pancreas (5).

Adequate exposure is the most important factor in determining whether resection of diaphragm disease can be performed safely (7). Once an exploratory laparotomy has been performed and the presence of bulky diaphragm disease confirmed on one or both hemidiaphragms, the midline incision is extended to the xiphoid process. For maximum exposure, the incision can be extended to the sternum to the right of the xiphoid, or in some cases the xiphoid can be divided or removed. The procedure can almost always be performed through this midline incision, and although extending a subcostal incision 2 to 3 cm below the costal margin has been described, we have not generally found this to be necessary.

The extent of liver mobilization required depends on the distribution of tumor involving the hemidiaphragm. Large volume disease is common on the right side, and a greater proportion of the right hemidiaphragm is obscured by the liver. A right-sided liver mobilization will be described primarily. Tumor involvement on the left diaphragm is more easily resected without fully mobilizing the liver, although in certain cases splenectomy may be necessary to clear the metastatic deposits on the left diaphragm.

The infrahepatic edge of the falciform ligament containing the ligamentum teres is grasped between two Kelly clamps, and is divided and ligated. The suture on the lower edge is left long to aid with downward traction of the liver and remaining falciform ligament. The falciform ligament should be transected all the way to the coronary ligament. This can be used for traction of the liver. The coronary ligament is incised from the falciform to the right triangular ligament. Care must be taken in the area of the hepatic notch. The hepatic notch contains the right hepatic vein as it enters the inferior vena cava and is found lateral to the

union of the falciform and coronary ligaments. If further mobilization of the liver is necessary, the lateral attachments may be incised and the liver bluntly lifted off Gerota's fascia of the right kidney and diaphragm.

The extent of diaphragm peritonectomy is determined by the distribution of the tumor implants, and the method can be modified accordingly. When a full right diaphragm peritonectomy is performed, the peritoneum on the anterior edge of the diaphragm is incised along the costal margin using either cautery or Metzenbaum scissors. This anterior free edge is grasped with several Allis or Mixer clamps, which are then retracted inferiorly to visualize the line of attachment between the diaphragm and its overlying peritoneum. The plane between is developed with a combination of blunt and sharp dissection as determined by the patient's tissue laxity and/or peritoneal adherence. This may not be possible if the tumor has extended through the peritoneum and diaphragm.

If tumor implants are securely fixed to the diaphragm muscle and/or are suspicious for full thickness diaphragm involvement, diaphragm resection should be considered. The technique for diaphragm resection depends largely on the size of the lesion to be resected. Small penetrating lesions can be resected using the EndoGIA stapler alone without entering the pleural cavity. The lesion is grasped with a long Allis clamp, the diaphragm tented downward away from the lung, and the EndoGIA used to staple and divide the tented diaphragm and invasive lesion. Larger lesions require entry into the pleural space and this is generally performed sharply with a Metzenbaum scissors to avoid an inadvertent cautery burn to the lung. Once entered and the lung visualized/retracted, cautery can be used to circumscribe the lesion and resect it en bloc with the peritoneal, muscular, and pleural layers. The defect can almost always be closed primarily with limited tension, using interrupted horizontal mattress or figure-of-eight permanent sutures. Larger defects that cannot be closed primarily without significant tension should be closed with a permanent mesh secured to the peritoneal diaphragm surface with interrupted permanent sutures (21). The majority of patients undergoing diaphragm resection can have their pleural cavity closed and the air from the thorax evacuated using the red Robinson catheter. A purse-string suture is placed widely around the hole and a #14 French red Robinson catheter is passed through the hole into the pleural cavity. The anesthesiologist is asked to give the patient a maximal inspiration, suction may be applied to the catheter, and the catheter is pulled as the purse-string suture is tied down. For patients undergoing more extensive resections or with other reasons to benefit from prolonged pleural drainage, such as pleurodesis, a chest tube can be placed in the operating room and removed postoperatively as required.

To remove tumor from the left upper quadrant, occasionally a splenectomy with or without distal pancreatectomy is required. Usually, the initial step is to enter the lesser sac to evaluate the posterior aspect of the stomach and pancreas. The gastrosplenic ligament and then the short gastrics are carefully divided. The spleen is mobilized medially and out of the left upper quadrant by dividing the splenophrenic and splenocolic ligaments and the other attachments to the adrenal gland and Gerota's fascia of the left kidney. The spleen can now be elevated out of the splenic bed and into the incision. The splenic hilum is now grasped between the fingers. Palpation of the pancreas is attempted. Identification of the pancreas may be facilitated by viewing the hilum posteriorly. The anterior splenorenal ligament is entered sharply. The splenic artery and vein can then be identified. These vessels should be ligated and divided separately. The splenic vessels may also be ligated prior to elevating the spleen in cases where lateral mobilization is not possible secondary to tumor and/or dense adhesions. A linear stapler may be placed across the tail of the pancreas if necessary to remove tumor involving the distal pancreas and/or splenic hilum. Reinforcement of this staple

line with 3-0 delayed absorbable suture, either continuously or interrupted, is optional.

Continent Urinary Diversion

Over the past two decades, interest in performing continent urinary diversions for patients with gynecologic malignancies has emerged. Most gynecologic oncologists will use a modification of the Indiana (22) or Miami (23) pouch. Poor candidates for continent urinary diversion include those with crippling arthritis or those psychologically unable to tolerate frequent self-catheterization of the pouch.

A modification of these pouches is shown (2). The colon is transected just proximal to the hepatic flexure (Fig. 9.27). The colon is then detubularized by a longitudinal incision along the tinea. The continent mechanism is created by two maneuvers. First, the terminal ileal segment is tapered down over a #14 French Foley catheter by using a gastrointestinal anastomosis (GIA) stapling device along the antimesenteric border of the ileum. The second maneuver is to plicate the ileocecal valve by placing concentric purse-string sutures of 0 silk or polypropylene around it. The ureters are then implanted under direct vision (Fig. 9.28) (2). After closing the pouch, the ileal stoma can be brought out in several areas of the abdominal wall (Fig. 9.29) (2). Some use the umbilicus as the exit site. The ureteral stents can exit the abdomen via the ileal stoma or through separate incisions in the pouch and abdominal wall. The use of a Penrose drain and a cecostomy tube for irrigation to remove mucus is optional.

Abdominal Closure

With the advent of more recently published closure methods and newer suture materials, the vertical, allegedly stronger paramedian incision is unnecessary. A midline incision is preferable in modern-day gynecologic oncology. It is the least hemorrhagic of all incisions, and rapid entry is feasible. Exposure is excellent, and minimal nerve damage occurs.

In the past, many surgeons have advocated the relatively time-consuming Smead-Jones closure (24). However, in the 1980s it was noted that midline incisions could be safely closed with a running, mass closure. In 1989, Gallup et al. (25) reported on 210 patients, most of whom were at high risk for evisceration. In those who had midline incisions closed with a running, mass closure using #2 monofilament polypropylene suture, no eviscerations occurred. Since that publication, several series have published excellent results using monofilament absorbable or monofilament permanent sutures in a running, mass closure method (26–28). Fascial closure should be performed with a suture length to wound length ratio of at least 4:1 (29). In addition, a randomized trial in nongynecologic cancer patients demonstrated that placement of fascial sutures 5 to 8 mm from the fascial edge (as compared to the traditional >10 mm from the fascial edge) results in fewer surgical site infections and fewer ventral hernias (28).

SURGICAL MANAGEMENT OF GYNECOLOGIC CANCER

The gynecologic oncologist must be able to evaluate the woman with a genital tract malignancy, direct her management, perform the necessary surgical procedures, and supervise her postoperative care and surveillance. A patient who is managed by a surgeon who is not a gynecologic oncologist may receive an operative procedure that is inappropriate or inadequate. Over 20 years ago, McGowan et al. (30) reviewed the intraoperative evaluation of

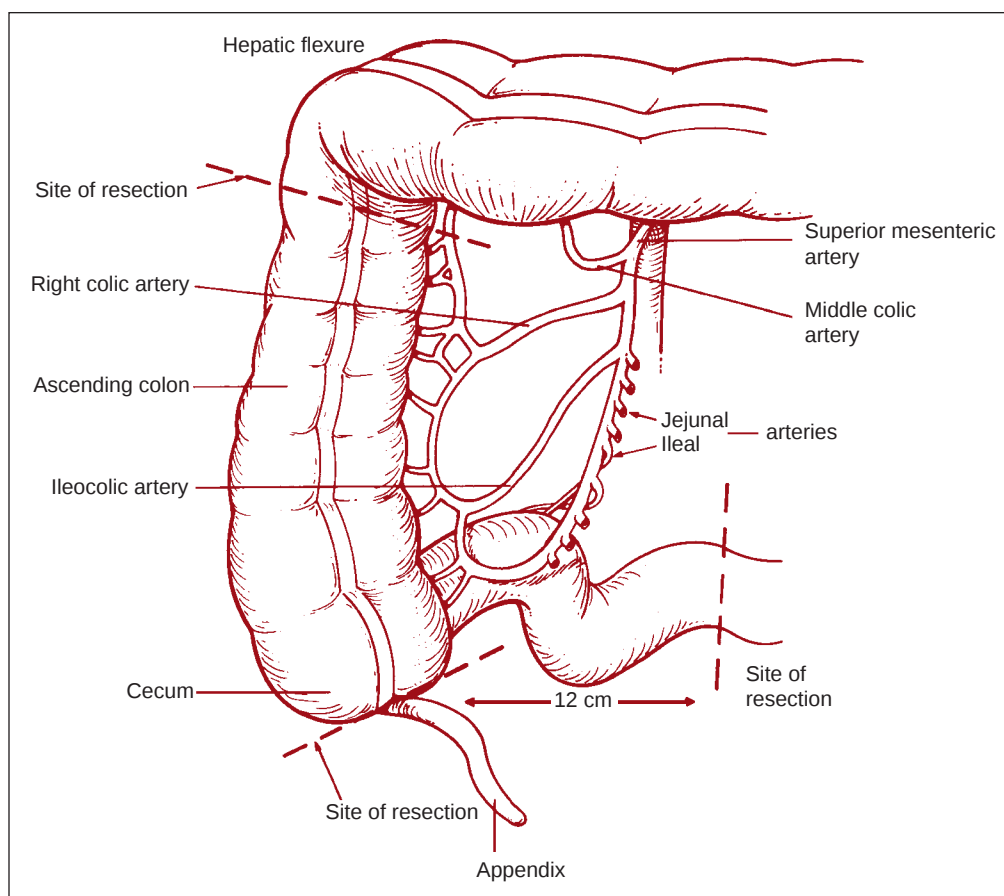


FIGURE 9.27. The anatomic location and vascularity of the right colon segment utilized for formation of the continent urinary pouch. Illustrated are the anatomic sites of division for creation of the continent pouch. The ascending colon is divided distal to the right colic artery. The terminal ileum is divided approximately 12 cm from the ileocecal valve. The resection can be accomplished with the use of surgical staplers or by intestinal clamps. If the appendix is present, it should be removed. The ileocecal segment has a rich blood supply derived from the right colic artery and the ileocolic artery. If one is performing the Miami pouch type of urinary diversion, the transverse colon would be divided distal to the middle colic artery.

Source: Reprinted with permission from Gallup DG, Talledo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA: WB Saunders Co.; 1994:186.

291 women with primary ovarian cancer. Ninety-seven percent of the patients who underwent surgery by a gynecologic oncologist received complete staging operations, but only 52% and 35% had adequate operations performed by an obstetrician-gynecologist or a general surgeon, respectively.

Two more recent British studies retrospectively analyzed the outcomes of over 1,800 patients with ovarian cancer (31,32). Both studies found on multivariate analysis that patients' survival was adversely affected when their initial operation was performed by a general surgeon, as opposed to a gynecologic surgeon. These results are similar to those obtained by Nguyen et al. in an American national survey of ovarian carcinoma (33). Eisenkop et al. analyzed the outcomes of 263 patients with stages IIIC and IV ovarian carcinoma (34). When the primary surgery was performed by gynecologic oncologists, as compared to general obstetricians-gynecologists and general surgeons, the rate of optimal cytoreduction was significantly higher, the operative mortality substantially lower, and the median survival significantly longer.

Accordingly, other countries have attempted to centralize the care of patients with ovarian cancer so that they are primarily operated on by gynecologic oncologists (35,36). However, patterns of care studies in the United States have demonstrated that a significant percentage of women with ovarian cancer are not receiving their primary treatment from gynecologic oncologists (37,38). Consequently, in this country, many women with ovarian cancer are still not receiving the recommended comprehensive primary surgery (39,40).

In the four decades since the establishment of gynecologic oncology as a subspecialty, cancer therapy has become increasingly sophisticated and complex, and it is difficult for any one physician to master all the skills necessary for treating gynecologic malignancies. More often, we must use multimodal therapy and participate in multidisciplinary care. There are many medical and radiation oncologists who have specialized in gynecologic cancer, and they are integral members of the multidisciplinary team. The Gynecologic Oncology Group (GOG), with its emphasis on multidisciplinary research, has demonstrated the effectiveness of such an approach.

Another important factor in providing optimal patient care is the environment in which gynecologic oncology is practiced. The facilities used by the gynecologic oncologist should offer state-of-the-art radiation therapy and chemotherapy. Patients should receive care tailored to the type and extent of their disease and not have their treatment determined by the limitations of the available facilities. Mortality rates for complex oncologic procedures, such as pelvic exenteration, have been demonstrated to be significantly lower in hospitals where the procedures are performed with a relatively high volume as compared to those in which the procedures are performed infrequently (41). The recent meta-analysis performed by Bristow et al. evaluated 81 studies involving 6,885 patients with advanced ovarian cancer (20). This study demonstrated a 50% increase in median survival if patients' primary surgery was performed at an "expert" center compared to less experienced centers.

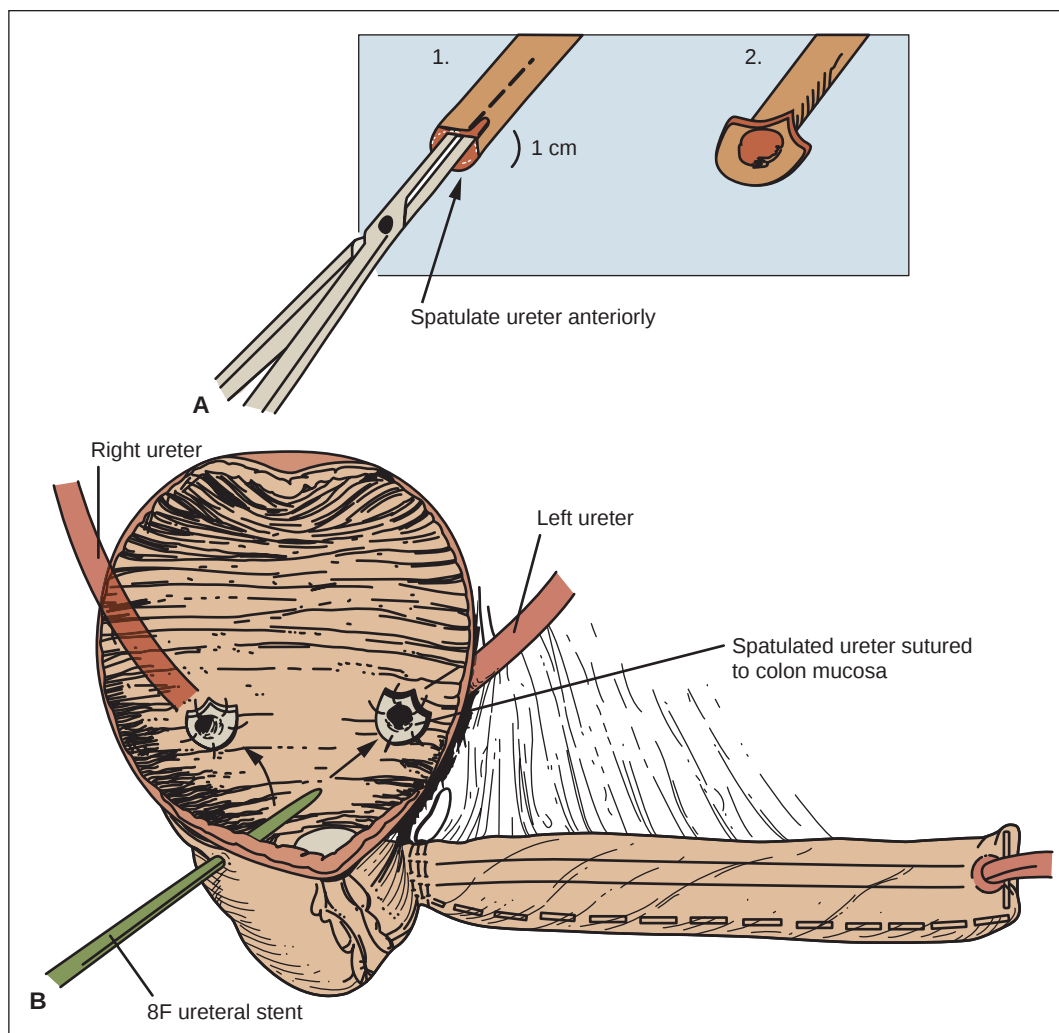


FIGURE 9.28. A, B: Prior to beginning the continent diversion, the ureters have been transected (usually at the pelvic brim) and mobilized so that they are able to be brought to the area where the continent pouch will be located without tension. If necessary, the left ureter can be brought through or under the mesentery of the colon to facilitate its placement into the urinary pouch. An appropriate site is selected on what will be the posterior wall of the pouch, and a long thin clamp is used to perforate the colon and pull the ureter through. An approximately 1-cm segment of ureter is brought into the pouch. For ease of ureterointestinal anastomosis, the ureter should be secured posteriorly to the pouch by suturing the adventitial tissue of the ureter to the seromuscular layers of the pouch with 3 or 4 permanent 3-0 sutures. The ureter is spatulated to increase the lumen diameter. The ureter is sutured directly to the colon and is not tunneled. We use 4-0 polyglycolic suture. This is a full-thickness approximation of the colon and ureter. Once both ureters have been sutured into the pouch, 2 #8 French ureterointestinal stents or long pediatric feeding tubes are placed retrograde into the renal pelvis. If a feeding tube is used, it should be sutured to the ureter with 4-0 chromic to ensure against displacement due to ureteral peristalsis. Note the 3 concentric sutures at the ileocecal valve.

Source: Reprinted with permission from Gallup DG, Talleo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA:WB Saunders Co.; 1994:191.

Early Diagnosis and Prevention

There is a role for early diagnosis and prevention in virtually all female genital cancers. The management of a patient with an abnormal Papanicolaou (Pap) smear allows the gynecologic oncologist to use limited surgery to prevent the development of an invasive malignancy of the cervix or vagina. Guided by colposcopy, the surgeon can employ traditional surgical excision, laser surgery, cryotherapy, or a loop electrosurgical excision procedure (LEEP) to preserve function and prevent cancer. Preinvasive lesions of the vulva can be diagnosed and managed by laser or local excision, thereby potentially avoiding progression to invasive disease and its associated extensive surgical therapy.

The proper management of endometrial hyperplasia can prevent the subsequent development of endometrial cancer. Optimal management requires individualization of treatment. Complex hyperplasia without atypia in a premenopausal patient indicates

the need for medical therapy with progesterone, but a similar problem in a postmenopausal patient may indicate the need for a hysterectomy. Atypia in either case requires consideration of hysterectomy to prevent the development of endometrial cancer. It is essential that the gynecologic oncologist recognize the significance of these cancer precursors.

No diagnostic test or early symptoms reliably herald the onset of ovarian or tubal cancer, and no preinvasive lesion has been identified. The only method of prevention for these cancers is surgical removal of the tubes or ovaries before cancer develops. Although it occurs very rarely, some women may have an identified lifetime risk of as high as a 40% of developing ovarian cancer. These are women who have a family history of ovarian cancer, who have a family history of breast and ovarian cancer, or who are members of hereditary nonpolyposis colorectal cancer (HNPCC) families. These cancer-prone families are described elsewhere in this book. These syndromes are seen infrequently,

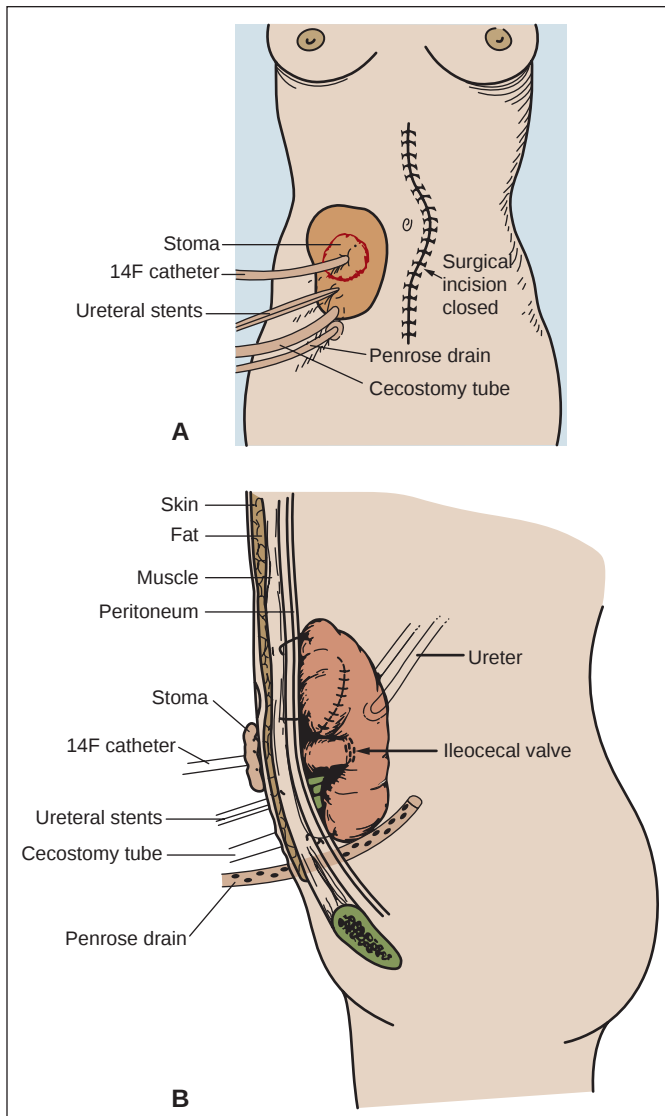


FIGURE 9.29. A, B: The site for the ileal stoma is selected on the anterior abdominal wall and then incised through all abdominal tissue layers. The stoma is created for catheterization and the #14 French catheter should exit the pouch through this stoma. It is critical that the ileal segment be at a 90° angle with the abdominal wall so that catheterization is a “straight shot.” The pouch may be sutured to the abdominal wall to accomplish this. All stents and drainage tubes are brought out through the anterior abdominal wall and secured. The pouch may also be anchored posteriorly (i.e., to the sacrum). Source: Reprinted with permission from Gallup DG, Talleo OE. *Surgical Atlas of Gynecologic Oncology*. Philadelphia, PA: W.B. Saunders Co.; 1994:193.

and certain criteria must be fulfilled before the diagnosis can be made. For women who fall into one of these high-risk categories, surgical removal of the tubes and ovaries (and the uterus in HNPCC) should be considered after childbearing is complete (42,43). Before that time, close monitoring is essential.

Diagnosis and Staging

The diagnosis of any gynecologic cancer requires a surgical biopsy. The manner in which the histologic diagnosis is obtained varies with the disease and the clinical situation. A punch biopsy or an instrument biopsy may be sufficient for the diagnosis of an invasive cancer of the vulva, vagina, or cervix, but an excisional biopsy is necessary for the diagnosis of microinvasive or preinvasive cancer. A fine-needle aspiration biopsy for cytologic analysis

Table 9.2 FIGO Staging of Gynecologic Cancers

Site	Staging
Vulva	Surgical and pathologic staging
Vagina	Clinical staging
Cervix	Clinical staging
Corpus (endometrium)	Surgical and pathologic staging
Corpus (sarcoma)	Surgical and pathologic staging
Fallopian tube	Surgical and pathologic staging
Ovary	Surgical and pathologic staging
Gestational trophoblastic disease	FIGO staging (clinical)
	WHO classification (risk-oriented)

FIGO, International Federation of Gynecology and Obstetrics; NIH, National Institutes of Health; WHO, World Health Organization.

may be adequate for establishing the extent of spread of a cancer, but not for providing histologic cell type and grade for the primary diagnosis. The histologic diagnosis of ovarian or fallopian tube carcinoma requires surgical exploration.

The current International Federation of Gynecology and Obstetrics (FIGO) staging system of gynecologic cancers requires surgical staging for vulvar, endometrial, and ovarian cancer. Cervical cancer remains a clinically staged disease, although many centers use surgical staging (by laparotomy or laparoscopy) for treatment planning. Table 9.2 lists the current methods of staging for the various gynecologic malignancies.

The initial surgical procedure in a patient with known or suspected gynecologic cancer should be performed by a trained gynecologic oncologist because the accuracy of diagnosis and staging significantly influences subsequent therapy. As stated earlier, numerous studies have demonstrated that ovarian cancer staging operations performed by general obstetricians-gynecologists or general surgeons are inadequate much more frequently than if the operation is performed by a gynecologic oncologist. Young et al. (44) reported excellent survival in patients with early ovarian cancer, but stressed that these data were applicable only to patients with adequate surgical staging.

In addition to the anatomic site and stage of disease, the plan of therapy for most gynecologic malignancies is also influenced by the histologic cell type and histologic grade (differentiation) of the cancer. The cooperation of the surgeon, pathologist, and cytologist cannot be overemphasized in the diagnosis and staging of cancer. It is the surgeon’s responsibility to provide the pathologist or cytologist with a complete clinical history and an indication of what he or she hopes to learn from the anatomic specimen. Without this communication, the pathologist and cytologist will be unable to provide the information needed to direct the clinical care of the patient. Both the pathologist and the cytologist must be sure that the surgeon is aware of any special handling that is necessary for a particular specimen. There is no excuse for misinterpretation of a tissue or cytologic specimen because of a failure in communication.

Surgery as Primary Therapy

Surgery is usually the treatment method of choice for preinvasive diseases of the vulva, vagina, and cervix, for which local excision

is both diagnostic and curative. Surgical margins should clear only gross and microscopic disease; removal of large areas of normal tissue is not required. For microinvasive lesions of these organs, wide local excision with a 1- to 2-cm normal tissue margin is appropriate.

Localized disease, such as stage I vulvar cancer, stage I posterior vaginal cancer, and stage IA2/IB1 cervical cancer, are usually managed by radical resection of the primary tumor and regional lymphadenectomy. Some centers utilize sentinel lymph node evaluation instead of complete regional lymphadenectomy. In these surgical procedures, the operations themselves are designed to be curative without adjunctive therapy unless high-risk conditions are identified. As described in the chapter on vulvar cancer, there is a trend toward more conservative therapy for vulvar malignancies. This allows preservation of normal tissues and prevents some of the disfigurement that can be associated with this surgery. Surgery may be curative without adjuvant therapy for other cancers as well, including early-stage endometrial cancer, stage IA ovarian cancer, and early sarcomas of the uterus.

Findings at surgery may indicate the need for additional treatment. This therapy is usually called adjuvant therapy. It is administered because of the potential for occult spread of disease based on a surgical finding (e.g., positive lymph nodes). The use of adjuvant therapy requires that information be available to allow the selection of patients with a high risk of recurrence. These risk groups are defined for each disease site in the appropriate chapters of this book.

Surgery Combined with Other Therapies

In some cancers of the female genital system, surgery is the cornerstone of treatment but is not curative when used alone. Primary cytoreduction of gross disease is vital in advanced ovarian and fallopian tube cancer, but it is of little benefit without adjunctive therapy. Chemotherapy after surgery is a vital and necessary part of the treatment regimen for these cancers. For patients with clinical stage I or II endometrial cancer who have high-grade cancer or deep myometrial penetration, surgical removal of the uterus is an extremely important part of therapy. However, depending on the histopathologic findings of the surgical specimens, additional regional radiotherapy and/or chemotherapy may be indicated. It is the responsibility of the gynecologic oncologist to coordinate surgical therapy with chemotherapy and/or radiation therapy to ensure that the patient receives optimal care.

Surgery as Salvage Therapy

Occasionally, surgical resection can be curative in patients in whom other therapies have been unsuccessful. These surgical procedures are almost always extensive and produce some limitation of function. After the failure of other therapies, radical surgery may be the patient's last chance of survival. The classic examples of this situation are vulvar, vaginal, cervical, or uterine cancers that have not been cured by primary surgery and irradiation or irradiation alone. In such cases, pelvic exenteration with removal of virtually all pelvic tissues may offer the only possibility for a cure. Five-year survival rates of 23% to 61% have been reported after pelvic exenteration (45–47).

The possibility of cure with pelvic exenteration is not without cost. The loss of the bladder and the rectum often requires permanent stomas, and sexual function is impaired or lost in many patients. For some patients, reconstructive techniques can prevent the need for stomas and may also restore sexual function. These procedures are described in detail in other chapters in this book. During the last three decades, improvements in initial surgery and radiation therapy along with refinements in selection criteria have made operations like pelvic exenteration infrequent (48). Today, most patients experience distant failure rather than regional failure, and they are therefore not candidates for attempts at curative pelvic exenteration.

Surgery as salvage therapy may also play an important role in the management of ovarian, fallopian tube, and some endometrial cancers. For patients who have not been cured by initial therapy and chemotherapy, second attempts at cytoreduction may be beneficial, provided that reasonable salvage therapy is available (49–51).

Surgery for Metastatic Disease

In selected cases, distant metastases from gynecologic tumors may be curable by surgical resection, or the resection may produce a prolonged disease-free interval. Fuller et al. (52) reported on 15 patients who underwent pulmonary resection of distant metastases from a variety of gynecologic malignancies. They reported a 5-year survival rate of 36% and a 10-year survival rate of 26%. Patients with solitary metastases had a median survival of 64 months, with a median survival of 48 months for those with multiple metastases. Levenback et al. (53) reported their experience with 45 patients who underwent pulmonary resection of metastases from uterine sarcomas. From the date of the pulmonary resection, the 5-year survival rate was 41%, with a 10-year survival rate of 35%. The investigators found a statistically improved chance of survival for patients who developed pulmonary metastases 1 year or longer from their original therapy and for those with unilateral metastases. There was no statistical difference in survival based on the number of nodules (in one lung), the size of the lesion, the age of the patient, or the use of postresection adjunctive therapy. However, the small number of patients in this study precluded adequate evaluation of these factors.

Resection of intra-abdominal or pelvic disease may offer palliation by removal of tumor bulk, or may allow chemotherapy or irradiation a greater chance of eradicating disease. Resection of tumors that have a poor blood supply often leaves behind smaller tumors with a better blood supply that are more amenable to treatment with chemotherapy or irradiation. Resection of bulk disease also increases the number of residual tumor cells that enter the active cell cycle, in which they may be more responsive to these adjunctive therapies. The availability of new techniques for intraoperative electron beam irradiation or intraoperative brachytherapy may result in more utility for resection of distant and regional metastatic disease.

There is increasing evidence that salvage therapy in ovarian and fallopian tube cancers is likely to be effective only in patients with minimal residual disease. Secondary cytoreduction or resection of regional and distant metastases may play an important role in the treatment of these patients. Recent reports have demonstrated promising results with surgical resection of isolated metastases to the parenchyma of the liver and spleen (54,55).

Surgical Procedures for Specialized Care

Surgical placement of indwelling intravenous access systems allows patients to receive chemotherapy and nutritional supplements and to have necessary blood samples drawn with relative ease and comfort. Placement of these devices, usually semipermanent subcutaneous systems, is safe, contributes to the patient's well-being, and allows for more effective therapy.

The use of intracavitary therapy requires the temporary or semipermanent placement of chest tubes or intraperitoneal access devices. Results of many studies confirm that peritoneal access or vascular access devices placed totally beneath the skin have a low infection rate and a low rate of malfunction (56,57). Implanted arterial infusion devices are being evaluated in research studies to allow direct infusion of therapeutic agents into a tumor mass by means of the arterial system. This therapy often requires intra-abdominal surgery to place the device into the appropriate portion of the vascular system.

Surgery for Reconstruction

Reconstructive surgery may be performed at the time of resection of the cancer, as a delayed procedure, or as required therapy to correct a complication of treatment. Vulvar reconstruction is usually done at the time of initial resection and may involve the use of free skin grafts, rotational flaps of adjacent skin and fat tissue, or myocutaneous grafts from the thigh, buttocks, or anterior abdominal wall. Vaginal reconstruction may also be performed, usually as a planned, delayed phase of reconstruction. Vaginal reconstruction requires free skin grafts or myocutaneous flaps, depending on the size of the defect and whether or not there has been previous irradiation of the vaginal bed. The techniques of vulvar and vaginal reconstruction are explained in detail in Chapters 19 and 20.

Reconstruction as therapy for complications of treatment may be required for the closure of defects from improper wound healing, radiation necrosis, or tissue loss after extravasation of chemotherapeutic agents. Although free skin grafts may be used to reconstruct surgical wound disruption or tissue loss due to chemotherapy extravasation, radiation necrosis usually requires the use of myocutaneous flaps because of a lack of adequate blood supply in the area of the injury.

Surgery for Palliation

Surgery for palliation may involve resection of tumor to relieve symptoms, or it may involve diversion or bypass of portions of the gastrointestinal or urinary tract to prolong life and provide comfort. Surgical procedures may also be used to provide pain relief by interrupting sensory nerve transmissions. Surgical removal of tumor bulk to provide palliation has been discouraged by many authorities. They point out that without effective adjunctive therapy, tumor regrowth occurs quickly and the surgical procedure proves to be futile. Although this may be true in most cases, the gynecologic oncologist should not uniformly dismiss the concept of surgical palliation. A surgical procedure to provide relief of symptoms is usually considered a failure if the tumor regrows in 6 to 12 months. However, palliative administration of a chemotherapeutic agent for 6 to 12 months is considered to be successful if there is minor tumor shrinkage or stabilization of disease despite the side effects of the chemotherapy. As a surgeon, the gynecologic oncologist must remember that a surgical procedure with limited risk and a reasonable recovery period may provide as much relief as 6 to 12 months of palliative chemotherapy or a course of palliative irradiation. The difficult decision about when to employ surgical palliation requires astute surgical judgment and a realistic assessment of the patient's condition and wishes.

Palliative surgery is more frequently used to relieve specific dysfunctions, such as obstruction of the urinary or intestinal tract. Relief of urinary tract obstruction may be accomplished by ureteroneocystostomy or by urinary conduit, depending on the location of the obstruction and the location or extent of disease. A urinary conduit can provide immediate and permanent relief to the patient who has a ureterovaginal, vesicovaginal, or urethrovaginal fistula. It may also provide relief of urinary obstruction, which will prolong life and allow for the administration of additional chemotherapy or irradiation. The judgment of the surgeon and the desires of the patient become essential factors in this decision process. For the patient who is miserable because of constant urinary leakage or who may benefit from additional therapy, the decision to perform a urinary diversion is quite simple. If diversion is done to prolong life, however, the decision must be weighed carefully. For a patient who has a limited life expectancy or is in uncontrollable pain, performing a urinary diversion may do more harm than good.

The gynecologic oncologist must also consider the relative benefits of nonsurgical urinary diversion, such as placement of a ureteral stent or a percutaneous nephrostomy. For many

patients, percutaneous nephrostomy is a better choice than surgical intervention. This is particularly true if the aim is to employ adjunctive chemotherapy or irradiation, or if a surgical procedure is not feasible because of medical conditions or other surgical considerations. Unfortunately, a percutaneous nephrostomy cannot help the patient with a fistula because the nephrostomy will not totally divert the urine.

Placement of a ureteral stent, by cystoscopy or antegrade through a percutaneous nephrostomy, is usually better and safer than urinary diversion for the relief of obstruction. Current technology allows the placement of stents that can be left in place for months and can be changed easily over a guide wire by means of the cystoscope.

Intestinal obstruction threatens the patient's quality of life, and the decision of whether to perform an intestinal diversion is usually easy. Deciding whether the operation is feasible can be more difficult. For the patient with localized disease, a diverting colostomy or an intestinal bypass is usually possible and is not very difficult. For the patient with intra-abdominal carcinomatosis, the decision is more complex. The surgeon may not be able to determine the extent of intestinal involvement preoperatively and may have difficulty deciding whether the surgical procedure will benefit the patient.

Pothuri et al. (58) evaluated 68 palliative operations performed on 64 patients with recurrent ovarian cancer and intestinal obstruction. In 84% of cases, it was possible to perform a corrective surgical procedure, whereas no corrective surgical procedure was possible for the remaining 16%. Of the 57 patients for whom corrective surgery was possible, 71% were successfully palliated ("successful palliation" is defined as the ability to tolerate a regular or low-residue diet at least 60 days postoperatively). If surgery resulted in successful palliation, median survival was 11.6 months compared to 3.9 months for all other patients.

THE FUTURE OF GYNECOLOGIC ONCOLOGY

As of 2012, the subspecialty of gynecologic oncology is over 35 years old. From a cadre of forward-thinking individuals with a variety of training backgrounds, a cohesive subspecialty has developed with consistent standards of training, a system of certification, and recognition in the medical community. None of this has come easily, and we owe a great deal to that first generation of gynecologic oncologists.

Several current issues are affecting the future role of gynecologic oncology within the medical community. Our relationship with our parent specialty of obstetrics and gynecology is being reexamined, as are our ties with general surgery and urology, specialties with which we often seem even more closely allied. As technologic advances occur, we are becoming more integrated with the specialties of medical oncology and radiation oncology. Although we remain primarily surgeons, and surgery remains our principal mode of therapy, it is critical to emphasize the integrated multidisciplinary management of the patient with gynecologic cancer.

The benefits of multidisciplinary care were recently highlighted in a clinical announcement by the National Cancer Institute (NCI) concerning concurrent chemoradiation for cervical cancer (59). In each of five randomized phase 3 trials of women with various stages of cervical cancer, the addition of chemotherapy to radiotherapy was found to provide a significant survival benefit (13,60–63). The risk of death from cervical cancer was decreased by 30% to 50% with the multimodality approach.

Changes in Surgical Therapy

If the past decade is any indication of the future, significant changes in the technology of surgery can be expected to occur as we proceed

through the new millennium. New materials, new surgical instruments, and new devices will be invented, and many of these will make surgical treatment better. Laparoscopic surgery has made a significant impact on our specialty, as well as on the other surgical specialties. With robotic surgery, the complexity of cases that can be successfully performed with minimally invasive surgery appears to have increased, and standard gynecologic oncologic staging procedures appear to be very amenable to the robotic platform.

Innovative methods of supportive care will be developed to advance the technical capabilities that we now possess, such as computerized anesthesia machines and transesophageal ultrasound. Anesthetic agents will become better and safer, and will be joined by a new generation of antibiotics and cardiovascular medications. We will be able to treat the older patient surgically with relative safety, which is especially important because of the increased incidence of cancer in the elderly, and because of the advancing age of our population. Our responsibilities include staying abreast of these advances and judiciously integrating them into our practices.

Changes in the Indications for Surgery

Early diagnosis will change the indications for surgery and the types of procedures that should be done. We will be able to treat more patients with less disfigurement and with greater preservation of function. A larger proportion of patients will present with early disease, allowing surgery to be used more frequently for definitive cure.

Better adjunctive therapies will increase the importance of initial surgical therapy. More patients will benefit from surgical cytoreduction to minimize disease. The availability of effective irradiation, chemotherapeutic, and biologic regimens will make adjuvant therapy feasible in more cases, and it will become more important for us to identify risk groups who are likely to develop recurrent disease after surgery.

Multidisciplinary Therapy and Primary Care

In outlining the extent of surgical training required for the gynecologic oncologist, the founders of this discipline were careful to include adequate training that would enable the gynecologic oncologist to become an accomplished abdominopelvic surgeon. The gynecologic oncologist must be trained to perform the gynecologic, gastrointestinal, and urologic surgery necessary to manage gynecologic cancer and its potential complications. As stated by John L. Lewis Jr. (64), in reference to pelvic exenteration by a team of gynecologists, general surgeons, and urologists, "Even when the

surgery was successful, the postoperative care required committee meetings and its outcome was often less than successful."

These same founders realized that, although training can produce a qualified surgical oncologist, the complete care of the cancer patient requires knowledge of the basic biologic, physical, and pharmacologic principles of radiation therapy and chemotherapy. This does not mean that the gynecologic oncologist must be a radiation oncologist or a medical oncologist, but it does demand that he or she know enough to ensure proper integration of all therapeutic modalities. Throughout the United States, this collaboration in the care of patients with gynecologic cancer has produced multidisciplinary teams of gynecologic oncologists, radiation oncologists, medical oncologists, and pathologists who provide state-of-the-art cancer care. The GOG, a national cooperative research group, has demonstrated how this multidisciplinary approach to gynecologic oncology research can be achieved.

Despite the emphasis on multidisciplinary care, the gynecologic oncologist should maintain active involvement during all aspects of a patient's care. The principle of being the patient's physician until she is either cured or dies of her disease has been an integral part of our subspecialty and must be maintained. The constant involvement of the gynecologic oncologist through all phases of cancer treatment ensures optimal integration of surgery, irradiation, and chemotherapy. The patient receives continuous care and the reassurance of a physician who is involved at each stage of her therapy and follow-up.

CONCLUSION

After three and a half decades, the gynecologic oncologist has emerged as a surgical oncologist for women. The specialist has sufficient familiarity with radiation oncology and medical oncology to ensure the proper integration of all modalities of treatment, and he or she is able to apply surgical skills for primary therapy, secondary therapy, reconstruction, and palliation. The gynecologic oncologist stands in the obstetrics and gynecology community, but has one foot in the community of surgeons.

The emergence of cooperative research groups, particularly the GOG, has allowed a generation of gynecologic oncologists to develop superior clinical research skills. These skills must be continually stressed in the training of young oncologists and as an integral part of the practice of our subspecialty. A growing number of young oncologists are receiving additional training in basic research. This training is vital for the continued development of the subspecialty and for progress toward the prevention and care of gynecologic cancers. Our position in the arena of clinical practice is well established, and we must now establish ourselves equally well as scientists and surgical researchers.

REFERENCES

- Morrow CP, Curtin JP, eds. *Gynecologic Cancer Surgery*. New York, NY: Churchill Livingstone; 1996.
- Bristow RE, Karlan BY, Chi DS. *Surgery for Ovarian Cancer: Principles and Practice*, 2nd Edition. New York: Informa Healthcare; 2010.
- Levine DA, Barakat RR, Abu-Rustum NR. *Atlas of Procedures in Gynecologic Oncology*. 2nd ed. London, UK: Informa Healthcare; 2008.
- Fowler JM, Johnson PR. Transperitoneal para-aortic lymphadenectomy. *Oper Tech Gynecol Surg*. 1996;1:8-12.
- Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stage IIIC-IV epithelial ovarian cancer. *Gynecol Oncol*. 2006;103:1083-1090.
- Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol*. 2009;114:26-31.
- Eisenhauer EL, Chi DS. Liver mobilization and diaphragm peritonectomy/resection. *Gynecol Oncol*. 2007;104(2):S25-S28.
- Skandalakis JE, Gray SW, Rowe JR, eds. *Anatomical Complications in General Surgery*. New York, NY: McGraw-Hill; 1983.
- Poulin EC, Schlachta DM, Maazza J. Splenectomy. Gastrointestinal tract and abdomen. In: Souba WW, Fink MJ, Jurkovich GJ, et al. eds. *ACS Surgery*. New York, NY: WebMd; 2005.
- Berman ML, Lagasse LD, Watring WG, et al. The operative evaluation of patients with cervical cancer by an extraperitoneal approach. *Obstet Gynecol*. 1977;50:658-664.
- Gallup DG, King LA, Messing MJ, et al. Para-aortic lymph node sampling by means of an extraperitoneal approach with a supraumbilical transverse "sunrise" incision. *Am J Obstet Gynecol*. 1993;169:307-312.
- Weiser EB, Bundy BN, Hoskins WJ, et al. Extraperitoneal versus transperitoneal selective para-aortic lymphadenectomy in the pretreatment surgical staging of advanced cervical carcinoma: a

- Gynecologic Oncology Group study. *Gynecol Oncol.* 1989;33:283–289.
13. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based chemoradiation for locally advanced cervical cancer. *New Engl J Med.* 1999;340:1144–1153.
 14. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol.* 1974;44(2):265–272.
 15. Querleu D, Morrow CP. Classification of radical hysterectomy. *Lancet Oncol.* 2008;9(3):297–303.
 16. Cibula D, Abu-Rustum NR, Benedetti-Panici P, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. *Gynecol Oncol.* 2011;122:264–268.
 17. Chi DS, Eisenhauer EL, Lang J, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma? *Gynecol Oncol.* 2006;103:559–564.
 18. Bristow RE, del Carmen MG, Kaufman JS, et al. Radical oophorectomy with primary stapled colorectal anastomosis for resection of locally advanced epithelial ovarian cancer. *J Am Coll Surg.* 2003;197(4):565–574.
 19. Mourton SM, Temple LK, Abu-Rustum NR, et al. Morbidity of rectosigmoid resection and anastomosis in high risk patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. *Gynecol Oncol.* 2005;99:608–614.
 20. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol.* 2002;20:1248–1259.
 21. Juretzka M, Abu-Rustum NR, Sonoda Y, et al. Full thickness diaphragmatic resection for stage IV ovarian carcinoma using the EndoGIA stapling device with diaphragmatic reconstruction using a gortex graft: a case report and review of the literature. *Gynecol Oncol.* 2006;100:618–620.
 22. Rowland RG, Mitchell ME, Bihle R, et al. Indiana continent urinary reservoir. *J Urol.* 1987;137:1136–1139.
 23. Penalver MA, Benjany DE, Averette HE, et al. Continent urinary diversion in gynecologic oncology. *Gynecol Oncol.* 1989;34:274–288.
 24. Wallace D, Hernandez W, Schlaerth JB, et al. Prevention of abdominal wound disruption utilizing the Smead-Jones closure technique. *Obstet Gynecol.* 1980;56:226–230.
 25. Gallup DG, Talledo OE, King LA. Primary mass closure of midline incisions with a continuous running monofilament suture in gynecologic patients. *Obstet Gynecol.* 1989;675–677.
 26. Gallup DG, Nolan TE, Smith RP. Primary mass closure of midline incisions with a continuous polyglyconate monofilament absorbable suture. *Obstet Gynecol.* 1990;76:872–875.
 27. Orr JW, Orr PF, Barrett JM, et al. Continuous or interrupted fascial closure: a prospective evaluation of no.1 Maxon suture on 402 gynecologic procedures. *Am J Obstet Gynecol.* 1990;163:1485–1489.
 28. Israelsson LA, Jonsson T. Suture length to wound length ratio and healing of midline laparotomy incisions. *Br J Surg.* 1993;80(10):1284–1286.
 29. Millbourn D, Cengiz Y, Israelsson LA. Effect of stitch length on wound complications after closure of midline incisions: a randomized controlled trial. *Arch Surg.* 2009;144(11):1056–1059.
 30. McGowan L, Leshner LP, Norris HJ, et al. Misstaging of ovarian cancer. *Obstet Gynecol.* 1985;65:568–572.
 31. Kehoe S, Powell J, Wilson S, et al. The influence of the operating surgeon's specialisation on patient survival in ovarian cancer. *Br J Cancer.* 1994;70:1014–1017.
 32. Woodman C, Baghdady A, Collins S, et al. What changes in the organisation of cancer services will improve the outcome for women with ovarian cancer? *Br J Obstet Gynecol.* 1997;104:135–139.
 33. Nguyen HN, Averette HE, Hoskins W, et al. National survey of ovarian carcinoma, part V. The impact of physician's specialty on patient's survival. *Cancer.* 1993;72:3663–3670.
 34. Eisenkop SM, Spirtos NM, Montag TW, et al. The impact of subspecialty training on the management of advanced ovarian cancer. *Gynecol Oncol.* 1992;47:203.
 35. Tingsulstad S, Skjeldstad FE, Hagen B. The effect of centralization of primary surgery on survival in ovarian cancer patients. *Obstet Gynecol.* 2003;102:499–505.
 36. Andersen ES, Knudsen A, Svarrer T, et al. The results of treatment of epithelial ovarian cancer after centralisation of primary surgery. Results from North Jutland, Denmark. *Gynecol Oncol.* 2005;99:552–556.
 37. Harlan LC, Clegg LX, Trimble EL. Trends in surgery and chemotherapy for women diagnosed with ovarian cancer in the United States. *J Clin Oncol.* 2003;21:3488–3494.
 38. Goff BA, Matthews BJ, Wynn M, et al. Ovarian cancer: patterns of surgical care across the United States. *Gynecol Oncol.* 2006;103:383–390.
 39. Chan JK, Kapp DS, Shin JY, et al. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. *Obstet Gynecol.* 2007;109:1342–1350.
 40. Goff BA, Matthews BJ, Larson EH, et al. Predictors of comprehensive surgical treatment in patients with ovarian cancer. *Cancer.* 2007;109(10):2031–2042.
 41. Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA.* 1998;280:1747–1751.
 42. Kauff ND, Satagopan JY, Robson ME, et al. Risk reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med.* 2002;346:1609–1615.
 43. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med.* 2002;346:1616–1622.
 44. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer: results of two prospective randomized trials. *N Engl J Med.* 1990;332:1021–1027.
 45. Lawhead RA, Clark GC, Smith DH, et al. Pelvic exenteration for recurrent or persistent gynecologic malignancies: a 10-year review of the Memorial Sloan-Kettering Cancer Center Experience (1972)–(1981). *Gynecol Oncol.* 1989;33:279–282.
 46. Morley GW, Hopkins MP, Lindenauer SM, et al. Pelvic exenteration, University of Michigan: 100 patients at 5 years. *Obstet Gynecol.* 1989;74:934–943.
 47. Matthews CM, Morris M, Burke TW, et al. Pelvic exenteration in the elderly patient. *Obstet Gynecol.* 1992;79:773–777.
 48. Chi DS, Gemignani ML, Curtin JP, et al. Long-term experience in the surgical management of cancer of the uterine cervix. *Semin Surg Oncol.* 1999;17:161–167.
 49. Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer.* 2000;88:144–153.
 50. Chi DS, McCaughy K, Schwabenbauer S, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent platinum sensitive epithelial ovarian carcinoma. *Cancer.* 2006;106(9):1933–1939.
 51. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. *Gynecol Oncol.* 2010;118(1):14–18.
 52. Fuller AF, Scannell JG, Wilkins W Jr. Pulmonary resection for metastases from gynecologic cancers: MGH experience, 1943–1982. *Gynecol Oncol.* 1985;22:174–180.
 53. Levenback C, Rubin SC, McCormack PM, et al. Resection of pulmonary metastases from uterine sarcomas. *Gynecol Oncol.* 1992;45:202–205.
 54. Yoon SS, Jarnagin WR, DeMatteo RP, et al. Resection of recurrent ovarian or fallopian tube carcinoma involving the liver. *Gynecol Oncol.* 2003;91(2):383–388.
 55. Gemignani ML, Chi DS, Gurin CC, et al. Splenectomy in recurrent epithelial ovarian cancer. *Gynecol Oncol.* 1999;72:407–410.
 56. Davidson SA, Hoskins WJ, Rubin SC, et al. Intraperitoneal chemotherapy: analysis of complications with an implanted subcutaneous port and catheter system. *Gynecol Oncol.* 1991;41:101–106.
 57. Makhija S, Leitao M, Sabbatini P, et al. Complications associated with intraperitoneal chemotherapy catheters. *Gynecol Oncol.* 2001;81:77–81.
 58. Pothuri B, Vaidya A, Aghajanian C, et al. Palliative surgery for bowel obstruction in recurrent ovarian cancer: an updated series. *Gynecol Oncol.* 2003;89:306–313.
 59. National Cancer Institute. Clinical announcement regarding concurrent chemoradiation for cervical cancer. February 22, 1999.
 60. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol.* 1999;17:1339–1348.
 61. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high risk cervical cancer. *N Engl J Med.* 1999;340:1137–1143.
 62. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999;340:1154–1161.
 63. Peters WA, Liu PY, Barrett R, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol.* 2000;18:1606–1613.
 64. Lewis JL Jr. Training of the gynecologic oncologist. In: Coppleson M, ed. *Gynecologic Oncology: Fundamental Principles and Clinical Practice*. Edinburgh, Scotland: Churchill Livingstone; 1981:4–20.

Minimally Invasive Surgery in Gynecologic Cancer

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Early history of laparoscopic surgery in gynecologic oncology came to an end when the whole range of surgical procedures used in uterine cancer, including pelvic exenteration, was demonstrated to be feasible laparoscopically (1). In a second phase, accumulation of evidence including long-term follow-up of patients managed laparoscopically, results of randomized controlled studies, and meta-analysis has led to unanimous acceptance of the concept of minimal invasive surgery (MIS) in gynecologic cancer. However, notwithstanding the spread of the technique in almost every country in the world, the open approach is still widely used in small institutions with limited caseload, or in academic centers without trained teachers and proctors, which implies that more efforts still have to be made in teaching and in concentrating the management of gynecologic cancer in experienced hands.

In this chapter, the evidence of short- and long-term benefits and safety of the laparoscopic approach, the teaching and learning issues, and the new technical developments will be detailed.

BASICS OF LAPAROSCOPIC SURGERY IN GYNECOLOGIC CANCER

The goal of this section is not to describe the standard technique of laparoscopy; this can be found in general gynecology textbooks. Two issues will be addressed: the risk of bowel and vascular complications related to the laparoscopic approach, and the pitfalls of the laparoscopic approach in cancer patients. Indeed, the potential for inducing severe intraoperative surgical complications and to favor tumor growth and port-site implants is not negligible. The goal of this section is to contribute to the prevention of such complications. Additional tips to make the laparoscopic surgeon's life easier will also be given. An insight on training issues that are critical to the development of laparoscopic surgery versus open and robot-assisted laparoscopic surgery will conclude the section.

Laparoscopic Entry

Laparoscopic surgery was initially performed via CO₂ insufflation to create a pneumoperitoneum through the umbilicus – a place where the layers of the abdominal wall are fused followed by blind insertion in the umbilicus of a 10-mm trocar to accommodate the endoscope. This mode of entry was responsible for bowel and vascular complications, some of them lethal. The use of disposable trocars with retractable blades for direct trocar insertion did not appear to significantly reduce the risk of bowel or vascular injuries. This is of particular concern since the majority

of complications following laparoscopic surgery are related to trocar insertion.

For that reason, the “open” technique in which the fascia and the peritoneum are surgically opened and the trocar inserted under direct visualization is considered by many to be the safest access technique. However, this is likely not to be true in patients with a history of laparotomy, as the majority of bowel adhesions are located on the midline below the umbilicus, at a location where even an “open” technique can result in bowel injury. Bonjer et al. (2) reviewed the literature and compared data between 12,444 open laparoscopic and 489,335 closed laparoscopic cases. Rates of visceral and vascular injury were 0.083% and 0.075%, respectively, after closed laparoscopy, and 0.048% and 0.0%, respectively, after open laparoscopy ($p = 0.002$). Mortality rates were 0.003% for the closed and 0.0% for the open laparoscopy techniques. In another randomized trial of blind versus open laparoscopy for laparoscopic cholecystectomy, the major complication rate was 4% in the blind group and 1.3% in the open group, respectively ($p < 0.05$) (3). However, a large series comparing 8,324 cases of direct laparoscopic entry versus 1,562 cases of open laparoscopy for gynecologic procedures did not show a difference in the rate of major complications. On the opposite, there were more conversions to laparotomy in the open technique group (4). A review on laparoscopic entry concludes that there is no evidence that the open entry technique is superior or inferior to other entry techniques currently available (level II-2C evidence) (5). The visual entry cannula system may represent an advantage over traditional trocars, as it allows a clear optical entry; however, that does not necessarily avoid all visceral or vascular injuries (5).

In patients with prior midline incisions, the use of the Veress needle in the left upper quadrant to first insufflate the abdomen prior to the trocar entry is favored. Once the pneumoperitoneum is established, the location of the first trocar is chosen at a place where the absence of adhesion is evident, as assessed by a 5-mm endoscopy through the left upper quadrant or the use of the “bubble test.” This test consists in exploring the abdominal cavity by puncturing the abdominal wall using a fine needle plugged to a syringe containing 1 to 2 mL of saline. If bubbles are not freely aspirated, there is a suspicion of bowel or omental adhesions. Using multiple punctures if necessary, an area free of adhesions large enough to safely accommodate the endoscope is defined. Although the umbilicus is the traditional site of placement of the first trocar, one must be prepared to use any position in the midline or any site of the abdomen, provided the risk of adhesion is low. It is the policy of the senior author to combine this technique (left upper quadrant insufflation, bubble test) with the use of trocar insertion under direct vision using the Ternamian trocar (6).

The ancillary trocars are placed under laparoscopic vision. Generally, one 10-mm trocar is placed in a suprapubic location. Two 5-mm trocars are then placed on the horizontal line of the

umbilicus, 10 cm lateral to it. This trocar position has many advantages. It allows access to the entire abdomen, from the pelvis to the diaphragm. It provides an adequate angulation between instruments, with a maximum distance between trocars. It provides a direct access, with a virtually 0-degree angle, to the ureteric tunnel at the time of radical hysterectomy. It is more adapted to performance of procedures at the abdominal level such as omentectomy or paraaortic lymph node dissection. Finally, it avoids injuring the iliohypogastric nerves that run oblique in the abdominal wall below the umbilical horizontal line, thus avoiding short and long-term postoperative pain. Any adhesion impairing vision or correct placement of trocar is taken down. When extensive adhesions are encountered, the first 5-mm trocar is placed in an area free of adhesions. Scissors are then introduced and other adhesions are divided to place the other trocars.

Port-Site Metastasis and Risk of Tumor Dissemination

In the early laparoscopic era, there has been concern about the apparent increased rate of port-site metastases following laparoscopic procedures. The first reports concerned borderline tumors of the ovary (7). Isolated case reports of abdominal wall metastasis following laparoscopic surgery for a variety of gynecologic cancers have been reported and reviewed by Ramirez et al. in 2004 (8). The fact that wound recurrences are not uncommon after conventional surgery clearly attenuates the responsibility of laparoscopic surgery in the occurrence of abdominal wall recurrences.

In addition, series from experienced centers have shown that the incidence of port-site growth is low. Zivanovic et al. (9) extended the investigation in the same institution and reported 18 abdominal wall metastases in 1,634 gynecologic cancer patients. Fifteen cases occurred in 767 patients with adnexal/peritoneal malignancy (2%), 2 in 160 cervical cancer patients and 1 in 457 endometrial cancer patients. Seventeen out of 18 of these patients had peritoneal disease, which indicates that abdominal wall metastases are extremely uncommon in the absence of peritoneal disease. In addition, they reported 2 cases in breast cancer patients with intra-abdominal disease, and reported on the outcome of a total of 20 patients. The median survival of patients in whom port-site metastases occurred within 7 months was 12 months, while the median survival of patients who developed port-site metastases after 7 months was 37 months. The conclusion is that the natural history of port-site metastases basically reflects the aggressiveness of the underlying tumor. Martinez et al. (10) reported on 921 patients who underwent laparoscopic staging for cervical cancer and 295 for endometrial cancer. The overall incidence of port-site metastasis after laparoscopy for cervical and endometrial cancer was 0.43% and 0.33%, respectively. Excluding patients with peritoneal carcinomatosis, the rate of port-site recurrence in this series lowered to 0.16%. The rate of isolated port-site metastases was 0%.

In contrast, there is evidence that the presence of peritoneal malignancy or ascites is a risk factor for port-site metastases. Vergote et al. observed 17% of port-site metastasis after laparoscopic surgery in patients with advanced ovarian cancer (11). However, port-site metastases are not lethal by themselves and are not associated with a worse outcome, as they are as chemosensitive as the underlying peritoneal disease and then generally reflect the aggressivity of the tumor (11). As a majority (22 out of 30) of port-site metastases in Vergote's series were not clinically diagnosed, it is reasonable to recommend the resection of the laparoscopic ports in a full-thickness fashion at the time of the subsequent laparotomy after a laparoscopic assessment of advanced ovarian cancer. Indeed, Heitz et al. found 47% incidence of port-site implant at the time of pathological

examination after routine resection of trocar site in 66 patients who underwent laparotomy after diagnostic laparoscopy (12). This implies that complete cytoreduction must be followed by trocar site resection. The conclusion is that port-site implant is not a complication of laparoscopic surgery in the absence of ascites or peritoneal malignancy. The early reports of port-site metastases may have been the result of faulty technique resulting in direct contamination of the abdominal wall by tumor cells.

Finally, it is logical to place all trocars in the midline when performing a laparoscopic evaluation of a clinically advanced adnexal or peritoneal cancer, to avoid muscle involvement and to easily resect the trocar sites at the time of final laparotomy. In addition, it is advised against placing the optical trocar in the umbilicus, which is a preferential site for abdominal wall tumor even in the absence of surgical scar, and would have to be fully resected at the time of final surgery.

The Issue of Intraoperative Rupture of Ovarian Masses

A recent population-based study in Norway definitively demonstrated that intraoperative rupture is associated with a worsened prognosis compared to no rupture, although to a lesser extent than spontaneous rupture (13).

The importance of the issue in laparoscopic surgery is the finding that inadvertent and unprotected ovarian cyst rupture is more frequent at laparoscopy compared to laparotomy with increased tumor size (14). On the basis of this evidence, and on concerns about the risks of peritoneal dissemination (see below), it is generally recommended that definitive surgery should be performed within 1 week in ruptured stage I cases. Although the grade of the tumor and the presence of ascites in stage I cancer of the ovary may have more important relation to survival than is rupture of the ovarian capsule at surgery, avoiding the rupture of low grade or stage IA is obviously an objective that gynecologic oncologists and general gynecologists must share, as adjuvant chemotherapy may have to be considered after extensive spillage. All pelvic masses should be considered potentially malignant, and consequently, every effort should be made to avoid rupture.

Influence of Pneumoperitoneum on Tumor Growth

On the basis of a review of experimental data, Canis et al. concluded that the risk of dissemination following laparoscopic surgery is increased when a large number of malignant cells are present (15). However, the results of various experiments are not consistent and the extrapolation of results obtained in experimental settings may be hazardous. On the contrary, using an ovarian cancer xenograft animal model, studies from Lécure et al. seems to indicate that CO₂ laparoscopy has a minor impact on visceral metastasis and survival and has no deleterious effect on tumor growth compared to gasless laparoscopy (16). In the laboratory of the first author, survival of mice injected intraperitoneally with ovarian tumor cell lines was similar after laparotomy, CO₂ laparoscopy, or Helium laparoscopy (17). Similar results have been shown in humans. Abu-Rustum et al. retrospectively reviewed patients with persistent metastatic intra-abdominal peritoneal or ovarian cancer at the time of second-look surgery. There was no difference in overall survival between patients who underwent laparoscopy or laparotomy (18). Data from animal studies suggest that the underlying immune or metabolic status of the host has a marked independent effect on tumor spread and implantation (19). Of interest are recent data showing that an 8-mm Hg pressure pneumoperitoneum is preferable to a 12-mm one. As a consequence, low pressure pneumoperitoneum may be preferable (20).

Gasless Laparoscopy in Oncologic Surgery

Due to concerns regarding the potential increased risk of tumor dissemination associated with CO₂ laparoscopy, some have advocated the use of gasless laparoscopy. The results of animal studies on peritoneal tumor growth and abdominal-wall metastasis comparing gasless laparoscopy, CO₂ laparoscopy, and laparotomy are conflicting (16,21). In contrast, a higher rate of port-site metastasis with gasless laparoscopy has been reported in some experiments (22). Although it can be used in patients for whom general anesthesia and CO₂ pneumoperitoneum are contraindicated, as it does not significantly increase the intra-abdominal pressures and since the procedure can also be performed under epidural anesthesia, gasless laparoscopy is not widely used.

Teaching and Learning Laparoscopic Surgery

Mastering laparoscopic surgery involves, apart from the skills and knowledge required to perform the same procedure by laparotomy, a variety of specific skills: translation of 3-D into 2-D perception, hand-eye coordination, ambidexterity, camera navigation, remote handling of instruments, modified tactile feedback, and fine motor skills to overcome the fulcrum effect and the lever forces. Several models can be used in resident, fellowship, or catch-up teaching programs: cadaver surgery, animal models, video trainers, and virtual reality (VR). The most realistic model is the animal model, generally the pig model (23). The cheapest is the video trainer. The “box model” training does improve surgical dexterity and economy of movement during virtual reality laparoscopy. Clevin et al. (24) used the metrics derived from a virtual reality laparoscopic trainer to assess whether a low cost box model trainer is a tool for the training of skills relevant to laparoscopic surgery. Sixteen gynecologic residents with limited laparoscopic experience were randomized to a group that received a structured box model training curriculum, and a control group. Objective parameters were registered by the computer system. The trained group showed significantly greater improvement in all performance parameters: economy of movement ($p = 0.001$), time ($p = 0.001$), and tissue damage ($p = 0.036$), confirming the positive impact of box-trainer curriculum on laparoscopic skills acquisition.

The much more expensive simulation-based training environment offers much promise as an alternative arena to cadaver, animal, or patient training. There is evidence suggesting that the skills acquired in simulation transfer to the real setting (25). In addition, it allows objective measurement of psychomotor skills. However, realism is still far from perfect, and more studies are required to strengthen the evidence base and to provide the evidence needed to determine the extent to which simulation should become a part of surgical training programs. In a review of 23 randomized trials (12 VR vs. video, 3 VR vs. VR, 4 VR vs. no or standard training, and 4 VR vs. video vs. no or standard training), Gurusamy et al. (26) identified only 3 trials at low risk of bias. VR – compared to no training – decreases the time to complete a task, increases accuracy, and decreases errors. Although the benefit of VR versus video training is not demonstrated for every criterion, a VR-trained group is more accurate than video trainer group, and shows a better composite operative performance.

As a substantial number of active gynecologic oncologists have not been trained during their fellowship, they have to catch up. Visiting surgeons may monitor established surgeons during the learning curve of an advanced laparoscopic procedure (27). Five-day–mini-residencies for urologists have been shown to result in improvement of skill tasks. However, skill acquisition is not durable if not consolidated by experience.

This is in accordance with the findings of Worley et al., who showed that surgeon volume is associated with higher complexity procedures, lower rate of conversions, less complications, and shorter hospital stay (28).

In addition, fundamental abilities (e.g., psychomotor skills, visuospatial ability, and depth perception) are critically important. In a pivotal paper of a VR trainer on this sensitive topic, Grantcharov et al. assessed the learning curve of 37 residents with limited laparoscopic experience (29). Five percent were proficient from the beginning, 70% needed 2 to 9 repetitions, 16% improved but did not reach the predefined criteria, and 8% underperformed and did not improve. The question is whether the residents lacking psychomotor skills required to perform laparoscopic surgery should be discouraged to engage in a general surgery or gynecologic oncology training involving laparoscopic surgery. It is not clear whether robot-assisted surgery is advisable to help the 16% group of low performers exposed to nonrobotic laparoscopic surgery.

As a matter of fact, the benefit of robotic surgery is mainly related to 3-D vision. Blavier et al. assessed the performance at needle-handling exercises on bench model of 40 medical students without surgical experience (30). A steeper learning curve and better performances were found for both 3-D conditions. The learning curve was steeper in 2-D robotic compared to 2-D laparoscopy. A negative impact of switching from 3-D to 2-D, and from one technique to another was observed. Evidence is given that 3-D vision is the most important factor of shortened robotic learning curve. Interestingly, students express less self-confidence in 2-D laparoscopy compared to the other modalities.

Frumovitz et al. (31) assessed in 2007 the adequacy of laparoscopic surgical training as perceived by gynecologic oncology fellows-in-training. Fellows were surveyed via mail or an internet website. One-hundred percent stated that laparoscopy is important or very important in gynecologic oncology practice. About 69% believe that their fellowship training in laparoscopy is very good or good. There is then space for improvement in fellowship training. The question of learning laparoscopic surgery before or after exposure to robotic-assisted surgery has been addressed by Öbek et al. (32). They provided evidence that beginners do better and faster with the robot in a crossover randomized experiment. Skills incompletely transfer from one modality to the other. Interestingly, skill transfer is greater from training with laparoscopy, and error rate is more decreased by laparoscopic training than by robot training (for example, no suture break occurs during robotic knot-tying after laparoscopic training). The conclusion is that dual experience is complementary and that starting with laparoscopic training is preferable.

DIAGNOSTIC AND STAGING PROCEDURES

Transperitoneal Pelvic Lymph Node Dissection

The transumbilical transperitoneal technique for laparoscopic lymphadenectomy remains the most popular approach employed by gynecologists. Early animal randomized studies have given evidence that the node yield is similar at laparoscopic and open approaches for pelvic and aortic lymph node dissections (33,34), thus justifying the spread of the technique.

The peritoneum is divided transversally between the round ligament and the infundibulopelvic ligament, which are best left undivided until the dissection is finished. An additional incision lateral to the infundibulopelvic ligament may be useful. Once the retroperitoneal space is reached, the surgeon searches for several landmarks that are, from lateral to medial, the psoas

muscle, the external iliac artery and vein, and the superior vesical artery. The paravesical space is then developed between the superior vesical artery and the external iliac vessels. The lateral wall of the bladder is retracted medially along with the superior vesical artery. This exposes the Cooper's ligament and allows identification of the obturator pedicle. The obturator nerve is the deep limit of the dissection. The nodes are separated from the obturator nerve and the external iliac from the Cooper ligament area to the bifurcation of the common iliac vessels. The nodes located between the 2 landmarks (referred to as obturator nodes) can then be firmly grasped and detached. The external iliac artery and vein are then freed from the pelvic side wall. The nodes located between the artery and vein, and the nodes located between the artery and the genitofemoral nerves are dissected. Finally, after retracting medially the external vessels, additional obturator nodes can be identified and retrieved.

Perioperative Outcomes

Querleu et al. (35) were the first to provide data describing the feasibility and safety of transumbilical transperitoneal laparoscopic pelvic dissection in 39 patients with cervical cancer stage IB to IIB. No conversion to laparotomy was required. All patients were followed for 5 years, and the 5-year survival rate was similar to the survival of a historical group of patients matched for age, stage, and therapy who underwent standard abdominal radical hysterectomy. In addition, the rate of radiation-induced bowel complications was reduced in the group submitted to radiation therapy after laparoscopic lymphadenectomy compared to the group managed by laparotomy (36).

Since then, a number of large series have documented the safety of the procedure. A similar study, comparing two groups differing only in the technique used for lymph node dissection, has recently demonstrated that laparoscopy does not have a detrimental effect on surgical or disease outcome, and can be safely applied to the treatment of early stage cervical cancer (37).

A meta-analysis of the available randomized studies comparing laparoscopy to laparotomy in endometrial cancer patients is available. The node counts after laparoscopic pelvic and para-aortic dissections, respectively, are similar in both groups of patients. However, although no heterogeneity was noted among studies regarding pelvic dissection, a significant heterogeneity was noted across studies regarding aortic dissection (38).

Benedetti et al. (39) randomly assigned to open transperitoneal, open extraperitoneal, or laparoscopic pelvic lymphadenectomy (58). All patients underwent classical radical hysterectomy. There were 168 patients who entered the study. The mean operative times were: 63, 54, and 75 minutes for transperitoneal, extraperitoneal, and laparoscopic dissections, respectively. The feasibility of the procedures, analyzed on an intention-to-treat basis was 96%, 93%, and 95%, and the average hospital stay was 5.6, 3.2, and 3.1 days, respectively.

Another recent study confirmed the early finding that the benefits of minimal-access surgery used to perform staging procedures may translate into long-term reduction in radiation-induced bowel injury (40). Staging procedures were performed on 159 patients either by open surgery (93 patients) or laparoscopy (66 patients). The site of primary tumor was the cervix in 61 patients and the corpus uteri in 98 patients. Multiple regressions revealed an independent protective effect of pretreatment laparoscopic staging against the risk of developing both grade ≥ 2 and grade ≥ 3 radiation-induced complications. The preoperative and postoperative complication rate of laparoscopic lymph node dissection has been investigated in several large series (41,42,43). The major complication and conversion rate is extremely low, inferior to 1%, in experienced hands.

Ghezzi et al. specifically evaluated the incidence of lymphoceles, lymphorrhea, and lymphedema after systematic pelvic lymphadenectomy in patients who underwent laparoscopic or

open abdominal staging for endometrial cancer (44). Overall, lymphoceles were diagnosed in 15.4% and 1.4% of patients who had open and laparoscopic staging, respectively. Symptomatic lymphoceles were more frequent after open staging than after laparoscopy. Lymphorrhea occurred in 1 and 4 patients after laparoscopic and open surgery. No difference in the incidence of lymphedema was observed.

Transperitoneal Aortic Dissection

The transperitoneal approach has been the first described technique. It mimics the open surgery approach while requiring a much shorter peritoneal incision – and virtually no mobilization of the right colon. As for every upper abdominal procedure, the surgeon stands between the patient's legs with the monitor at the head of the bed. The bowel loops are packed along with the omentum in the left upper quadrant. The dorsal peritoneum is opened alongside the axis of the right common iliac vessels, then of the lower aorta. The upper peritoneal flap is elevated along with the third part of the duodenum. The anatomical landmarks are carefully identified. The aorta and vena cava are the main landmarks. On the right side of the patient, the right ureter is identified and then moved laterally. The right ovarian vessels are identified up to the point where the ovarian vein floods into the vena cava. The ventral aspect of the aorta is dissected, and the origin of the inferior mesenteric artery is identified. The caudal aspect of the left renal vein is then identified. This step may require applying bipolar cautery and dividing the ovarian arteries to fully elevate the third duodenum. Finally, the left ureter is identified and moved laterally in the inframesenteric area. The left ovarian vein is identified in the supramesenteric area and gently moved laterally.

Since the feasibility of such an extensive dissection has been demonstrated in the early report by Querleu and Leblanc in 1994 (35), the yield of 20 nodes, with acceptable morbidity, has been reached in a large series of patients (41). When comparing the infrarenal lymphadenectomy to the inframesenteric lymphadenectomy, Köhler et al. (45) confirmed that this could be performed safely.

Extraperitoneal Lymph Node Dissection

The extraperitoneal approach is historically the first approach used to perform pelvic node sampling. It is the logical way to gain access to the aortic nodes. It has gained increasing popularity as it does have several advantages over the transperitoneal technique. Most of the advantages are related to bowel: the vision is not impaired by bowel loops, it is not influenced by the presence of bowel adhesions, and it creates less *de novo* adhesions (46,47), which is critical for patients/candidates for radiation therapy. The disadvantages are a smaller space, a higher risk of lymphoceles as a result of the absence of intraperitoneal drainage, an increased reabsorption of CO₂, and the lack of assessment of the peritoneal cavity, which is mandatory in gynecologic oncology patients. The latter is overcome by the routine use of an associated intraperitoneal diagnostic laparoscopy.

Extraperitoneal Aortic Node Dissection

In addition to the advantages mentioned above, the extraperitoneal route is more ergonomic for aortic dissection, as the surgeon stands lateral to the patient and works in a horizontal plane, watching the screen placed on the other side of the patient. The left lateral approach is preferred to the right-sided approach for several reasons: the upper part of the dissection, which is the left infrarenal area, is more easy to reach; at the same time, it is the preferred site of node metastasis; in addition, the key areas of the right side, including the precaval and laterocaval nodes, can be

easily dissected from the left side. After preparation of the space (see below), an 8- to 10-mm Hg pressure is enough to maintain the working space.

Extraperitoneal aortic dissection has been first reported by Vasilev and McGonigle in a small series (48). The mature technique has been fully described in earlier papers from French groups (49). An extraperitoneal approach to the aorta is begun by using a 3-cm incision made in the left lower quadrant, medial to the iliac spine. The successive layers of the abdominal wall are transected, including the parietal fascia, leaving the parietal peritoneum intact. Using finger dissection, the peritoneal sac is elevated off the underlying structures. A 10-mm incision of the anterior axillary line and a 5-mm incision in the left upper quadrant are made to accommodate corresponding blunt trocars that are inserted under finger guidance in the extraperitoneal space. A second ancillary trocar is introduced in the infracostal area in the midaxillary line. A laparoscopic balloon trocar is then introduced in the first incision. It will accommodate the endoscope. The extraperitoneal space is inflated while the peritoneal cavity is exsufflated. The initial landmarks (psoas muscle, left common iliac artery, and left ureter) are identified; the initial dissection plane is found between the ureter and the common iliac artery. The space is developed by elevating the peritoneal sac along with the ureter. Access is gained to the presacral area and then to the right common iliac area. Further development is obtained in the cephalic direction by clearing the psoas muscle and the lateral aspect of the left common iliac artery and of the aorta. The inferior mesenteric artery and the left renal vein are generally identified by following the left ovarian vein up to the point where it ends. The nodes are then separated from the vessels and from the sympathetic chain by a combination of hemostasis and section. Multifunction instruments are more adapted, as they avoid changing instruments and allow to overcome the fact that only two ancillary instruments can routinely be placed in the narrow retroperitoneal space.

Sonoda et al. (50) reported on a large series of 111 patients with locally advanced cervical cancer who underwent surgical staging. The mean duration of the procedure was 157 ± 46 minutes and the average number of nodes was 19. The mean postoperative stay was 2 days. Perioperative complications occurred in 14 patients. The majority of these complications were symptomatic lymphoceles that occurred in 11 patients: 8 of these lymphoceles were drained under radiologic guidance, 2 required a catheter placed under anesthesia, and 1 required laparoscopic drainage. The rate of symptomatic lymphoceles was later reduced by opening the peritoneum at the end of the procedure ("marsupialization" of the peritoneum) to drain the retroperitoneal fluid into the peritoneal cavity.

The typical indication for extraperitoneal aortic dissection is the patient with locally advanced cervical carcinoma. Knowledge of the status of the aortic nodes allows tailoring of the radiation therapy fields. With this indication, common iliac nodes are generally removed along with the aortic nodes. The potential benefit of surgical staging of locally advanced cervical cancer is based on the lack of sensitivity of positron emission tomography in the identification of micrometastases less than 5 mm (51), knowing that the group of patients with small lymph node metastases is the most likely to benefit from surgical removal of nodes (52). However, the indication and extent of the dissection, including or not the supramesenteric nodes, is still controversial (53).

The finding that this approach is more feasible than the transperitoneal approach for aortic dissection, particularly in obese patients, has led to the adoption of the extraperitoneal route as an elective choice in the staging or restaging of obese endometrial or ovarian cancer patients. In such patients, the aortic dissection is performed retroperitoneally following which the other steps of the procedure are performed transperitoneally. To achieve this, the extraperitoneal trocars are replaced in the peritoneal cavity.

Extraperitoneal Pelvic Node Dissection

Laparoscopic pelvic lymphadenectomy can be performed using the direct extraperitoneal approach. Historically, this approach was the first application of panoramic surgical endoscopy in oncology. This approach starts with a blind digital preparation of the preperitoneal space or with the use of direct vision trocar devices. A midline suprapubic access or an infraumbilical access may be used. Ancillary trocars are placed in the preperitoneal space.

This approach which has no definitive benefit over the transperitoneal approach while featuring all the shortcomings of the extraperitoneal approach, and which is limited to the pelvic area, has been largely abandoned in the gynecologic field. However, it is still used in urologic indications, with similar results compared to the transperitoneal approach (54) and has been recently rediscovered more than 20 years after having been pioneered by Dargent (55). It may be useful in cases where the pelvic cavity is not accessible or not easily accessible such as in pregnancy more than 16 weeks or when severe postoperative adhesions are present.

An innovative variant has been described recently using the same left lateral approach as used to perform an aortic dissection (56). The method may be useful to retrieve pelvic nodes when deemed necessary at the time of surgical staging of advanced cervical cancer, or to shorten the transperitoneal step of the surgical staging of endometrial or ovarian cancer. However, but in some favorable cases, it is limited to the left pelvic area.

Laparoscopic Identification of Sentinel Nodes

The laparoscopic identification of sentinel nodes can be considered as the symbol of the trend toward minimizing the surgical trauma of staging gynecologic malignancies and optimally using the possibilities of laparoscopic surgery. The original goal of the sentinel node concept was to avoid a complete lymphadenectomy in node-negative patients and, in some circumstances, in node-positive patients as well. The laparoscopic approach is fully adapted to the objectives of a pre-therapeutic workup procedure: defining the extent of disease and commensurate therapy without exposing the patient to an excessive risk; in addition, the magnification associated with the laparoscopic view is ideal to identify minute lymphatic channels. The development of endoscopic gamma probe has made possible the use of the combined (isotopic and colorimetric) assays that are mandatory to increase the accuracy of the method.

Technically, the identification and retrieval of pelvic sentinel nodes involves several steps. Intracervical injection of radiolabeled colloid is performed before the surgery. Planar or Single-photon emission computed tomography-computed tomography (SPECT-CT) imaging is a useful tool in locating sentinel nodes, particularly the nodes located outside the field of usual pelvic lymphadenectomy (57,58,59). Injection of blue dye is performed at the time of surgery. The 4-quadrant approach is being gradually replaced by a 2-quadrant approach that reduces the risk of injecting the pouch of Douglas. After having established the laparoscopic view, the surgeon uses the gamma-probe to globally locate nodes before incising the peritoneum in front of the "hot" node. Blue lymphatic channels may also be identified occasionally below the peritoneum. The peritoneum is then incised. On either side, the node closest to the cervix (the closest at isotopic identification, the first to be connected to a blue channel coming from the cervix) is bluntly dissected. Special care must be taken not to injure adjacent structures, as the sentinel node technique does not imply identifying at first the major anatomical landmarks of the area.

Several systematic reviews (60,61), 2 prospective multicenter studies (62,63), and the recent report of pioneers in the

field (64) have established the diagnostic value of sentinel node identification in the staging of uterine cancer. Detection rate is 97% to 99% using the combined technique (60,64). Laparoscopic sentinel node identification is highly reliable, with 100% sensitivity, using the full pelvic dissection as the gold standard. However, definitive conclusions can be drawn only when sentinel nodes are identified bilaterally (60,64). This implies that full dissection remains mandatory on the site where no sentinel has been identified. The sentinel node concept does not apply to massive involvement of the nodes, stressing the fact that careful preoperative imaging is required to identify patients with grossly enlarged nodes. Interestingly, 17% of sentinel nodes are found in “aberrant” locations and would have been missed by a standard lymph node dissection. Frozen section of sentinel nodes is of value only if positive, as over 40% of positive nodes are identified after “ultrastaging” involving serial sections and immunohistochemistry in cervical cancer (64). Interestingly, of the metastatic sentinel lymph node (SLN) metastases not identified on frozen section in Roy et al. series, only one measured more than 2 mm (2.9 mm), seven measured between 0.4 mm and 2 mm (micrometastases), and two had isolated tumor cells only. The same finding has been reported in endometrial cancer patients (63). This finding is not a flaw of the sentinel node concept in uterine cancer, but a shortcoming of the frozen section examination. Thus, awaiting the development of novel intraoperative imaging techniques such as fluorescence of tumor cells (fluorescence of lymph channels is not a solution), a reasonable strategy may include: (a) laparoscopy with sentinel node biopsy, (b) frozen sections of the sentinel nodes, and (c) systematic dissection if the frozen section is negative. In the cases where either the sentinel node biopsy or other nodes have metastasis, aortic node dissection is performed during the same operative session and chemoradiation can be proposed only to avoid combining radiation therapy and surgery in the same patient after laparoscopy.

The concept of laparoscopic sentinel node has first been developed in cervical cancer, as a tool to select patients most suitable for surgical management. In low- and intermediate-risk endometrial cancer, the rationale is different as the need for lymph node dissection is controversial. Sentinel node could be a midterm between no dissection (leaving the small proportion of node-positive patients) and full dissection (adding a useless procedure in the majority of node-negative patients). In addition, ultrastaging of the sentinel nodes using intracervical injection of dye and colloid detects micrometastases otherwise undiagnosed by conventional histology even in patients considered at low risk on the basis of grade and depth myometrial invasion (63). The question of alternative injection sites, hysteroscopic or fundic, in endometrial cancer patients has been addressed (65,66), without evidence of benefit of the more demanding and less practical modalities.

Laparoscopic Diagnostics of Pelvic Masses

The management of early ovarian cancer and borderline tumor of the ovary will be addressed in a later section. The topic of this section is to explore the advantages – diagnosis and management of benign masses – and the drawbacks of introducing laparoscopy in the flowchart of the assessment of a pelvic mass. The laparoscopic management of pelvic masses significantly reduces the length of hospital stay, operative morbidity, and overall postoperative recuperation time. Despite careful preoperative evaluation, it appears inevitable that some of those masses will turn out to be malignant. Proper management and adherence to strict surgical guidelines are very important in achieving optimal results.

Large series reported that among all patients approached laparoscopically for pelvic masses, the overall rate of malignancy

is low. The rate varies greatly among the studies according to the preoperative selection criteria used and the study design. In 1994, Canis et al. (67) published an extensive, retrospective 12-year analysis with long-term follow-up of 757 patients from 1980 to 1991. The rate of inadvertent malignancy was 2.5% (19 of 757), including 12 borderline and 7 invasive cancers. Additionally, 27 masses were falsely diagnosed as malignant (3.6%), which means that these patients had an unnecessary laparotomy. Canis et al., based on that experience, considered laparoscopic management of pelvic masses to be safe and reliable. The findings of this early publication have been consistently confirmed in several studies. Leng et al. retrospectively reviewed a series of 2,083 patients laparoscopically managed for adnexal masses. Sixteen patients had a malignant or borderline tumor, 14 of them were diagnosed intraoperatively. No adverse outcome related to laparoscopic diagnosis was reported in this study (68). A randomized controlled study on 102 patients comparing laparotomy to laparoscopy showed that inadvertent cyst rupture was frequent in both groups and operative time was comparable. The laparoscopic approach was associated with significant reductions in operative morbidity, postoperative pain, required analgesia, hospital stay, and recovery period (69).

However, the surgeon must keep in mind that failure to diagnose malignancy; underestimation of the extent of disease; tumor spillage from rupture of the masses; inability to perform complete staging (implying another surgery for the patient); and, most important, long delays before a staging procedure or definitive treatment can adversely affect the ultimate prognosis of the patient (70). Maiman et al. (71) surveyed Society of Gynecologic Oncologists (SGO) members with regard to their management of ovarian neoplasms later found to be malignant. The response rate from members was 42% and 42 cases of ovarian malignancy were reported. In that survey, immediate staging had been performed in 17% of cases, delayed in 71% (median, 36 days), and not performed in 12%. The authors raised significant concerns with regard to the negative outcome of the significant number of patients who were not restaged and to the delay between the initial procedure and the definitive treatment. They concluded that delays of more than 4 weeks had a negative impact on patient outcome. Blanc et al. (72,73) conducted a similar multi-institutional French survey and recorded 5,307 ovarian lesions treated laparoscopically, of which 1.4% were malignant. Staging of cancer cases was performed immediately in 25% of the cases, delayed in 58% (median, 78 days), and not performed in 16%. In those who had delayed staging, 22.4% were upstaged. Kindermann et al. (74) also sent a questionnaire to 273 German departments of obstetrics and gynecology with a response rate of 46%. They collected a total of 192 ovarian cases managed laparoscopically. Capsule rupture and tumor morcellation with intra-abdominal spillage occurring at laparoscopy was associated with spread of disease and port-site metastases identified at staging laparotomy. Endoscopy bags were used in only 7.4% of ovarian cancer cases. Leminen and Lehtovirta (75) reported on 8 patients who had their staging laparotomy after laparoscopic surgery within a mean of 17 days (range, 7 to 29). In 4 patients, the disease had spread from a localized to an advanced stage. The authors concluded that laparoscopic surgery of ovarian masses later found to be malignant can cause considerable and rapid spread of the disease. Lehner et al. (70) sent a questionnaire to all gynecology departments in Austria regarding laparoscopic management of ovarian masses later found to be malignant. They found that patients in whom definitive surgery was delayed more than 17 days were more likely to be upstaged (odds ratio of 5.3 for borderline tumors and 9.2 for invasive cancers).

A series of 141 patients undergoing laparoscopic surgery for a pelvic mass looked at the accuracy of frozen section to guide the surgical management. This study showed that the frozen section diagnosis was accurate in 95.5% of benign tumors, 77.8% of borderline tumors, and in only 75% of cancers (76).

The accuracy of the frozen section (FS) is also size-dependent: for masses larger than 10 cm, FS becomes less reliable (77). These results confirm that FS is a useful but inconsistently reliable tool to guide the intraoperative management. Thus, an alternate effective policy consists in removing every adnexal mass without spillage or contamination of the abdominal wall, waiting for definitive pathology and then planning whenever necessary for definitive laparoscopic staging and management of the disease.

The concept that patients with a suspicious pelvic mass should necessarily undergo laparotomy has been challenged. A diagnostic laparoscopy can be performed regardless of the ultrasonographic appearance of the pelvic mass, although an immediate laparotomy is recommended for staging and management of obvious cancer cases at laparoscopy. Laparoscopic management of high-risk pelvic masses can be successfully performed in an oncology referral population if there is expertise in operative laparoscopy, availability of immediate and accurate pathologic evaluation, and appropriate further treatment where indicated (78). In some cases, having an onsite oncologist skilled in advanced laparoscopic procedures allows laparoscopic completion of the staging procedure. However, when skilled assistance is unavailable, it is best to terminate the laparoscopic procedure after a cancer diagnosis and to promptly refer the patient for definitive surgery. Laparoscopy for the management of pelvic masses can eliminate the need for unnecessary laparotomy in most cases. Statistically, the majority of them will be benign and can be adequately managed laparoscopically. However, surgeons should be technically meticulous to minimize the risk of ovarian cyst rupture and spillage, and specimens should always be retrieved intact through an endobag to reduce the risk of trocar-site metastasis.

In a series reported by Havrilesky et al., the ovarian malignancies discovered at the time of laparoscopy for pelvic masses were managed laparoscopically and this was not associated with an adverse outcome (79). Lécuru et al. found no deleterious influence of laparoscopy as first surgical access on outcome of patients with early-stage ovarian cancer (80).

Abdominal Staging or Restaging Procedures

Working in the upper abdomen generally requires using the same position of the surgeon and the same placement of trocars adopted to perform a transperitoneal aortic dissection: trocars are placed lateral to the umbilicus, and the surgeon stands between the legs of the patient. Some advise to place the endoscope in the suprapubic area. Alternatively, the surgeon can use the position adopted to perform an extraperitoneal aortic dissection: 2 trocars are placed in the left flank, and the surgeon stands on the left side of the patient, working horizontally. This position is quite ergonomic, and can be used to perform an omentectomy after an extraperitoneal aortic dissection, after replacement of the trocars in the abdominal cavity.

Taking peritoneal biopsies is straightforward. A grasping forceps creates a fold on the peritoneum. The fold is incised, taking care not to injure underlying structures. The peritoneal flap is then elevated and excised. The same technique is used to perform biopsies of undersurface of the diaphragm. Once the diaphragmatic peritoneum is incised, the pressure of the CO₂ contributes to develop the space between the peritoneum and the muscle fibers. There is usually no need for hemostasis or specific instrumentation.

Omentectomy is a mainstay of peritoneal staging. Infrahcolic omentectomy is the standard diagnostic procedure. The procedure is straightforward using the modern multifunction instruments that allow to grasp, to apply hemostasis, and to cut. Controlled bipolar energy with cutting or ultrasonic shears can indifferently be used. Additional bipolar cautery or clip may

have to be used to control bleeding. The omentectomy generally starts at the left splenic flexure. The transverse colon is identified by elevating the omentum. The assistant constantly stretches the omentum to constantly identify the angle between the omentum and the transverse colon. The cutting instrument is used parallel to the caudal aspect of the transverse colon and gradually detaches the omentum from the colon, taking care not to injure the transverse colon. The omentum is then placed either in a bag, or left in the pouch of Douglas if a hysterectomy is planned.

Infragastric omentectomy is less frequently performed laparoscopically. It requires two additional steps: separating the transverse colon from the gastrocolic ligament, and controlling the vascular supply at the level of the greater curvature of the stomach. Separating the transverse colon is achieved by cutting the peritoneal layer attaching the omentum to the transverse colon, then elevating the omentum from the mesocolon while entering the lesser sac. Controlling the vessels of the greater curvature of the stomach is best achieved using blocking clips (Hem-o-lok) inserted via a 10-mm instrument. Incidentally, a similar technique is used to prepare omental flaps when necessary.

The technique of appendectomy is beyond the scope of this chapter. Briefly, the appendix is grasped and elevated, the meso-appendix is coagulated and cut, the base of the appendix is tied using a loop or a blocking clip, and the appendix is divided.

Laparoscopic Assessment of Advanced Adnexal or Peritoneal Malignancy

Assessment of Resectability

The technique described in this section refers to the assessment of the peritoneal disease in patients with advanced ovarian cancer characterized by ascites, carcinomatosis, and omental cake, to take biopsies and select the patients for optimal surgical debulking by laparotomy. Unfortunately, there is no perfect tool to determine preoperatively whether patients can be optimally debulked surgically, or be proposed neoadjuvant chemotherapy. CT scan can be used for this purpose, and biopsies under radiologic guidance may be performed. However, CT scan may underestimate the extent of the disease, in particular the extent and location of carcinomatosis, and biopsy under radiologic guidance is not always feasible. Other malignancies, particularly of gastrointestinal origin (such as colon, pancreas, stomach, and others), or rare peritoneal malignancies (mesothelioma) can mimic adnexal or peritoneal cancer. Definitive pathologic diagnosis is critical before initiation of any chemotherapy. This is why laparoscopy has become a valuable diagnostic tool in the workup of advanced peritoneal disease.

The diagnostic laparoscopic procedure can have some pitfalls: first, the presence of a large amount of ascites may lead to a reduced visibility; second, the gastrointestinal (GI) anatomy can be distorted, or the colon and/or small bowel may be adherent to the anterior abdominal wall or omentum, which may increase the risk of bowel injury. The entire abdominal cavity may not be accessible to laparoscopic vision. Lastly, the issue of trocar-site implantation remains controversial, particularly in patients with adenocarcinoma, ascites, and carcinomatosis (see section on Port-site metastasis and risk of tumor dissemination). Technical details have been provided in this section concerning port-site metastases: placing the trocars in the midline, preventing port-site metastases, and excising the trocar sites at the time of laparotomy are mandatory.

Diagnostic accuracy essentially depends on the quality of sampling. Prediction of resectability is a much more complex question, as it depends on the skills and aggressivity of the surgeon. Angioli et al. reported on 87 patients with advanced ovarian cancer who underwent first a diagnostic open laparoscopy (81). In 61% of patients, optimal cytoreductive surgery was deemed possible and those patients underwent a laparotomy

and debulking surgery. The goal was achieved in 96% of cases. Conversely, in 39% of cases, optimal debulking appeared impossible and the first cycle of chemotherapy was quickly initiated the day following laparoscopic surgery, which is an obvious advantage of minimal access surgery and a possible prevention of the development of port-site metastases. The authors concluded that diagnostic open laparoscopy is a valid diagnostic tool to evaluate the extent of disease and avoids unnecessary laparotomies in patients where optimal debulking cannot be accomplished. Consequently, Fagotti et al. proposed a simple laparoscopy-based scoring system to estimate the chances of achieving optimal cytoreduction based on the presence of an omental cake, peritoneal carcinosis, diaphragmatic carcinosis, mesenteric retraction, bowel infiltration, stomach infiltration, and liver metastases. Each parameter was assigned 2 points if present. A score of greater than 8 predicted a suboptimal surgery with a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 70% (82). Other investigators later performed an external evaluation (83) that provided an external validation of Fagotti's score and showed that a simplified score (excluding omental cake and peritoneal carcinomatosis) could also be used. Fagotti et al. tested the ability of a fellow to accurately use the scoring system (84).

Laparoscopy still may be a valuable approach to avoid incomplete interval debulking surgery in patients deemed inoperable of the initiation of therapy, and in whom resectability is still questionable after completion of three cycles of chemotherapy. The results of this policy have been reported by Fagotti et al. in 2010 on 98 patients, resulting in a rate of exploratory laparotomies as low as 10% (85).

Second-Look Procedure

Second-look surgery – systematic surgical and pathologic assessment of the abdominal and pelvic cavity in patients who are clinically without evidence of disease – in advanced ovarian cancer has lost popularity. However, the model has allowed to establish the practical value of laparoscopic assessment of the peritoneal cavity. Husain et al. reported that the rate of negative evaluations and the rate of recurrences in patients with negative laparoscopic second looks are equivalent to those described in studies of second-look assessment by laparotomy (86). Conversely, in a prospective comparative study, a French group found the laparoscopic second-look evaluation to be suboptimal when compared to the abdominal approach, mainly because of the presence of adhesions which appeared to limit the thoroughness of the evaluation (87). In that study, the positive predictive value was 100%, but the negative predictive value was 86% (2 false-negative cases). Clearly, if residual tumor implants are readily confirmed at laparoscopy, then a laparotomy can be avoided in those patients. In patients with negative laparoscopic evaluation, it remains uncertain if laparotomy is more accurate, particularly in patients with diffuse adhesions. Littell et al. reported on 99 patients who had achieved a complete clinical response following first-line chemotherapy and underwent second-look surgery (88). Nearly 70% had a negative second-look laparoscopy and were converted to a planned laparotomy, whereas 32% had positive findings at laparoscopy and thus were spared a laparotomy. In that study, the negative second-look laparoscopy predicted a negative laparotomy in 91% of the cases. The authors concluded that the small increase in sensitivity offered by laparotomy does not warrant the increased morbidity. A pilot study from the Memorial Sloan-Kettering demonstrated that the laparoscopic approach results in less morbidity, shorter operating time, shorter hospital stay, less blood loss, and lower total hospital charges (89). Husain et al. later concluded, in a series of 150 cases, that the complication rate of the laparoscopic approach is low and that it is a safe approach even in patients who had a prior abdominal surgery (86).

LAPAROSCOPIC OR LAPAROSCOPICALLY ASSISTED SURGICAL MANAGEMENT PROCEDURES

In this section, only the surgical procedures required for the management of primary gynecological malignancies will be detailed. Lymph node dissection and other procedures associated to the comprehensive management of gynecologic malignancies have been described above. The extent and indications of specific surgical procedures, and the extent of lymph node dissection are beyond the scope of this chapter. It is assumed that the reader masters these techniques enough to be able to provide the patient a standard of care consistent with the current guidelines.

Surgical technique

Simple hysterectomy

“Simple” – as opposed to radical – hysterectomy and bilateral salpingo-oophorectomy remains the cornerstone for the treatment of endometrial cancer. In addition, the trend toward a reduction of radicality in microinvasive or low-volume early cervical cancer has put simple hysterectomy in the armamentarium for the surgical management of cervical cancer. Total hysterectomy has been traditionally performed through an open approach to completely assess the peritoneal cavity and perform lymph node sampling or lymphadenectomy. Vaginal hysterectomy only has been used in the management of endometrial cancers in patients with multiple comorbidities. However, the vaginal route does not allow for the evaluation of the peritoneal cavity and the retroperitoneal lymph nodes, which has been made possible by the introduction of laparoscopic lymphadenectomy. For that reason, MIS has become increasingly popular in the management of gynecologic malignancies to the point that it has become a standard in surgery for endometrial cancer (90).

From a technical point of view, knowing that the uterus is invariably retrieved vaginally, the whole range of combinations of laparoscopic and vaginal approach (laparoscopically assisted vaginal hysterectomy) is available to the surgeon. Theoretically, several combinations are available: laparoscopic staging only, laparoscopic staging with management of the upper pedicles, laparoscopic staging with management of the upper pedicles and of the uterine arteries, laparoscopic hysterectomy followed by closure of the vaginal cuff through a vaginal approach, and full laparoscopic hysterectomy. However, considering the shortcomings of shifting from laparoscopic to vaginal approach, which requires changing surgeon's and patient position, and an additional set of instruments, full laparoscopic hysterectomy has gained more acceptance. Only patients not suitable for laparoscopic hysterectomy for whatever reason will benefit from an additional vaginal approach. Even when the vaginal approach is elected, it is made much safer and easier, particularly in obese patients, if the infundibulopelvic pedicles have been divided. The conclusion is then that practically, only two logical options are opened to surgeon's choice: (a) laparoscopic staging and management of upper pedicles followed by vaginal hysterectomy and (b) full laparoscopic hysterectomy.

Full Laparoscopic Hysterectomy

The full laparoscopic hysterectomy is mastered by many modern gynecologists. The mainstay of the technique, both cheap and reliable, is the use of monopolar energy for the division of the peritoneum and vagina and of bipolar cautery for the hemostasis of the main pedicles. It is substantially facilitated by the use of a cul-de-sac presentator. Although reservations about the use of

these instruments have been raised, no objective detrimental effect on cancer outcome has been demonstrated. In addition, at least one needle holder is necessary to complete the closure of the vagina laparoscopically.

The round ligaments are typically divided using monopolar cautery. Preventive hemostasis of infundibulopelvic ligaments is achieved using bipolar cautery, or blocking clips, or any other adapted device. The only potential danger is the ureter, which is running at a distance from the ovarian vessels if the corresponding adnexa is grabbed and firmly moved medially to stretch the infundibulopelvic ligament. The peritoneum of the posterior leaf of the broad ligament is then divided in the direction of the torus uterinus, taking care to incise the peritoneum only and not to injure the underlying vessels. The uterine insertion of the uterosacral ligaments is then cauterized and cut. The peritoneum of the ventral part of the pouch of Douglas is opened. The peritoneum of the vesical fold is then incised and the vesicouterine septum is developed, down to the point where the anterior vaginal cul-de-sac delineated by the cul-de-sac presentator is fully separated from the bladder. The uterine pedicles are then visible in either broad ligament. The ascending branches are cauterized and cut slightly above the uterine isthmus. The last attachments of the uterus are then cauterized and cut medial and caudal to the uterine vessels. The lateral cul-de-sacs, featuring their characteristic white color, are freed from the surrounding tissues. The vagina is incised anteriorly and then grabbed. The vaginal incision is completed using a monopolar hook. The uterus is delivered. Hemostasis is checked and completed if necessary using bipolar cautery. The vaginal cuff is closed by a continuous suture running from one angle of the vagina to another.

Laparoscopic Management of the Upper Pedicles and Vaginal Hysterectomy

This option is more appealing to surgeons who have been trained in vaginal surgery. The management of the infundibulopelvic and round ligaments is straightforward even for any modern gynecologic surgeon, and does not require specific training. The laparoscopic management of the upper pedicles can be occasionally complemented by the division of the posterior leaf of both broad ligaments, thus favoring the vaginal mobilization of the uterus, and by the coagulation of the origin of the uterine arteries that is routinely identified at the time of lymph node dissection.

The technique of vaginal hysterectomy is beyond the scope of this textbook. The uterine cervix is firmly grabbed using grasping forceps. The full thickness of the vagina is incised. The pouch of Douglas is entered, and the vesicouterine space is developed. Interestingly, the remaining steps can be completed using the instruments and the technique of laparoscopic surgery: serial bipolar coagulation and division of the attachments of the cervix, the isolation and placement of a blocking clip on each uterine artery mimic in a retrograde way the technique of laparoscopic hysterectomy (91). Obviously, both vaginal and laparoscopic techniques are “minimally invasive” and are complementary. The patient highly benefits from any combination of both techniques, and the surgical technique by both approaches is improved by the dual training.

Perioperative Outcomes: Evidence-Based Benefits of Laparoscopic Surgery

Simple hysterectomy technique and results are extensively documented in the literature addressing benign gynecology procedures. It conveys obvious advantages over the open procedure. With exceptions, the choice should be made between the laparoscopic and the vaginal approach. When the choice is open, with a patient suitable for both approaches, and a surgeon trained in both techniques, full laparoscopic hysterectomy may be the preferable approach, as it has been found to be associated with

less postoperative pain in a randomized trial (92). However, vaginal hysterectomy has a shorter operating time, and possibly less complications, as evidenced in another randomized trial in women with benign uterine disease (93). This is true even in patients generally deemed to present a contraindication of vaginal surgery (94).

In gynecologic oncology, most of the literature refers to the combination of hysterectomy and lymph node dissection in the surgical management of endometrial cancer, thus making the analysis of perioperative data concerning hysterectomy by itself more difficult. However, high level evidence in favor of laparoscopic surgery including data from controlled studies is available. Interestingly, one of the studies from the Netherlands compared only hysterectomy in a cohort of endometrial cancer, with no interference of lymph node dissection (95).

Hauspy et al. recently reviewed the literature until January 2009 (96). They reviewed 23 articles: 5 were randomized controlled trials (RCTs), 4 were prospective reviews, and 14 were retrospective reviews. More recently, a meta-analysis of the available randomized trials has been published (38). Estimated blood loss and hemoglobin or hematocrit change was consistently less after laparoscopy in the six studies where they were reported (95–101).

After combining the data from all of the RCTs included in their meta-analysis, Zullo et al. found that intraoperative complications rates were not different between laparoscopy and laparotomy (RR, 1.25; 95% CI, 0.99–1.56) without significant heterogeneity across the studies (98). They found a significant advantage of laparoscopy over laparotomy in terms of postoperative complications (RR, 0.71; 95% CI, 0.63–0.79) with significant heterogeneity across the studies. In a recent study, a significantly higher proportion of patients in the open surgery group experienced adverse postoperative grade 3 or higher (23.2% vs. 11.6%) (102).

The largest randomized trial is the LAP2 study (99) that was designed to compare laparoscopy versus laparotomy for comprehensive surgical staging and management of stage I to IIA uterine cancer including hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and paraaortic lymphadenectomy. Patients were randomly assigned to laparoscopy ($n = 1,696$) or open laparotomy ($n = 920$). A significantly longer operative time (204 vs. 130 minutes) was observed in the laparoscopy group. Intraoperative complication rates were similar. Laparoscopy had significantly fewer moderate to severe postoperative adverse events than laparotomy (14% vs. 21%). Hospitalization of more than 2 days was significantly lower in laparoscopy versus laparotomy patients (52% vs. 94%). Although pelvic and paraaortic nodes were not removed in 8% of laparoscopy patients and 4% of laparotomy patients ($p < 0.0001$), no difference in overall detection of advanced stage was seen. The study has a major shortcoming related to its multicentric design: a high conversion rate. About 25.8% of patients assigned to the laparoscopic arm were converted to laparotomy, reflecting the learning curve of some investigators, particularly for node dissection. However, as it is likely that further training would have resulted in even better results of laparoscopic surgery, this does not weaken the conclusions of the paper. This study gives evidence that laparoscopic surgical staging for uterine cancer results in fewer complications and shorter hospital stay.

A few recent open series specifically addressed the issue of complications. Tinelli et al., in 2011, compared the complication rates of laparoscopic and open surgeries in a multicenter series of 226 women with early stage endometrial cancer (103). Patients underwent total hysterectomy and pelvic dissection. One patient of the laparoscopy group had an uretero-vaginal fistula and another patient had a ureteral stricture temporarily treated with a stent. One patient of the laparoscopy group had a bowel perforation due to dense adhesions with the peritoneum under the umbilicus, resolved with a bowel resection and an

end-to-end anastomosis. In 3 patients of the laparoscopy group a vaginal cuff dehiscence was observed and in one case a pelvic lymphocyst was reported. Barnett et al., in 2011, retrospectively compared a group 107 women patients who underwent laparoscopy with a group of 269 patients matched on age and body mass index (104). Adverse event rates were nonsignificantly different between cohorts (37% laparoscopy vs. 43% laparotomy). Laparoscopy had higher unexplained rates of mild sensory peripheral nerve deficit (5% vs. 0%) and lymphedema (7% vs. 1%), whereas laparotomy had higher rates of cellulitis (16% vs. 7%) and open wound infections (9% vs. 2%).

Palomba et al. reported in 2012 on 1012 endometrial cancer patients operated between 2000 and 2010 in 6 Italian centers (105). Although retrospective, the study reflects the use and benefits of laparoscopic surgery in clinical practice out of the experimental setting of pioneering centers. Overall, 403 patients were managed laparoscopically while 609 had open procedures. Advanced stage, grade 3, and papillary serous subtypes were more often managed by laparotomy. Interestingly, the rate of laparoscopies increased in all centers throughout the time of the study. Feasibility in the laparoscopy group was 86.8%. Operative time was significantly longer in the laparoscopy group (199 vs. 135 minutes). The overall rate of pelvic and aortic dissection and the number of retrieved pelvic and aortic nodes were similar in the two groups. Complication grade was higher in the laparotomy group. Blood loss was less in the laparoscopy group. Recurrence and survival rates were similar in both groups. This study has several flaws: retrospective and unbalanced by nature (731 patients were excluded from the study because of lack of relevant pathologic and clinical data), it encompasses a long period of time with a trend toward the development laparoscopic surgery in all centers. Stage I endometrial cancer is indisputably an elective indication for laparoscopy, stage II patients must be operated in tertiary centers, and the rationale of surgery in clinical stage III is not different from the rationale adopted in ovarian cancers, with similar reservations.

A theoretical pitfall to laparoscopic management of endometrial cancer is the potential for retrograde seeding with the use of a uterine manipulator. On this basis, some surgeons seal the fallopian tubes before beginning the hysterectomy. However, whether or not the incidence of positive peritoneal cytology is higher after laparoscopic surgery is controversial (106). This is probably a nonissue, as any intrauterine diagnostic procedure is associated with retrograde reflux of endometrial cancer cells, and since the presence of isolated cells is not associated with a higher risk of recurrence (107).

Cost Issues

A systematic review of cost issues based on randomized trials is available (108). Analysis was performed on 2,226 patients, of which 1,013 were managed laparoscopically. While the total direct costs in the laparoscopy group (\$63,997) were marginally higher than the abdominal surgery group (\$60,114), the total indirect costs of the laparoscopy group (\$1,609) were substantially lower than in the abdominal surgery group (\$3,139). The authors concluded that the shorter hospital stay and a lower complication rate in the laparoscopy group compensates for the increased procedure costs but called for further research with a broader cost perspective. The same team later published on the economic aspects of the Dutch randomized study. The median utility scores were comparable between laparoscopy and laparotomy at 3 months. The increased intraoperative cost of laparoscopy, reflecting the longer duration of surgery and the use of disposable instruments, was compensated by a less costly postoperative hospital stay (+ \$1,129 vs. - 1,350, respectively) (109).

In a societal perspective approach, Barnett et al. found laparoscopy (\$10,128) as the least expensive approach followed by robotic and (\$11,476) and open hysterectomy (\$12,847) (110).

They also found that in the hospital perspective, laparoscopy was least expensive compared to laparotomy only if hospital stay after open surgery was more than 2.9 days (109).

Conclusion

There is thus definitive evidence of the short-term benefit and cost-effectiveness of laparoscopic hysterectomy in gynecologic cancer patients. This includes patients with comorbidities, obesity, or advanced age. The issue of the obese patient will be addressed in a specific section later in the chapter (The Case of The Obese Patient). Regarding comorbidity, Tozzi et al. found that patients with serious comorbidities benefit the most from laparoscopy (111). The case of the elderly patient has been addressed in the gynecologic oncology literature. Siesto et al. reported a series of 48 patients older than 65 years (112). This group of patients was comparable to younger patients in operative time, blood loss, need for blood transfusions, nodal count, and intraoperative and postoperative complications. They concluded that in the absence of absolute anesthesia contraindications, laparoscopy is feasible and safe in older women with endometrial cancer. As the group of older patients was more frequently upstaged than the group of younger patients, they stated that comprehensive surgical staging should be offered, regardless of age, to avoid understaging and to optimize treatment strategies.

The major shortcoming of laparoscopic surgery is increased operative time. However, operative time is directly dependent on the surgeon's factor. Interestingly, in the first study involving laparoscopically assisted vaginal hysterectomy by surgeons experienced in vaginal and laparoscopic surgery, operative time was higher by only 10 minutes (not significant) (96).

Laparoscopic Radical Hysterectomy

The term "radical" or "extended" hysterectomy encompasses a variety of different surgeries. Classification is not standardized, and the most widely used ones are not satisfactory, not universal, and not anatomically relevant. A new classification was proposed in 2009, taking into account the lateral extent of excision of the paracervix (type A, midway between the ureter and the cervix; type B at the ureter; type C, at the pelvic sidewall; and type D, with resection of the pelvic sidewall) (113). Two type C subtypes have been defined: C1, with nerve preservation and C2, without nerve preservation. In addition, the radicality of the type B subtype can be extended without impairing the bladder function by adding a lateral paracervical dissection or "parametrial lymphadenectomy" (114). The full laparoscopic hysterectomy will be detailed as the main choice, but options derived from combinations of vaginal and laparoscopic surgery will be mentioned, as they may be useful for subgroups of patients.

Full Laparoscopic Hysterectomy: Technique and Perioperative Outcome

The cul-de-sac presentator is installed as in simple hysterectomy. The upper pedicles are managed as in simple hysterectomy. If the adnexa are preserved, the utero-ovarian vessels are divided 1 cm lateral to the uterine cornua. The peritoneum of the vesical fold is incised and the vesicouterine septum is widely developed. The paravesical space is developed at the time of pelvic lymphadenectomy. The ureters are identified at the pelvic brim and left attached to the lateral pelvic peritoneum. The pararectal space is opened between the ureters and the iliac vessels. The origin of the uterine artery is identified and skeletonized and then controlled using bipolar cautery or a blocking clip (Hem-o-lok) then divided. The superficial uterine vein is cauterized and then divided. The uterine pedicle can then be firmly grasped and elevated, thus opening the tunnel of the ureter. Occasionally, the ureter is attached to the uterine artery by a small ureteric artery that must be carefully

cauterized at a distance from the ureter and then cut. The vesicouterine ligament is then delineated between the vesicouterine space and the ureter; it is stretched by the combined use of the cul-de-sac presentator and of an instrument elevating the bladder. Bipolar cautery can then be safely applied midway between the uterus and the bladder. The bladder base is thus fully separated from the uterus and upper vagina.

The dorsal steps can be achieved before or after the ventral steps. The peritoneum of the posterior leaf of the broad ligaments is incised down to the “uterosacral” fold. The sacrouterine space is found immediately lateral to the uterosacral fold. Once the sacrouterine space is found and developed, the hypogastric nerve and the ureter can be moved medially. The rectouterine ligaments are cauterized and cut at a distance (generally 1 cm) from the uterus. The peritoneum of the pouch of Douglas is then incised and the rectovaginal septum is developed down the posterior vaginal cul-de-sac.

The excision of the paracervix (“cardinal ligament,” “lateral parametrium”) is the next step. The extent of the excision defines the radicality. The dorsal aspect of the cardinal ligament has been made visible after the section of the rectovaginal ligament. The ventral aspect is delineated by opening a narrow space below the ureter (“retrovesical fossa”). The paracervix is then cauterized and divided. It generally contains the deep uterine vein that can be skeletonized and then electively cauterized and transected. The caudal aspect is then freed from the paracolpos from the line of division to the vagina. To achieve this, the paracervix is firmly grasped and elevated. Successive small cauterizations and divisions are made in a horizontal plane until the white structure of the vaginal is visible. The vagina is then divided using the monopolar hook at 1 cm distance from the cervix. The uterus is delivered vaginally. The vaginal cuff is sutured using intraperitoneal suturing techniques. The integrity of the ureter and the hemostasis are checked before closing the trocar sites.

Preoperative Data, Complication Rate, and Postoperative Outcome

Noncomparative data in large series are available, as reported by Spirtos et al. (115) in 2002 on 78 patients. In that series, 94% of the procedures were completed laparoscopically. The mean operative time was 205 minutes, and the mean blood loss was 225 mL. One patient required a blood transfusion. Three patients had unintended cystotomies, 2 patients required laparotomy to control bleeding, and one patient suffered an ureterovaginal fistula. Pomel et al. (116) reported in 2004 on 50 patients. The median operating time was 258 minutes. No conversions to laparotomy were required. Ten patients had early complications (within 2 months of surgery); 3 of them required reoperation. Three patients had late complications (more than 2 months after surgery); 2 of them required reoperation. Three patients experienced recurrence with a median follow-up time of 44 months. A Chinese group (117) reported in 2007 the largest series ever published. Among 317 candidates to laparoscopic radical hysterectomies with lymphadenectomy, 313 procedures were completed laparoscopically. Four patients were converted for bleeding ($n = 2$), colon injury, and hypercapnia. Five cystotomies and 5 vascular injuries were repaired laparoscopically. Postoperative complications occurred in 5% of patients, including five uterovaginal fistulas, one with stenosis of the ureter and 4 with vesicovaginal fistula. In the same year, an Indian group reported on 248 patients with stage IA2-IB1 cervical cancer (118). No patients were converted to laparotomy. Fifteen intraoperative complications were managed laparoscopically and 17 had postoperative complications within 2 months of surgery.

In 2008, Chen et al., in the same team as Xu et al., reported on 295 procedures (119), 290 of which were successful. Para-aortic lymphadenectomy was performed in 156 patients (52.9%), and pelvic lymphadenectomy was performed in all 295 patients.

The median blood loss was 230 mL. The mean operation time was 162 minutes. In 5 cases, conversion to open surgery was necessary due to bleeding (3 cases), bowel injury (one case), and hypercapnia (one case). Other major intraoperative injuries occurred in 12 patients (4.1%). Postoperative complications occurred in 10.8% patients, ureterovaginal fistula in 5 cases, vesicovaginal fistula in 4, ureterostenosis in 3 cases, deep venous thrombosis in 9 cases, lymphocyst in 4 cases, lymphedema in 5 cases, and one case with trocar insertion site metastasis.

In 2009, Pellegrino et al. reported the surgical outcome in a series of 107 patients (120). Conversion to laparotomy was necessary in 6 patients. Median blood loss was 200 mL and median duration of surgery was 305 minutes. Minor intraoperative complications occurred in 2 patients. Five patients needed a second surgery for postoperative complications. In 2010, Lee et al. (121) published a series of 139 patients. Average operation time was 231.1 minutes. Major intraoperative complications included one great vessel injury, one ureteral injury, one colon injury, and 6 cystotomies. In 2011, Yan et al. evaluated the morbidity and oncological outcome in another large series of 240 cervical cancer patients treated with laparoscopic radical hysterectomy and pelvic lymphadenectomy (122). The conversion rate was 1.25%. Intraoperative and postoperative complications occurred in 7% and 9% patients, respectively.

A number of retrospective comparative studies are available. Only series of over 50 patients with laparoscopic radical hysterectomy will be mentioned. In 2004, Jackson et al. reported on 57 women candidates for laparoscopic radical hysterectomy (123). Conversion to laparotomy occurred in 5 cases. A matched control group of radical abdominal hysterectomy was constituted. Statistically significant differences were found: duration of surgery was shorter (median 180 vs. 120 min), blood loss was less (median 350 vs. 875 mL), and hospital stay was less (median 5 days vs. 8 days) in the laparoscopic surgery group. There were no statistically significant differences with regard to nodal yield, completeness of surgical margins or perioperative complication rate. Four major complications (8%, 3 cystotomies and one enterotomy) occurred in the laparoscopic surgery group and three in the open surgery group (6%, one pulmonary embolism, one ureteric injury, and one major hemorrhage). Steed et al. compared 71 patients managed laparoscopically to 205 patients managed by laparotomy (124). No conversion occurred in the laparoscopic group. Blood loss was 300 mL in the laparoscopy group versus 500 mL in the open surgery group. Operative time was longer (3.5 vs. 2.5 h) in the laparoscopy group, in which an increased perioperative complication rate was observed, with 7 cystotomies, one ureteral injury, one bowel injury, and a longer time to normal urine residual. In 2007, Frumovitz et al. (125) compared patients undergoing total laparoscopic radical hysterectomy with patients undergoing total abdominal radical hysterectomy. The mean estimated blood loss was significantly lower in the laparoscopic-surgery group than in the open-surgery group (319 vs. 548 mL). The average operative time was significantly longer with laparoscopic surgery (344 vs. 307 min), but the median hospital stay was significantly shorter (2 vs. 5 days). Infectious morbidity was substantially less frequent (18% vs. 53%) after laparoscopic approach. In 2007, Li et al. reported on a series of 90 laparoscopic radical hysterectomies that were compared to 35 open radical hysterectomies performed during the same period of time (126). Two cases were converted to laparotomy. Consistent with other reports, they found an increased operating time (263 vs. 217 min) for laparoscopic procedures. However, they did not find a reduced blood loss. Interestingly, they investigated the time to recover bowel movements and found a significantly reduced time after laparoscopy (2 vs. 2.4 days). In 2009, Malzoni et al. compared 2 series of laparoscopic ($n = 65$) and open ($n = 62$) radical hysterectomies (127). Consistent with earlier reports, there was less blood loss (55 vs. 145 mL),

median operating time was longer (196 vs. 152 min), and hospital stay was shorter (4 days vs. 7 days) in the laparoscopy group.

The specific question of the extent of parametrial resection and its relationship with urinary complications has been addressed in two studies. Ghezzi et al. (128) compared radical hysterectomy specimens of sequential patients undergoing laparoscopic radical hysterectomies (n = 50) with those of historical controls selected from women who have had conventional open radical hysterectomy (ORH; n = 48). The parametrial width was similar between laparoscopic and abdominal radical hysterectomies. Uccella et al. compared 50 laparoscopic surgeries to 48 patients' historical cohort managed by open surgery. There was no statistically significant difference in intraoperative urinary complications between the groups. Four intraoperative urinary tract injuries in the laparoscopic surgery group (3 cystotomies and 1 ureteral lesions, all repaired laparoscopically) and 2 in the open surgery group (2 cystotomies) occurred. Urinary postoperative complications were: 1 ureterovaginal, 1 vesicovaginal fistula, and 1 delayed ureteric fistula in the laparoscopic group versus none in the open surgery group. In patients without urinary complications, the average width of parametrial tissue removed in the laparoscopy group was 32 mm in patients versus 39.5 mm (129).

Finally, a small-size randomized controlled study is available. The Gateshead group recently evaluated perioperative surgical outcomes and resection size for laparoscopically assisted radical vaginal hysterectomy compared with radical abdominal hysterectomy in early stage IB cervical cancer (128). Fifteen patients were accrued in each group. Statistically significant differences were found between laparoscopic and abdominal approaches, respectively: median duration of bladder catheterization, 4 versus 21 days; average operating time, 180 versus 138 minutes; median blood loss, 400 mL versus 1000 mL, median hospital stay, 5 days versus 7 days; and median opiate requirement in the first 36 hours postoperatively, 30 mg versus 53 mg. All parameters were in favor of laparoscopic surgery. On the other hand, the mean resected lengths were smaller for laparoscopic surgery: mean resected vaginal cuff, 1.26 cm versus 2.16 cm; mean resected cardinal ligament length, 1.30 cm versus 2.79 cm; and mean resected uterosacral ligament length, 1.47 cm versus 4.68 cm. This has to be put in perspective with the trend to reduce radicality in the surgical management of less than 2 cm cervical cancer with negative nodes that are associated with a negligible risk of parametrial involvement.

The technique is thus feasible with a high success rate for a trained gynecologic oncologist with laparoscopic skills, and can be taught by experienced proctors. However, a steep learning curve is observed that prevents widespread use of the technique despite obvious merits. The cut-off is generally set at 45 to 50 cases (131,132). Interestingly, the learning curve has no impact on survival (131), is mainly based on operative time. In 2007, Zakashansky et al. (133) specifically examined the use of total laparoscopic radical hysterectomy in a fellowship program. They demonstrated that greater node counts, decreased hospital stay, and less blood loss are possible without increased morbidity in a training program.

However, provided the necessary efforts to improve skills have been made, excellent results can be achieved. This statement applies to so-called developing countries. The first 50 cases performed in Colombia were as successful as the first 50 cases performed at the M.D. Anderson Cancer Center (134). This adds to the evidence that with adequate teaching and proctorship, and willingness to learn, the technique of laparoscopic radical hysterectomy can be implemented in any place in the world, and all the more in developed countries where the incidence of cervical is still high, and where the additional cost of robotic surgery is not affordable.

Despite the inherent limitations of laparoscopic radical hysterectomy and its associated learning curve, the procedure conveys many documented advantages over the open technique

mainly in terms of blood loss and hospital stay. The outcome balance combining improved quality of life (QOL) without compromising survival is in favor of adopting MIS as the gold standard for radical hysterectomy.

Nerve-sparing Radical Hysterectomy (Type C1)

Nerve-sparing radical hysterectomy has been designed to prevent the frequent urinary dysfunctions associated with classical (type C) radical hysterectomy. Logically, the magnification and lighting provided by the laparoscope has also been used to achieve a precise dissection of the pelvic autonomic nerves.

The technique was pioneered by Possover et al., who identified the middle rectal artery as a landmark separating the neural part from the vascular part of the paracervix (135). The bladder function was significantly less altered after their attempt at preserving the neural part of the paracervix (cardinal ligament).

Since 2010, several investigators reported on full laparoscopic nerve sparing radical hysterectomy (LNSRH). Liang et al. (136) reported on 163 consecutive patients with cervical cancer who underwent laparoscopic radical hysterectomy and pelvic lymphadenectomy, of whom 82 women underwent LNSRH. The average time taken to obtain a post-void residual urine volume of less than 50 mL after removal of the urethral catheter was 7.4 in the LNSRH group compared to 16.75 days. The bladder function recovered to no or minor symptoms in 94% of patients of the LNSRH group compared to 73% for the LRH group. Kavalalis et al. (137) published a series of 32 patients who underwent LNSRH with pelvic lymphadenectomy. The average operating time was 221 minutes. The authors reported that in all patients spontaneous voiding was possible on the third postoperative day with a median residual urine volume <50 mL. Park et al. (138) carried out a retrospective study of consecutive 125 patients with cervical cancer stage IB1 (n = 105) and IB2 (n = 20). In this series, a high rate of urological complications (13/125, 10.4%) was observed. However, these surgical morbidities were corrected with increased experience. Patients were able to self-void at a mean of 10.3 days postoperatively. The return rates to normal voiding function at postoperative 14 and 21 days were 92.0% and 95.2%, respectively. The authors concluded that an LNSRH for stage IB cervical cancer is comparable to the corresponding open procedure in terms of early recovery of bladder function. To summarize, nerve-sparing techniques are feasible laparoscopically.

Type B Radical Hysterectomy with Paracervical Lymph Node Dissection (Type B2)

Paracervical cellulolymphadenectomy consists of removing all the lymph node-bearing tissue located in the vasculonervous web making up the lateral part of the paracervical ligament. The ventral, dorsal, and lateral component of the paracervix are successively cleared. First, the paravesical space is fully developed and the ventral part of the paracervix is exposed; the cellulolymphatic pad ventral to the deep uterine vessels is elevated by blunt dissection, taking care not to injure the vesical, vaginal, and obturator vessels forming the "web." As the anatomy is unpredictable, careful dissection is mandatory. The pararectal space is then opened between the ureter and the internal iliac artery and developed down the level of the sacrospinous muscle, taking care not to injure the hypogastric vessels. The dorsal aspect of the paracervix is exposed. The fatty tissue is less abundant and more fibrous in this area, and must be carefully detached from the vessels of the paracervix. Finally, the lateral part of the paracervix, which is located lateral to the iliac vessels and medial to the obturator muscle, is cleared. The cellular tissue overlying the pudendal vessels and the lumbosacral nerve is visible. It is gently grasped using an atraumatic forceps and bluntly dissected with the tip of a suction cannula.

The technique is designed to offer, in combination with a modified radical hysterectomy (type B), an increased radicality

without additional risk of urinary complications. The concept has been proved in a comparative study of radical hysterectomies with or without paracervical dissection, which concluded that adding a bilateral paracervical lymphadenectomy does not increase the preoperative complications and urinary dysfunctions rates (114).

Laparoscopico-Vaginal Operations

The combination of laparoscopic lymph node dissection and radical vaginal surgery was a major breakthrough in gynecologic oncology. The question is the current place of combined techniques (137). The key issue is training in radical vaginal surgery. Full description of the technique can be found in textbooks (91).

Although the Schauta operation is mastered by only a few gynecologic oncologists, it is of note still the best option in particular patients, such as patients with stage 4 uterine prolapse. The technique involves, after laparoscopic lymphadenectomy, creating and incising the vaginal cuff, opening the pouch of Douglas, opening the paravesical and pararectal spaces, developing the vesicouterine space, and identifying the ureters in the bladder pillar. The uterine arteries are then controlled and the paracervix are then divided under direct vision of the ureters. Type A or B radical hysterectomies, according to tumor extent, are achievable without the perineotomy used by the early pioneers.

Only the laparoscopico-vaginal operations and their results are in the scope of this chapter. Two combinations are available: the Coelio-Schauta procedure – a name designed by Dargent after the French “coelioscopie” (for laparoscopy) – and the Schauthem – a hybrid name designed by Leblanc after the Schauta and Wertheim eponyms. The former name describes a surgery starting laparoscopically and finished vaginally. The latter describes a procedure starting vaginally and finished laparoscopically.

Coelio-Schauta

After the initial description of laparoscopically assisted radical vaginal hysterectomy involving a laparoscopic step (division of the uterine artery and of the superficial uterine vein at its origin) and a vaginal management of the ureters and cardinal ligaments (10–11), several variants of different extent have been described (138).

Large series have been published with reassuring results. Sardi et al. (141) reported on 47 patients who underwent a procedure closer to a classical radical vaginal hysterectomy than a laparoscopically assisted procedure. After 4 years, the overall survival was 100% for stage IA, 88% for stage IB1, and 85% for stage IB2. They suggested that 20 cases were needed to obtain the minimum skill to perform CS. Hertel et al. (142) reported a large series of 200 patients with cervical cancer stages IA to IIIA who underwent a variety of radical hysterectomies, including type III (type C) procedures. A variant including laparoscopic nerve sparing preservation has also been described (140).

Two studies compared the safety, efficacy, and short-term benefits of the Coelio-Schauta (CS) procedure with open Wertheim/Meigs radical abdominal hysterectomy in cervical cancers. Sharma et al. (143) retrospectively analyzed records of 35 consecutive stage IB patients undergoing Coelio-Schauta for early cervical cancer and 32 ORHs. There were statistically significant differences between CS and ORH for duration of surgery (mean 160 vs. 132 min), intraoperative blood loss (479 vs. 715 mL), hospital stay (mean 5 vs. 9.3 days), postoperative complications (6 vs. 20 patients), and duration of bladder catheterization (mean 4.4 vs. 8.8 days). Four CS patients and no open-surgery patients had urinary tract injury. None had long-term sequelae. Their data confirmed that although CS is a suitable alternative to ORH for small-volume stage IB1 cervical cancer with similar clinical efficacy and a superior postoperative recovery and postoperative morbidity profile, urinary tract trauma is a clear risk in the early stages of the learning curve.

Pahisa (142) included 67 patients in the study group. The number of pelvic nodes, disease-free margin, and complications rate were similar in the study and control groups, but blood loss and blood transfusion rates were marginally less in the CS group. Operating time was longer in the first 20 CS patients, but it became comparable to open surgery once the learning curve was completed. Hospital stay was significantly shorter in the CS group and so was the bladder function recovery time. However, no differences were seen regarding long-term urinary and bowel functions between groups. Six percent from the CS group and 13% from the open surgery group had recurrence. Mortality rates were 3% and 9%, respectively.

Schauthem

In 2007, Leblanc described a technique that involved making the vaginal cuff as a first step of the procedure, thus making the laparoscopic step easier (91,145).

In conclusion, radical vaginal hysterectomy combined with laparoscopic lymphadenectomy or laparoscopico-vaginal procedures are still a safe alternative to full laparoscopic radical hysterectomy in the treatment of early stage cervical cancer in selected patients. In clinical practice, the various “minimally invasive” techniques for radical hysterectomy are not concurrent but complementary, and indication of each method is adapted to the individual patient. The full laparoscopic procedure has gained more acceptance.

It must be stressed that familiarity with the radical vaginal hysterectomy technique would facilitate performing specific fertility-sparing radical vaginal trachelectomy in young women with early cervical cancer. Training programs in gynecologic oncology should continue to cultivate radical vaginal surgery training, or alternately selected patients should be referred to a few centers that have kept a sufficient experience in this technique.

Laparoscopic Radical Trachelectomy

Radical trachelectomy is a conservative variant of radical hysterectomy for young patients affected by early invasive cancer on the superficial aspect of the cervix. The first pregnancies were described by Dargent, who used a laparoscopico-vaginal approach allows successful outcomes.

Contrary to radical hysterectomy, the vaginal approach (Dargent operation) remains the gold standard approach for radical trachelectomy. Its oncological and pregnancy outcomes have been extensively documented in large series (146,147,148). As it is essentially a radical vaginal procedure, associated with a laparoscopic lymphadenectomy, a topic that has been addressed above, the Dargent operation is beyond the scope of this chapter and will only be briefly described.

The operation proceeds the same way as the Coelio-Schauta. The first difference is that the uterine artery is preserved. The second and major difference is that the uterus is divided 5 mm below the isthmus. The specimen is sent to the laboratory for assessment of its superior margin by frozen section. The cavity is sounded and a dilator is inserted to widen the canal and facilitate the reconstruction. Once the results of the frozen section determine negative margins, the reconstruction is undertaken. The pouch of Douglas is closed with a running suture. An isthmic cerclage, using the same suture used for the conventional prophylaxis of miscarriage, is then placed. Finally, an isthmovaginal anastomosis is performed using Sturmdorf stitches or interrupted sutures approximating the vaginal mucosa and the isthmic mucosa with great care not to involve the internal os.

Abdominal techniques have been developed, and quickly mimicked by laparoscopic procedures (149) involving a variety of combination of vaginal and laparoscopic steps. The laparoscopic step is generally used for the resection of parametrium. The uterine artery can be preserved. Nerve-sparing techniques

have been described (150,151). The full procedure can be completed laparoscopically, but the surgeon may elect to use a vaginal step that may involve incision of the vagina, retrieval of the specimen, and uterovaginal anastomosis.

In the largest series to date, 27 patients underwent laparoscopic radical trachelectomy (152). The mean operating time was 290 minutes and the mean estimated blood loss was 332 mL. There were no perioperative complications requiring further surgical management. After a median follow-up time of 31 months, there was one recurrence and death from disease. Regular menstruation returned in 24 patients. Six patients attempted to conceive, and three succeeded.

Laparoscopic Pelvic Exenteration

Positive peritoneal cytology, microscopic or macroscopic peritoneal disease, and positive aortic nodes are contraindications to exenteration. As all these conditions can be ruled out using laparoscopic technique, the laparoscope is an ideal tool to assess the feasibility of pelvic exenteration, thus avoiding aborted laparotomies. The issue was addressed for the first time by Plante and Roy (153) and subsequently reported by Köhler et al. (154).

Pomel et al. (1) extended the procedure by actually performing a total laparoscopic pelvic exenteration with a small incision to create an ileal conduit and the diverting ileostomy. The operative time was 9 hours, and the postoperative course was uneventful. The operative technique was then refined to include the making of a continent urostomy through a minimal incision (155). Later, the Toulouse group retrospectively compared patients who underwent laparoscopic pelvic exenteration with open cases from the same period of time (156). In this series, 14 patients underwent laparoscopic pelvic exenteration while 29 patients underwent an open exenterative procedure. Criteria to define a patient as an ideal candidate for laparoscopic approach were: central pelvic tumors of less than 5 cm without pelvic side-wall involvement, body mass index (BMI) inferior to 30, and no need to perform vaginal reconstruction. Operative time, margin status, length of hospital stay, operative and postoperative morbidity, and disease and overall survival were not significantly different between both groups. The benefit of laparoscopic exenteration is then questionable.

Overall, 36 documented cases of laparoscopic pelvic exenteration for gynecological malignancy have been identified in the medical literature (156). The conclusion is that although laparoscopic pelvic exenteration with curative intent is feasible and safe in selected patients, its advantages are not obvious.

A major shortcoming of laparoscopic surgery is the inaccessibility to the full range of techniques to fill the pelvic dead space and reconstruct the vagina. After pelvic exenteration the pelvic space is a main source of postoperative complications, such as pelvic abscess, bowel obstruction, and fistula formation. Filling the pelvic dead space with vascularized tissue, especially with myocutaneous flaps and omental J flaps has contributed to better wound healing, and has dramatically reduced major complications. Pelvic/vaginal reconstruction also restores anatomic appearance, improves body image, and allows sexual intercourse. Vertical rectus abdominis flap (VRAM) is actually the most frequently used, as it is easy to perform, anatomic restoration of the pelvic empty space is very good, and it is associated with a low rate of necrosis and complication rate. Unfortunately, VRAM flap is obviously illogical for patients undergoing laparoscopic PE. Other flaps used for laparoscopic approach are gracilis and gluteal flaps, but both of them require longer operative time and are associated with higher rate of necrosis. Omental J flap covered with skin graft can be used as reconstructive technique. It is the most adapted technique for laparoscopic approach, as it does not require additional incisions. However, pelvic filling is not as good as with VRAM flaps, and long-term results are disappointing.

Therefore, laparoscopic pelvic exenteration is not advisable when patients desire vaginal reconstruction or when there is a large

pelvic defect to cover. Interestingly, the older group of patients is thus more amenable to laparoscopic pelvic exenteration.

Other Procedures

General surgery procedures associated with gynecologic malignancies, such as colostomy or splenectomy for isolated metastasis can be performed laparoscopically or hand-assisted by laparoscopy (157) (see also corresponding section below). Laparoscopy may help the radiation therapist or medical oncologist through the placement of pelvic displacement prosthesis, and guiding the placement of interstitial radiation implants (interstitial brachytherapy implants, placement of intraperitoneal port-a-cath [158]). Laparoscopic ligation of the hypogastric artery has been described as an alternative to embolization in severe hemorrhage related to uterine cancers. We have managed laparoscopically lymphocysts by intraperitoneal marsupialization, and vaginal eviscerations by laparoscopic omentoplasty combined with vaginal closure. New developments may be found using photodynamic detection of implants in follow-up laparoscopies of ovarian cancer patients in apparent complete remission. In an experimental setting, HIPEC (hyperthermic intraperitoneal chemotherapy) has been successfully achieved (159), with interesting pharmacokinetic parameters (160).

A controversial topic in gynecologic oncology is the laparoscopic management of bulky nodes. Freezing such a node laparoscopically is technically possible even in the presence of vascular adhesions. One should, however, consider with caution this dissection because of the hazard of tumor dissemination from nodal rupture. Two options for management are suggested: (a) referring the patient to the radiotherapist after having documented the metastatic involvement by fine-needle aspiration, or (b) opening the abdomen and performing nodal debulking. The senior author feels that limiting to 3-cm nodes, performing an extremely careful dissection with a combination of blunt dissection, sharp dissection, and hydrodissection, and extracting the node via a laparoscopic bag is feasible and safe. Tozzi et al. (161) reported on the debulking of nodes up to 6.9 cm in the aortic or pelvic area in 22 cervical cancer patients. The surgery was successful in 21 patients. One attempt failed as a result of the impossibility to dissect the lumbosacral nerve. One patient experienced postoperative leg palsy and one had chylous ascites. The two complications eventually recovered but the adjuvant treatment was delayed. All women were discharged within 2 days from the operation, except for the two women with complications who remained until day 4. Excluding the two women with complications, adjuvant treatment was started within 7 days postoperatively.

The Case of the Obese Patient

Obesity is a limiting factor for laparoscopic surgery. Visibility is poor, with a short and adipose mesentery, bulky sigmoid colon, and at times inability of the anesthesiologist to adequately ventilate the patient in Trendelenburg position. The surgeon's fatigue is obviously increased compared to nonobese or moderately obese patients. Even if hysterectomy is feasible using the resources of vaginal and laparoscopic techniques, pelvic lymphadenectomy and particularly aortic lymphadenectomy may not be achievable.

While the early reports investigated the feasibility of laparoscopic surgery in obese patients with gynecologic malignancies – there were reservations among surgeons and anesthesiologists at that time of history – several studies soon showed that obesity is an elective specific indication, whenever possible, for the minimally invasive approach. A systematic review has been published by Martinek et al. in 2010 (162). Thirty-nine papers were identified, while only eight met the quality criteria: one randomized trial, two prospective, and 5 retrospective studies. The vast majority of papers report on surgical management of endometrial cancer. The finding is that the conversion rate is in the range of 7.5% to 36% and increases proportionally with

the BMI (163). While former studies suggested that obesity can be the limiting factor when attempting lymph node dissection, more recent reports show similar lymph node counts regardless of BMI in endometrial cancer patients (164).

Laparotomy in the obese patient obviously prolongs hospital stay and increases wound complications. As a result, more morbidity is seen in the open group than in the laparoscopic group. When comparing group of patients managed laparoscopically with a historical group managed by laparotomy, several outcomes are significantly improved: shorter hospital stay, less pain medication, and smaller drop in postoperative hematocrit, at the expense of longer operative time.

In the LAP2 study, conversion rates were 27% in patients with BMI greater than 35 kg/m² and 57% in women with BMI greater than 40 kg/m² (101). The high conversion rate reflects the multicentric design of the study, including less experienced surgeons. In contrast, conversion rate was only 10.6% of 47 obese patients and 7% in 85 with BMI higher than 40 in monocentric series (163,165).

A French study investigated the feasibility of laparoscopic and vaginal surgical approaches in obese patients with endometrial cancer (164). After matching 41 obese patients treated by laparoscopy with 29 obese patients treated by laparotomy, hospital stay was found to be significantly shorter in the laparoscopy group (3.8 vs. 7.4 days), whereas pelvic nodes counts (16.3 vs. 11.5), operative time (149.9 vs. 167.9 min), and disease-free survival (93% vs. 80%) were similar in both groups. One patient treated by laparotomy never received intended radiotherapy because of a delay greater than 3 months caused by cutaneous necrosis.

In a recent series from Louisville (167), 168 women underwent surgery: laparotomy *n* = 103 and laparoscopy *n* = 65, including 12 of them converted to laparotomy. There were 29 patients with BMI over 35 who were managed laparoscopically. Complication rates were significantly lower after laparoscopy compared to laparotomy: overall complications 53.8% versus 73.8 (*p* = 0.01); grade ≥3 complications, 9.2 versus 34.0 (*p* < 0.01); greater than or equal to 3 wound complications, 3.1 versus 22.3 (*p* < 0.01); and greater than or equal to 3 wound infections, 3.1 versus 20.4 (*p* = 0.01).

The limitations mentioned above can be overcome using refinements of laparoscopic technique. Suspension of the sigmoid colon may help. Correct placement of trocars, above the umbilicus, helps to keep a proper distance between the endoscope, the pelvic contents, and the symphysis pubis. Furthermore, the extraperitoneal technique can be used for aortic dissection. The technique overcomes the obstacles mentioned above, as the bowel is not in the way, a Trendelenburg position is not required, and the ergonomics of the surgeon is more acceptable. This approach has been successful in 92% of obese patients in the Mayo Clinic Rochester team (168). In the same mindset of combining available approaches, Benedetti-Panici et al. used a combination of laparoscopy and transverse minilaparotomy, with a success rate of 87% in a series of 39 – none of the conversions in this series was related to obesity (169).

The literature on radical hysterectomy and obesity is scant. Moss et al. (170) reported on the laparoscopic management of 15 patients with early-stage cervical cancer and BMI greater than 30 (up to 56). No case was converted to laparotomy. This group was compared to a group of 43 patients with BMI less than 30. Median duration of surgery, estimated blood loss, median hospital stay, number of retrieved nodes, length of vaginal cuff, and parametrial excision were not affected by obesity.

recurrence, and long-term QOL issues will be addressed, with an emphasis on large series, comparative studies, and randomized controlled studies.

Endometrial Cancer

The mainstay of surgery for endometrial cancer is simple hysterectomy with bilateral salpingo-oophorectomy, along with retroperitoneal staging according to guidelines.

Oncological Outcomes

Six randomized studies comparing oncological outcomes after laparotomy and laparoscopy, respectively, are currently available. The first 5 were included in a meta-analysis published then updated by Palomba et al. in 2009 (171). Only three studies were selected, resulting in a sample of 359 patients (97,124,170). No significant heterogeneity was observed among studies. No significant effect of laparoscopic approach on the disease-free survival, overall survival, and cancer-related survival (OR 0.95, 0.96, 0.91, respectively).

Long-term outcomes of the randomized controlled LAP2 study were published in 2012 (173). The primary study end point was noninferiority of recurrence-free interval. Noninferiority was defined as no more than a 40% increase in the risk of recurrence with laparoscopy compared with laparotomy. Laparoscopy was compared with laparotomy regarding recurrence after surgical management of uterine cancer stage I to IIA. Patients were randomly allocated (2 to 1) to laparoscopy (*n* = 1,696) versus laparotomy (*n* = 920). The estimated hazard ratio for laparoscopy relative to laparotomy was 1.14 (90% confidence interval 0.92–1.46). The actual recurrence rates were substantially lower than anticipated, resulting in an estimated 3-year recurrence rate of 11.4% with laparoscopy and 10.2% with laparotomy. The estimated 5-year overall survival was almost identical in both arms at 89.8%.

In a comparative historical study, Ghezzi et al. (174) presented the outcomes of consecutive patients with clinical stage I endometrial cancer managed laparoscopically with greater than 3-year follow-up (median follow-up of surviving patients, 52 months). Data from 117 consecutive women were compared with a historical cohort of 122 consecutive patients with endometrial cancer who had undergone open surgery. The laparoscopy and laparotomy groups were similar with regard to potentially confounding factors. Similar 3-year recurrence-free survival rates (91.4% vs. 88.5%), as well as similar 3-year overall survival rates (94.0% vs. 93.4%) were observed in the 2 groups.

Quality-of-Life Issues

Patients who undergo laparoscopic surgery seem to report a higher level of satisfaction with laparoscopy when compared to patients treated with total abdominal hysterectomy. They benefit from a shorter recovery time and are able to return to work and full activity more quickly. In a recent prospective, randomized study comparing laparoscopy to laparotomy in the management of endometrial cancer, Zullo et al. (175) prospectively demonstrated that patients treated with laparoscopy did indeed have improved QOL for the first 6 months after surgery.

Quality of life up to 6 months after surgery was also assessed in an RCT comparing total laparoscopic hysterectomy with total abdominal hysterectomy for stage I endometrial cancer (100). A total of 361 participants were enrolled and 332 completed the QOL analysis. Analysis was done according to the intention-to-treat principle. In the early phase of recovery, and up to 6 months after surgery, patients who had laparoscopic surgery reported significantly greater improvement in QOL from baseline, in all subscales apart from emotional and social well-being that are related to patients dealing with cancer.

Surgical Management of Gynecological Malignancies

This section describes oncological issues related to the incorporation of laparoscopic surgery in the management. Survival,

GOG LAP2 also required patients to complete QOL assessments at baseline and then at 1, 3, and 6 weeks, and 6 months postoperatively (176). The first 802 eligible patients randomized in LAP2 participated in the QOL study. Within 6 weeks of surgery, patients assigned to laparoscopy reported significantly better QOL on all scales other than fear of recurrence. In summary, during this 6-week postoperative period, patients assigned to laparoscopy were found to have superior QOL, fewer physical symptoms, less pain and pain-related interference with functioning, better physical functioning and emotional state, earlier resumption of normal activities, earlier return to work, and better body image as compared to those assigned to laparotomy.

The Dutch randomized study also addressed the QOL of endometrial cancer patients having undergone hysterectomy and bilateral salpingo-oophorectomy (95,109). The results of this study are not consistent with others, as laparoscopy patients scored significantly higher only on the physical functioning subscale at 3 months after the procedure. Median quality adjusted life-years (QALYs) were similar in both arms at 3 months.

Reassessment of Incompletely Staged Endometrial Cancers

Occasionally, the diagnosis of endometrial cancer is not established preoperatively. To define the extent of disease, some high-risk patients may benefit from completion staging. Laparoscopy is electively indicated in this setting, to minimize morbidity inherent to a second operation. A faster recovery may also minimize delay of any adjuvant therapy. A recent GOG study of patients with incompletely staged gynecologic malignancies showed that laparoscopic staging was possible in 80% of patients (177).

Cervical cancer

Upfront Radical Hysterectomy

The oncological safety of laparoscopic radical hysterectomy has been questioned. It is now documented in several comparative or noncomparative studies. Follow-up data on the oncologic outcomes have been reported. Spirtos et al. (177) reported on 78 consecutive patients who underwent laparoscopic radical hysterectomy with aortic and pelvic lymphadenectomy. With a mean follow-up of 66.8 months, the estimated 5-year disease-free survival was 89.7% and the estimated 5-year overall survival was 93.6%. Pomel et al. reported a 5-year survival rate of 96% in 50 patients with stages IA2 and IB1 cervical cancers treated with laparoscopic radical hysterectomy (1). Chen et al. (178) reported a 95.2% for IA, 96.2% for IB, 84.5% for IIA, 79.4% for IIB, 66.7% for IIIA, and 60.0% for IIIB overall disease-free survival. The median follow-up was 36.45 months. In 2009, Pellegrino et al. (179) observed a series of 107 patients with IB1 cervical cancer. After a median follow-up of 30 months, 11 patients had a recurrence and survival rate was 95%. Lee et al. (180) reported cumulative 91% and 93% disease-free and overall survival rates, respectively, after a median follow-up of 92.1 months in a group of 139 patients (stage IA $n = 60$, stage IB $n = 76$, stage IIA 3). Yan et al. (181), excluding the lost cases, and including patients with positive nodes, reported in 2011 the outcome of 221 cases after a median 35 months follow-up. The 5-year survival rates for IA2, IB1, IB2, and IIA were 100%, 82%, 66%, and 60%, respectively.

Several groups have compared the oncologic outcomes of laparoscopic radical hysterectomy with those of abdominal radical hysterectomy. After a median follow-up of 49 to 52 months, Jackson (182) did not report a significant difference in recurrence rates or overall survival between the laparoscopic and open surgery group of their trial. Steed et al. (183) found no difference in recurrence rates and similar 2-year recurrence free survival. Li et al. (126) compared 90 patients treated with laparoscopic radical hysterectomy to 35 patients treated with traditional

open surgery. Although the median follow-up was only 26 months, the recurrence rates for the laparoscopic and laparotomy groups were similar. Sobiczewski et al. (185) found a similar 3-year survival in 22 IA-IIA cervical cancer patients managed laparoscopically, compared to 58 patients who underwent laparotomy. However, they observed intraperitoneal recurrence in 2 patients.

The largest comparative study with follow-up has recently been published by Nam et al. (186). A total of 263 patients with stage IA2 to IIA cervical cancer were followed up over 24 months and matched to an equivalent number of patients with comparable prognostic factors. Compared with open surgery, laparoscopic surgery was not associated with a higher risk of recurrence (hazard ratio = 1.28; 95% CI 0.62–2.64) or death (hazard ratio = 1.46; 95% CI 0.62–3.43). Specifically, 16 versus 15/263 had recurrent disease and 12 versus 11 died of disease in the laparoscopy and open surgery groups, respectively. Even in patients with tumors greater than 2 cm in diameter, the risks of recurrence were not higher for laparoscopic radical hysterectomy. Five-year recurrence-free survival rates were 92.8% and 94.4%, respectively ($p = 0.499$).

Selecting Node-Negative Patients with Early Cervical Cancer Most Suitable for Surgery

In many centers, postoperative radiation therapy is routinely given to node-positive patients, thus duplicating the burden of therapy and increasing the complication rate of therapy. There is then a rationale for selecting node-positive patients by performing lymph node dissection first, and proposing radiation therapy only to node-positive patients. In this context, laparoscopy with pelvic lymph node dissection is used as the final workup procedure. In addition, the precaution of excluding node-positive patients is mandatory before proceeding to a radical trachelectomy. Whether the procedure can be limited to the sentinel nodes is still an open question. The reduction of complication rate after sentinel node only versus full pelvic dissection is currently being investigated in a French randomized controlled study.

Surgical Management of Locally Advanced Cervical Cancer

The majority of investigators laparoscopically manage stage IA2 or IB1 patients only. IB2 and II patients are managed by concomitant radiation therapy in most Western institutions. However, the short and long-term outcomes of laparoscopic surgeries for more advanced cases are worth being documented. Yan et al. (181) performed laparoscopic radical surgeries in 34 stage IB2, 35 IIA, and 6 IIB cervical cancers. The number of positive margins was not reported. The 5-year survival rate was 66% and 60% in stage IB2 and IIA, respectively. Hong (187) recently reported on a relatively large series of 34 radical hysterectomies in IB2 cervical cancer patients. The resection margin was free of disease in all patients. Five patients recurred in this group. However, 85% had adjuvant therapy. The rate of long-term radiation induced complications was not reported. It is then still questionable to submit IB2 cervical cancers to upfront laparoscopic surgery rather than concomitant radiation and chemotherapy.

Staging Locally Advanced Cervical Cancer

The surgical staging of locally advanced cervical cancer was initially proposed using laparotomy (transperitoneal or extraperitoneal) and then abandoned as a result of poor cost-effectiveness and major complications. The advent of laparoscopic surgery and the development of extraperitoneal aortic dissection in this indication opened a new era for surgical staging. In addition, an experimental study demonstrated that the adhesion formation rate in the radiation field was minimal after extraperitoneal endosurgical dissection (46). Positron emission tomography/computed tomography (PET-scan) imaging is not sensitive enough to detect metastases less than 5 mm in size (51). There is a significant

proportion of patients with locally advanced cervical who have low-volume metastases and negative PET scans in the aortic area (51,188). The proportion is higher in patients with positive pelvic nodes at PET-scans (22%) as compared with patients with no pelvic node uptake (12%). As a consequence, aortic dissection using the lateral extraperitoneal laparoscopic technique has been adopted by a number of institutions to define the extent of radiation fields (189). In this setting, common iliac dissection is generally added. However, to perform a pelvic dissection or not is still controversial. The therapeutic value of dissection that removes positive nodes and identifies a subgroup of patients likely to benefit from extended field radiation therapy (52), has been suggested but has yet to be demonstrated by a controlled study.

Completion Hysterectomy after Radiation Therapy

The issue of completing definitive radiation therapy by a hysterectomy in locally advanced cervical cancer is controversial. Some patients with incomplete response to radiation therapy with concomitant chemotherapy may benefit from salvage surgery. The extent of such a surgery is adapted to the size and localization of persistent disease. Should the team decide to perform such a surgery, the elective choice is a type A radical hysterectomy, which is potentially associated with less complications. Only one paper addressed the issue of laparoscopic surgery in this context. Colombo et al. (190) retrospectively reviewed 102 patients and were able to compare 46 laparoscopic with 56 abdominal radical hysterectomies after radiation therapy. Seven patients in the laparoscopic group required conversion to laparotomy (15%). Mean estimated blood loss (200 vs. 400 mL) and the median duration of hospital stay (5 vs. 8 days) were significantly lower in the laparoscopic group. Morbidity rates and urinary complications were reduced in the laparoscopic group ($p = 0.04$). Local recurrence rates, disease-free, and overall survival rates were comparable in the 2 groups.

Ovarian Cancer

Reassessment of Apparent Early Ovarian Cancers

On occasion, despite thorough preoperative investigation, patients are operated on for a presumed benign ovarian mass, yet an unexpected diagnosis of ovarian cancer occurs on final pathology, or the operating surgeon does not feel comfortable completing the staging procedure. In such situations, a complete surgical reassessment is required. In presumed stage I disease, the chances of finding more advanced disease in the peritoneum and/or lymph nodes is in the range of 20% to 30%. Laparoscopy may be an excellent alternative to complete the surgical management and staging as contralateral bilateral salpingo-oophorectomy and hysterectomy along with a complete pelvic and paraaortic node sampling, an infracolic omentectomy, and a complete peritoneal assessment may be performed laparoscopically. An extensive review of this indication has recently been published by Iglesias and Ramirez (191).

Over a 10-year experience, Leblanc et al. laparoscopically restaged 42 patients with apparent early ovarian cancer and 7 with fallopian tube cancers (192). Only one patient had to be converted to a laparotomy because of adhesions, and 19% of patients were upstaged as a result of the staging procedure. The authors concluded that laparoscopic surgery meets the standards of a complete staging procedure, spares the patients the inconvenience of a laparotomy, and accurately identifies patients with more advanced disease who require adjuvant chemotherapy.

In a recent GOG trial, Spirtos et al. completed the staging of incompletely staged gynecologic malignancies including ovarian and fallopian tube cancers. They noted a conversion rate of 20% to laparotomy, most often due to the presence of adhesions. Nevertheless, nearly 70% of patients had a successful complete laparoscopic staging and 11% were found to have more advanced disease (193).

In a retrospective review of 20 laparoscopic staging cases and 30 laparotomy staging controls, Chi et al. (194) found no differences between the 2 groups in pelvic or paraaortic lymph node counts and omental specimen size. While there were no complications in the laparoscopy group, there were 3 minor complications in the laparotomy group (2 wound infections and one postoperative ileus). The laparoscopy group had a significantly longer operative time (321 vs. 276 min) but significantly less blood loss (235 vs. 367 mL), and a shorter hospital stay (3.1 vs. 5.8 days).

In a comparative retrospective study comparing 17 patients managed by laparoscopy to 19 patients managed by open surgery, Park et al. (195) confirmed that the number of lymph nodes retrieved and operating time was similar. The laparoscopy group had significantly less estimated blood loss, faster return of bowel movement, and a shorter postoperative hospital stay compared to the laparotomy group. Transfusions were required only in 2 laparotomy patients, and postoperative complications occurred only in 4 laparotomy patients. In contrast with more reassuring data, they observed that 2 patients with stage IA grade 1 and 2 disease in laparoscopy group had recurrence with 1 patient dying of disease.

Although there are no randomized trials comparing both approaches, it appears that a comprehensive laparoscopic of patients with early-stage ovarian cancer is feasible and accurate. The morbidity is lower compared to the same procedure done by laparotomy. However, this procedure should only be performed by experienced and skilled laparoscopists capable of performing advanced and complex oncologic laparoscopic procedures, and with a careful follow-up of patients.

Laparoscopic Surgical Management of Early-Stage Adnexal Cancer

There are uncertainties that are still not well answered with regard to the safety and efficacy of minimally invasive surgery in early-stage ovarian cancer. Until such solid data are available, oncologists should remain very cautious with regard to the use of laparoscopy in the management of suspicious complex adnexal masses and early-stage ovarian cancer. First and foremost, minimal access surgery should not compromise outcome, particularly for patients with early-stage disease who have an excellent prognosis.

This being stated, two series involving a substantial number of patients have been published. Nezhat et al. reported in 2009 a series combining restaging surgeries, surgeries for borderline tumors, and including 25 full laparoscopic management of early ovarian cancers presenting as ovarian masses (196). There were 20 epithelial ovarian tumors and 5 were germ-cell or sex-cord stromal tumors. Only one patient with clear cell carcinoma of the ovary recurred after a mean follow-up of 56 months. A series of 82 cases has been published by Ghezzi et al. in 2012 (197). Although including 17 patients who had reassessment only and were not studied separately, 3-year overall survival and 3-year disease-free survival were 97% and 91.2%, respectively, in the subgroup of 34 patients who had reached or exceeded 3 years' follow-up. No conversion to laparotomy occurred in this series. Thirteen patients (15.8%) experienced postoperative complications. Only one patient had intraoperative hemorrhage requiring blood transfusion. These results are reassuring and confirm the findings of an earlier report (198) in which 2 patients in a series of 24 presented with recurrent disease after a 46-months follow-up.

Laparoscopic Debulking of Advanced Ovarian Cancer

Some investigators have elected to debulk laparoscopically advanced ovarian cancers, mainly after neoadjuvant therapy.

The debulking procedure relies on the electrosurgery or use of devices such as the Argon Beam Coagulator.

Trinh et al. reported in 2004 on 36 patients with chemosensitive (recurrence after 6 months) recurrent ovarian cancer identified on the basis of rising CA-125 (199). About 34 patients underwent successful laparoscopic debulking without requiring laparotomy, 32 had all visible disease resected at laparoscopy and 6% had surgical complications. Median time for surgery was 2.6 hours, median blood loss 70 mL, and median hospital stay 1 day. Seventy-four percent had a complete response after laparoscopic debulking and chemotherapy with a median progression-free survival of 1.1 years. In the same team, Fanning et al. (200) reported on 23 procedures without conversion to laparotomy. Median operative time was 2.3 hours and median blood loss was 340 cc. Median length of stay was 1 day. Six patients (24%) had postoperative complications; none were grades 3–4. They stated that the patients were successfully cytoreduced laparoscopically. However, although all tumors were debulked to less than 2 cm as assessed by laparoscopy, only 36% had no residual disease, which is the current standard of care. Nezhat et al. (201) reported in 2010 on 17 patients who underwent total laparoscopic primary or interval cytoreduction, with 88.2% optimal cytoreduction, as defined by a less than 5-mm disease. Only 2 had a complete cytoreduction. This policy should be thus still considered as investigational.

Surgical Management of Borderline Tumors of the Ovary

Borderline tumors often present as multilocular lesions on sonogram and may have elevated CA-125 levels. Three French and one Italian studies showed that the initial laparoscopic surgery in the management of borderline tumors is associated with a lower rate of complete staging, a higher rate of cyst rupture, and a higher recurrence rate following conservative treatment (202–205). However, despite an incomplete staging, there does not appear to be a detrimental effect on outcome in patients with apparent early borderline tumors (205).

In 2007, a Scandinavian group also retrospectively compared the short-term outcome of 107 patients with borderline tumors (52 serous, 53 mucinous, and 2 endometrioid tumors) operated by laparoscopy ($n = 38$) or laparotomy ($n = 69$), 14 of them being converted from laparoscopy to laparotomy (206). When tumor diameter exceeded 10 cm, intraoperative tumor rupture was significantly more frequent during laparoscopy than during laparotomy. During the 14 to 78 months follow-up time, no relapse occurred in either group. After fertility-sparing surgery, there was no statistically significant difference regarding successful pregnancies between the two groups. The authors concluded that laparoscopic treatment of borderline tumors is feasible in moderate size tumors (<10 cm) and is associated with fewer complications and shorter hospital stay. Laparotomy is still an option in large-size borderline tumors. The cutoff has been set between 5 cm (204) and 10 cm (206).

A majority of papers address only early-stage borderline tumors. The outcomes of 18 patients treated with pure laparoscopic management (treated conservatively in 14 patients) of serous borderline ovarian tumors with peritoneal implants were reviewed by Kane et al. (207). Eight patients relapsed (three with an invasive recurrence), but none of the patients without residual disease at the end of surgery, or invasive implants or disease with a micropapillary pattern relapsed under the form of invasive carcinoma.

The value of a restaging procedure in borderline tumors is controversial since the prognosis of patients with presumed stage I disease is excellent, and the value of adjuvant treatment is questionable even in more advanced disease. In a series of 56 patients referred with a suspected stage IA disease, only 4 (7%) were upstaged (208). Indeed, Darai et al. recently published

their results regarding the laparoscopic restaging of borderline tumors and confirmed the feasibility of that surgical approach. In their series of 42 patients, there were no conversions and no intraoperative or postoperative complications. As expected, they noted that ovarian cystectomies were associated with a higher risk of persistent lesions, and the risk of upstaging was higher in cases of serous borderline tumors (209).

Radical Surgery for Vaginal Cancer

Surgery for the management of cancers of the vagina and/or vulva includes lymph node dissection. For cancers of the upper half of the vagina, the management is similar to that of patients with cervical cancers. Open surgery is the standard, but full laparoscopic surgery or laparoscopically assisted vaginal radical surgery can be used as well. The best indication for laparoscopy may be for the reoperation of patients with incidental cervical cancer discovered at simple hysterectomy. Again, a full laparoscopic surgery, or a radical vaginal procedure assisted by laparoscopy, described as “Schauta *sine utero*” (210), seems to be safe. In this indication, the “Schauthem” procedure may also be used.

PROPHYLACTIC SURGERY

Laparoscopic Bilateral Salpingo-Oophorectomy

Patients at risk of adnexal/peritoneal disease related to a *BRCA* mutation are routinely proposed for risk-reducing surgery consisting of bilateral salpingo-oophorectomy at the age of 40 years or after completion of fertility. It is now widely accepted that the tubes must be removed at the time of oophorectomy, as a number of high-grade serous ovarian cancers are supposed to arise from the lateral part of the tube. As a consequence, removal of the cornual part of the tube is not necessary, as it induces more risks than benefit.

Logically, laparoscopy has become the elective approach. Minimal invasive surgery, which is routinely performed on a day-care basis, is obviously adapted to the concept of prophylactic surgery. The technique is straightforward for any gynecologist. The adnexa is grasped and moved away from the pelvic sidewall. This results in stretching the infundibulopelvic ligament, which can then be individualized, and controlled using bipolar cautery and section, or blocking clips (Hem-o-lok) without any risk of kinking or injuring the adjacent ureter. The peritoneum anterior and posterior to the adnexa is then incised parallel and close to the adnexa. The adnexa are then moved laterally so that its attachments to the cornua are stretched. The tube and the utero-ovarian vessels are then gradually cauterized and cut at a distance from the uterine cornua.

Laparoscopic Radical Fimbriectomy

Young *BRCA*-carrier patients benefit from prophylactic surgery before the age of 50 years. Some of them, particularly those who have not completed their fertility desires, and those who have already experienced breast cancer (and cannot be proposed hormone replacement therapy) may be understandably reluctant to accept early menopause and definitive infertility. In view of the recent literature on ovarian carcinogenesis, Leblanc et al. have recently proposed a novel conceptual surgical procedure they called “radical fimbriectomy” to address the specific issues raised by this particular group of patients (211). Radical fimbriectomy consists of removing the fallopian tube and the fimbrio-ovarian junction, which is the presumed origin of high-grade serous

carcinomas of the fallopian tube, ovary, and peritoneum. The authors hypothesized that this procedure might protect *BRCA* carriers from high-grade serous pelvic carcinoma while preserving their ovarian function until completion of their childbearing desire or the age of natural menopause.

In their seminal paper, they established a surgical technique consisting of removing the tube and the adjacent portion of the ovary. To fully preserve the blood supply to the ovary, care is taken to remove the tube without coagulating the utero-ovarian artery. This is achieved by carefully controlling the tubal vessel after transection of the isthmus. The medial part of the ovary attached to the fallopian tube by the tubo-ovarian ligament is then excised. Approximately one-quarter of the ovary is removed. Care is taken to preserve the infundibulopelvic blood supply to the uterus. To achieve this step of the operation, efficient hemostasis, minimal trauma to the remaining ovary, and preservation of the specimen for pathological examination are required. The authors compared four methods of partial ovarian transection: sharp division, stapler, bipolar division, and harmonic scalpel. Fourteen women were enrolled in a pilot study. They underwent radical fimbriectomy, and after assessment of hemostasis, had definitive oophorectomy in the same operating session. Sharp and EndoGIA appeared to be the safest methods of ovarian resection providing the best specimen quality for pathological examination.

The benefit of approach in terms of fertility and prevention of ovarian cancer is still hypothetical and is currently assessed in a prospective study in France. Although it does not prevent type 1 ovarian cancer, it might be preferable to no prophylactic surgery at all, as it prevents fallopian tube cancer or ovarian cancer precursor, and may prevent type 2 ovarian cancer, which is the most frequent histologic subtype observed in *BRCA* carriers. Indeed, Leblanc et al. found p53 signature and/or overexpression of KI 67 in four tubes or inner part of the ovary. No cancer precursor was identified in the remaining part of the ovaries.

If the proof of concept is obtained in the future, laparoscopic radical fimbriectomy may benefit a subset of *BRCA* carrier patients. Women who undergo radical fimbriectomy should continue to receive regular multimodal evaluation and be advised of the risks involved until they finally accept secondary oophorectomy after completion of fertility desire or after the age of 40.

Laparoscopic Ovarian/Adnexal Preservation

Discussion about the indication for ovarian preservation at the time of radical hysterectomy for cervical cancer is beyond the scope of this chapter. From a technical point of view, laparoscopic ovarian preservation is straightforward. Bipolar cautery followed by section, or more sophisticated instruments ensuring preventive hemostasis and section, is used to gradually separate the adnexa from the uterus. It is advised not to divide too close to the uterus, as the vascular supply is more easily controlled stepwise at a 1-cm distance from the uterus. The round ligament is divided first. The isthmus of the fallopian tube and the internal tubal artery are coagulated and divided. A firm divergent traction of the uterus and the adnexa stretches the area of the utero-ovarian vessels and the utero-ovarian ligament. These structures are gradually cauterized and cut. The ovaries are left in place in the pelvis or alternately can be transposed if a postoperative radiation therapy in young women is expected.

The main indication for ovarian or adnexal transposition is the case of young patients undergoing pelvic radiation therapy for malignant disease such as lymphoma, pelvic sarcoma, or rectal cancer. In this context, ovarian transposition is the preferred option to keep functional tubes. Laparoscopy is the logical approach in this indication. It results in shorter recovery and reduced adhesion formation rate, which is especially important in patients when radiation therapy is to be given. In gynecologic

oncology, ovarian transposition has been proposed in patients with cervical or vaginal cancer managed by preoperative brachytherapy. In this context, before definitive radiation therapy or postradiation hysterectomy, adnexal transposition is more likely to preserve the ovarian vascular supply. Again, laparoscopy is the preferred approach for the same reasons.

The benefit of prevention of estrogen deficiency is minimal considering: (a) the availability in gynecologic cancer patients of hormone replacement therapy, (b) the risk of ovarian failure immediately after transposition, and (c) the frequency of early menopause when the ovaries are transposed. On the other hand, the psychological benefit of retaining normal ovaries and a normal hormonal cycle is not to be neglected. The preserved ovaries are available for assisted reproductive technologies followed by surrogate pregnancy. However, the benefit decreases with age. The age of 40 is generally considered as the upper age limit for ovarian transposition. The risks are represented by the high incidence of ovarian cysts and by the risk of ovarian metastasis from cervical cancer. An estimate of the risk is available in a large study by Shimada et al. (212). The incidence of ovarian metastasis in patients with cervical cancer was 0.22% for stage IB, 0.75% for stage IIA, 2.17% for stage IIB with squamous cell carcinoma, and 3.72%, 5.26%, and 9.85%, respectively, in adenocarcinoma. Ovarian metastasis occurred more frequently among patients with adenocarcinoma than among those with squamous cell carcinoma (5.31% vs. 0.79%). Outcome for patients with ovarian metastasis was poor. In that study, the presence of ovarian metastasis did not correlate with lymph node involvement or parametrial invasion, in contrast with earlier studies. Ovarian preservation is thus safe in young patients presenting with early squamous cell carcinoma of the cervix. It can be proposed at the time of a staging laparoscopy for sentinel node procedure or staging lymph node dissection (213).

The technique of adnexal transposition is based on several principles. (a) The adnexa is detached from the cornua and left with the infundibulopelvic vascular supply. Kinking or torsion of the adnexal pedicle must be avoided to preserve the vascular supply. (b) The ovaries must be placed intraperitoneally as high, anterior, and lateral as possible to reduce exposure to radiation therapy. In this regard, placing radiopaque clips on the most caudal aspect of the transposed ovaries is of help to estimate the dose of radiation therapy received by the ovaries. (c) The high positioning of the adnexa must be secured with a minimum of direct trauma to the ovary by suturing or manipulation, using the tube to anchor the adnexa. Staples, tackers, or blocking clips can be used to attach the fallopian tube to the peritoneum. The pedicle can be left in the peritoneal cavity after division of the peritoneum of the paracolic gutter. It may be preferable not to incise the peritoneum, and rather create a peritoneal tunnel between the pelvis and a peritoneal opening created at the appropriate location. The adnexa is pushed in the tunnel and retrieved in the peritoneal cavity through the high opening. The technique has the advantage of further maintaining the high position of the adnexa, and avoiding the risk of bowel obstruction secondary to an incarceration of a bowel loop below the adnexal pedicle. However, the success rate of the procedure may be as low as 65% (214). Incidentally, the successful laparoscopic management of a metastatic adenocarcinoma arising on a transposed ovary has been reported (215).

NEW TECHNIQUES IN MINIMAL INVASIVE SURGERY

Some limitations of laparoscopic surgery are overcome by the development of new techniques. The case of the big mass may be managed using the hand-assisted laparoscopy (HAL). The limitations due to surgeon's fatigue or the difficulties of laparoscopic training are addressed by the development of robotic-assisted

laparoscopic surgery (RALS). A number of investigators are pushing the envelope and are investigating a further reduction of trocar incision, in size (microlaparoscopy), or in number (single-port), or using natural orifices transluminal endoscopic surgery (NOTES).

Hand-Assisted Laparoscopy

Hand-assisted laparoscopy (HAL) has been introduced as an adjunct to conventional laparoscopic surgery to facilitate the surgery and reduce the rate of conversion to laparotomy. It is used more frequently by gastrointestinal (GI) and genitourinary (GU) surgeons, and procedures such as splenectomy, pancreatectomy, hepatectomy, nephrectomy, prostatectomy, aortofemoral bypass, and colectomy have been successfully performed by HAL. The HAL approach implies a 6- to 8-cm skin incision to place the gel port through which the surgeon's hand and the laparoscopic instruments can be introduced while maintaining the pneumoperitoneum. HAL confers several advantages over laparoscopy alone: return of tactile sensation, improved spatial relationships, rapid exploration of the abdomen, palpation of intra-abdominal organs and masses, retraction and reflection of tissue planes, atraumatic blunt dissection, rapid control of bleeding, and lysing of dense adhesions. Even though a longer incision has to be made, HAL appears to maintain all the benefits of conventional laparoscopic surgery, that is, less postoperative ileus and pain, less blood loss, and shorter hospital stay. In addition, HAL frequently reduces the operating time and shortens the learning curve.

Only a few groups have reported their experience so far in gynecologic oncology surgery. Spannuth et al. reported their experience with the management of 29 patients with a pelvic mass by HAL versus 41 managed by conventional laparotomy. The two groups were comparable in terms of age, BMI, and size of the mass, and they found that HAL was associated with statistically lower blood loss, shorter hospital stay, and fewer postoperative complications (216). Krivak et al. approached 25 patients with ovarian cancer by HAL; 88% of the cases were successfully completed by HAL (217). HAL has also been used to manage recurrent disease. The ideal situation is one where the recurrence appears to be an isolated mass. Chi et al. described the technique for HAL splenectomy in 5 patients with an isolated recurrence in the spleen. The procedure was safely performed without complications (218).

The reason why HAL has not spread in gynecologic oncology is probably the competition with a simple and less expensive approach, which is the combination of laparoscopy and minilaparotomy. In an RCT, Benedetti-Panici et al. addressed the efficacy in terms of intraperitoneal spillage of laparoscopically guided minilaparotomy (LGM) compared with operative laparoscopy for large adnexal cysts (219). Sixty eligible patients affected by adnexal cysts with diameter between 7 cm and 18 cm were randomly assigned to either operative laparoscopy or LGM. In the per-protocol analysis, spillage occurred in 87% of the laparoscopy patients versus 29% in the minilaparotomy group. In an intention-to-treat analysis, operative times were significantly shorter in patients who underwent LGM (48 vs. 85 minutes). Surgical difficulty was significantly higher in patients treated with laparoscopy. However, postoperative stay was shorter (1 day vs. 1.5 days).

The combination of laparoscopy and midline minilaparotomy is thus a practical approach for the management of large ovarian cysts. Considering the need for a comprehensive assessment of the peritoneal cavity, minilaparotomy by itself is not acceptable. Considering the risk of spillage attached to laparoscopy, minilaparotomy is the logical complement to laparoscopic exploration of the abdominal cavity. Minilaparotomy for the decompression of the cyst without spillage, laparoscopy, or diagnostic laparoscopy

followed by a focused minilaparotomy can be chosen depending on the presentation.

Benedetti-Panici et al. recently assessed the role of LGM using a transverse incision in morbidly obese patients (169). There were 39 patients with BMI equal to or over 40 who underwent a variety of gynecologic surgical procedures including surgical management of early endometrial cancer. LGM was feasible in 34 patients. Peritoneal malignancy was found in two patients. In three patients, conversion to laparotomy was necessary due to adhesions, parametrial involvement, and vascular injury, respectively. The use of transverse minilaparotomy is logical in obese patients with early uterine malignancy. In contrast, primary laparoscopy avoids inadapted transverse incision in patients with peritoneal spread.

Microlaparoscopy

Further decrease of invasiveness of the conventional laparoscopic approach may derive from the reduction of trocar incision. Whether such an effort is relevant or not in gynecologic oncology is another question. As microlaparoscopy has been shown to be associated with reduced analgesic need in benign surgery, any technique aimed at improving patient outcome deserves consideration.

Ghezzi et al. recently presented an initial experience with microlaparoscopy in the surgical treatment of endometrial cancer and compared its outcomes with those of conventional laparoscopic approach (220). About 23 patients underwent surgical staging of endometrial cancer using exclusively 3-mm working ports and a 3- or 5-mm laparoscope at the umbilicus. Historical controls selected from consecutive women who have had staging with conventional laparoscopy ($n = 80$). Conversion from microlaparoscopy to a conventional laparoscopic technique occurred in 2 cases (9.7%), while there was no conversion to open surgical staging in either group. There were no significant differences between the microlaparoscopy group and the control group with regard to estimated blood loss, number of pelvic lymph nodes (average 19.2 vs. 18.6), and complication rate (intraoperative: 0% vs. 2.5%, postoperative: 8.7% vs. 13.7%). Operative time was similar between the two. The median length of hospital stay was 2 (1–10) days for women undergoing microlaparoscopic procedures compared to 3 (1–15) days for those undergoing conventional laparoscopy ($p = 0.001$). However, the same group did not find any benefit in terms of postoperative pain after microlaparoscopic hysterectomy compared to laparoscopic hysterectomy (221).

Single-Port Laparoscopic Surgery

The single-port approach represents the logical development of multiport laparoscopy toward less invasive procedures. Although the transumbilical approach is the most generally used, the extraperitoneal approach is being developed especially for paraaortic node dissections.

Instrumentation

A single incision of 2 to 3 cm seems enough to introduce the single port device. Different systems are available. The first attempts of single port surgery use a wound retractor on which was fixed a surgical glove. Instruments and optique were passed and secured through the extremities of the glove fingers. The TriPort (Olympus) has a dedicated endoscope with a curved handle to facilitate the use of the regular straight instruments. All the stuff is passed through a specifically designed port with trocars. The SILS system (Covidien) provides a small rubber doughnut that accommodates dedicated or regular 5- to 10-mm trocars for a regular 10-mm optique, and two to three conventional 5- to

10-mm laparoscopic instruments. Recently, curvable instruments are available. The Gelpoint system (Applied) offers a specific 8-cm protected ring (Alexi) on which is fixed a 10 cm Gelpoint. This port is made of jelly through which four dedicated 5- to 10-mm ports are passed for the regular optique and instruments (222). One experimental study compared the 3 systems and did not observe any significant difference (223). The choice of the technology is only the effect of surgeon's preference. The advantage of the Gelpoint system is the possibility to extract specimen through the port-site or the jelly with no need of bags since the orifice is protected by the wound retractor ring.

Current Experience in Gynecologic Oncology

Single-port laparoscopic surgery (SPLS) has been attempted first to perform simple procedures such as adnexectomy or hysterectomy for endometrial cancer. So far, results do not show any increase in complication rate and patients seem to be satisfied with the cosmetic results. Recently pelvic and paraaortic node dissections were reported through SPLS. Escobar et al. published the first results using a transumbilical approach (224), while Gouy et al. reported their initial experience using the extraperitoneal approach (225). Results of these preliminary reports show that this approach is feasible and reproducible with no apparent increase in morbidity. However, the initial experience is challenging and advantages are not clear and warrant further investigation. A first single institution compared SPLS using the SILS system and laparoscopy and the Gelpoint system combined with the Da Vinci robot. It showed that surgery through a unique site was feasible and reduced the need of postoperative analgesics in patients. Recent development may come from the use of single port technology in robotics to perform a single-port robotic surgery (SPRS). Current experiments in animals and cadavers seem satisfactory and attractive for the human transfer of this technology (224,226).

Advantages and Shortcomings of LPLS

A multi-institutional retrospective comparative study compared SPLS to conventional multiport laparoscopy or robotics for the management of early endometrial carcinomas. Three groups of 30 patients operated with one of each method were pair-matched according to age, BMI, and pathological characteristics of the tumor. Finally, results did not significantly differ between the three methods in terms of operative time, complication rates, node counts, or length of stay (227). Another possible advantage of SPLS is the possible reduction in postoperative pain level or pain killer consumption. However, so far, results did not show a clear advantage over traditional laparoscopy. Finally, cosmetic satisfaction seems the only objective advantage of SPLS.

In contrast, SPLS needs a clear learning curve necessary to overcome the drawbacks of this approach. Paek claimed that 40 cases were necessary to master single-port total laparoscopic hysterectomy (228). A steep Trendelenburg positioning is necessary to permanently clear the pelvis from bowel loops. A good coordination with the video assistant is necessary to avoid "knitting" between the instruments and optique. Another problem due to reduced triangulation is the difficulty to see the tips of the regular laparoscopic instruments, which may result in injuries, especially if cutting, monopolar cautery, or ultrasound is activated. The advent of an efficient 3D vision and the development of articulated instruments are eagerly awaited. However, a good experience in conventional laparoscopy is necessary before engaging in complex radical procedures. Despite these limitations, Yim et al. showed improved short-term outcome, albeit in a retrospective study, with reduced blood loss, shorter hospital stay, earlier diet intake, and reduced postoperative pain, when 52 patients following single-port hysterectomy were compared to 157 patients who underwent conventional total laparoscopic hysterectomy (229).

Variants

A variant of single port surgery is the use of flexible endoscopes. In the Toulouse Cancer Center group, flexible endoscopy has been investigated as a tool to explore remote areas of the peritoneal cavity. In an experimental study in cadavers, flexible endoscope was compared to 0° and 30° rigid endoscopes. Diaphragmatic areas explored with the flexible endoscope are significantly larger than with the other techniques. On average, 135 (range, 66–225), 168 (range 96–306), and 201 (range, 128–399) cm² were observed using 0°, 30°, and flexible laparoscopes, respectively. *P* values deriving from exact Wilcoxon test for paired data was 0.0019 between 0° and 30° endoscopes and between 30° and flexible endoscopes. The 30° endoscopes were consistently better than 0° endoscopes for the observation of the underface of the diaphragm and the spleen (230).

Natural Orifice Transluminal Endoscopic Surgery (NOTES)

Natural orifice transluminal endoscopic surgery has recently emerged as a new frontier resulting in endoscopic surgery without visible and painful scars. NOTES uses natural orifices as port of entry. Although in some regards the single port transumbilical laparoscopy may be defined as a natural orifice surgery, we will address in this section only the accesses involving no skin scar, mainly the vaginal route in female patients.

NOTES has mainly been developed in general surgery. The most common procedures are cholecystectomy, appendicectomy, and peritoneoscopy mainly performed via transvaginal access. Applications in clinical practice and the evidence base for each application were recently reviewed (231). An electronic literature search was performed. There were no randomized controlled studies in the literature on the date of review. The strongest evidence came in the form of large, multicenter trials with 300 to 500 patients. However, the vast majority of NOTES procedures worldwide are performed in a hybrid fashion with a variable amount of laparoscopy. The results are encouraging, comparable with gold standard techniques on morbidity and mortality when the transvaginal route is used. Short-term operative outcomes were also similar when compared to the gold standard techniques. However, morbidity appears to be higher when the transgastric route is used.

To our knowledge, no clinical application in gynecologic oncology has been described in the literature. The feasibility of SLN biopsy using NOTES has been assessed in an animal model. In 10 female pigs, the endoscope was introduced through a right lateral colpotomy. Internal iliac vessels were visualized followed by the identification of external iliac vessels. The aorta and vena cava were visualized. All but one sentinel nodes were identified by NOTES procedure. No major complication was observed in this series. A total of 19 SLN were harvested, of which 11 were from the left side and 8 from the right side. Fifteen lymph nodes were obtained from the iliac vessels or the promontory and 4 from the lateral aortic or preaortic region (232).

In another innovative investigation, Nassif et al. assessed the feasibility of extraperitoneal lymphadenectomy using NOTES in a porcine model (233). Using a transvaginal access to the retroperitoneum, they successfully performed 3 pelvic lymph node excision and 3 others in the laterocaval, intraaorticocaval, and lateroaortic regions. All animals survived. One accidental peritoneal perforation, 1 diffuse anterior abdominal wall emphysema, 1 abdominal wall bleeding secondary to electrical muscle stimulation, and 2 pneumoperitoneums evacuated by Veress needle insertion were experienced.

In conclusion, experimental studies suggest in the future that NOTES may be a potential alternative to reduce morbidity during staging procedures for gynecologic malignancies. Prospective pilot randomized series are necessary to establish the safety and

the real benefits of this new technique. The absence of any visible scar (“the memory of the operation”), and the reduction in postoperative pain (still to be demonstrated) must be balanced, as for SPLS, with significant technical difficulties related to the method: first is the risk of intra-abdominal infection and spillage by the opening of a hollow viscus (that needs to be securely closed at the end of the procedure by a clip or a suture) and the difficulty to sterilize flexible endoscopes and operative channels. Control of the gas pressure through endoscope is another difficulty and a technologic challenge. Then the absence of tactile sensation due to the length of the endoscope and flexible instruments, not compensated by a stereoscopic vision (as in robotics), the disorientation due to the use of a flexible endoscope, which should be compensated in the future by a navigation system using either augmented or virtual reality. A dissection through a colpotomy may be questionable from an oncological point of view. Finally, the sexual outcomes of this vaginal scar should be assessed. However, in spite of these current drawbacks, NOTES is an attractive approach, still in development, that deserves to be watched, especially when it will be possible to couple dedicated instruments to a robot.

Computer-Assisted (robotic) Surgery

Prepared in collaboration with Arie Reiss, MD

With the advent of laparoscopy, the concept of MIS developed, reaching challenging levels in the more complex surgeries performed by very skilled gynecologic oncologists. Limited by straight rigid sticks allowing 5° of freedom in a counter-intuitive hand-eye coordination environment, with an often unsteady two-dimensional image, the technology has remained a challenge to master for most clinicians, with a long learning curve, leading to low implementation in complex oncologic surgery. Although the landmark LAP-2 study, a randomized study comparing between laparoscopy and laparotomy for endometrial cancer, clearly established the benefits of minimal invasive approach (101); implementation has not followed, with most patients not benefitting from the MIS approach (234).

The drive of the military and NASA to develop tele-surgery has ultimately led the FDA to approve a civil computer-assisted surgical system, a “robot,” the da Vinci Surgical System, by Intuitive Surgical (Sunnyvale, CA) in July of 1997. Computer assistance, an integral and crucial part of the robotic platform, enhances dexterity as a result of improved articulation, scaled tremor-free motion, and true stereoscopic immersion vision with improved ergonomics. The development of the robotic platform is reflected by the increasing number of publications, most using the da Vinci robots, the only approved robotic platform at the present time.

As with every new line of thought or technology, robot-assisted surgery has met a lot of resistance, often with excellent argumentation (235). In a nutshell, critics of computer-assisted (robotic) MIS claim that it is associated with high capital and operating costs and with longer overall operating room times. To assess the value of this new platform, a systematic evaluation of clinical effectiveness and economic analysis is presented.

Robotics as a Tool to Increase the Patient Population Benefitting from MIS

The technical advantages offered by the robotic platform allows for the use of maneuvers similar to open procedures, with the added value of magnified immersion images. The robotic platform has thus helped overcome many of the limitations of traditional laparoscopy, enabling more gynecologic oncologists to feel comfortable and perform more complex cases via MIS, which ultimately allows more patients to benefit from the advantages of MIS. In many centers the introduction of robotics has drastically changed the surgical approach and increased the proportion of

Table 10.1 Theoretical Considerations for Robotic-Assisted Surgery in Gynecologic Oncology

Advantages	Disadvantages and Concerns
Intuitive operation Increased dexterity Improved vision Faster adoption Availability of MIS to most patients.	Short-term outcome: lack of level I evidence. Long-term oncologic outcome: no data presently available Increased operative time compared to open surgery.
Reduced Complication rates Pain Bleeding, transfusion rate Length of hospital stay compared to open surgery. Conversion rate compared to laparoscopy.	Cost Upfront high cost of system Significant maintenance cost Instruments cost.
Lymph node yield comparable to laparoscopy and increased compared to laparotomy	Access to more than one quadrant challenging Robot size Lack of haptics (force feedback) Removal of large uteri intact through the vagina may be challenging.

MIS, minimal invasive surgery.

patients benefitting from MIS. In one of the most extreme cases, the rate of patients with endometrial cancers, uterine sarcomas, and cancers of the cervix treated by MIS increased within 2 years from the introduction of the surgical robot from 17% to 98% (236), and a similar evolution was reported by others (237,238). Two populations of patients with a high surgical risk due to comorbidities, the elderly, and obese, had a high conversion rate in the laparoscopic arm of the LAP-2 study (101). In the following paragraphs, data are presented that indicate that this new platform is associated with a neutralization or reversal of the risk factors associated with poor outcome following MIS in obese and elderly patients, allowing these women to benefit equally, if not more, from MIS.

Obese Patients

The prevalence of obesity in North America has increased steadily and is now considered endemic, with significant health implications (239). Currently 2 out of 3 U.S. adults are estimated to be overweight or obese (239). For this reason, it is imperative to determine the most efficacious surgical approach for this patient population that is at risk of significant morbidities from open surgery both intra- and postoperatively (240). MIS has clearly shown benefits for obese patients, but its general application in the obese and morbidly obese populations remains poor in large part due to surgeons' perceived and practical difficulties in completing the procedure laparoscopically (241). In the largest prospective randomized trial comparing laparoscopy with laparotomy for the surgical staging of uterine cancer, GOG LAP2, patients with a BMI of greater than 35 kg/m² were initially ineligible for the study (101). Subsequently in the final analysis of LAP2, BMI was identified as a risk factor for conversion to laparotomy with a rate of conversion of 26.5% in patients with BMI of 34 to 35 kg/m², and 57.1% in patients with BMI greater than 40 kg/m². Gehrig et al. retrospectively compared 49 obese or morbidly obese patients who underwent robotic surgery with a similar historical cohort undergoing laparoscopic surgery for endometrial cancer (242). Robotic surgery resulted in shorter operative times, less blood loss, increased lymph node yield, and shorter hospital stays (242).

Seamon et al. at Ohio State University compared robotic surgery and open surgery in obese patients with endometrial cancer and demonstrated that robotic procedures were associated with a reduced transfusion rate and fewer complications, be it wound or other complications (243). Robotic-assisted MIS was shown to be not only feasible, but also appeared to neutralize the risk factors for surgery associated with obesity. In the report by Lau et al. obese patients had the same clinical outcome with similar perioperative experiences, and low conversion rates (5.6%), compared with nonobese women. The conversions were all at the end of the procedure only to remove enlarged uteri that could not be delivered intact via the vagina (244). These authors then adopted side docking and in patients with enlarged uteri, bisected the specimens within large endobags introduced via the vagina at the end of procedure, with a decrease of conversions to below 1% (244). Overall, in light of the reduced morbidity and high patient satisfaction, robotic surgery appears superior for obese women, and should be considered when counseling these patients with gynecologic cancers for surgery (243,244,245,246).

Applications of Robotic Surgery in Gynecologic Malignancies

Cancer of the Cervix

Robotic Radical Hysterectomy

Radical hysterectomy is a complex surgery with well established potential complications. The average blood loss during laparotomy is around 500 mL. Loss of bladder sensation and lymphocyst formation were each reported in about 5% to 15% of cases, and urinary tract injuries occur in 1% to 2.5% of cases. More severe complications, such as urinary fistulas or rectal injury, occur in up to 5% of patients.

In spite of the reports of the advantages of the laparoscopic over the open approach, laparoscopic radical hysterectomy has scarcely been adopted in surgical practice, remaining in the hands of a few highly skilled surgeons, due to the inherent complexity and difficulty of the technique.

With the advent of the robotic platform, several programs that did not offer MIS for patients with cancers of the cervix in view of the perceived complexity of the laparoscopic approach for radical hysterectomy, shifted uneventfully to robotic surgery, allowing more patients to benefit from the minimal invasive approach (247,248,249). Similar to laparoscopy, the MIS approach using the robotic platform was associated with reduced blood loss and transfusion rates, fewer complications, and significantly shorter postoperative length of stay when compared to radical hysterectomy by laparotomy (Table 10.2).

The currently published studies, although limited by small group sizes and short follow-up periods, support equivalent oncologic outcome with laparotomy, laparoscopic, or robotic radical hysterectomy. Nezhat et al. compared radical hysterectomy following robotic surgery (13 patients, median follow-up 12 months) and laparoscopic approach (31 historical patients, median follow-up 29 months) (250). There were no recurrences in either group. Magrina et al. followed 27 patients after robotic radical hysterectomy for early cervical cancer (251). At a mean follow-up length of 31 months (range, 12–51), no patient had experienced recurrence. Cantrell et al. retrospectively assessed the progression-free survival and overall survival for 63 women with cervical cancer who underwent type III robotic radical hysterectomy (249). Median follow-up was 12.2 months (range, 0.2–36 months). The comparison was made to a similar historical group of ORHs. There was no statistically significant difference in progression-free survival (94% vs. 89%, $p = 0.27$) or overall survival at 36 months (94% vs. 93%, $p = 0.47$).

Overall, early evidence suggests that robotic radical hysterectomy may be a valid alternative to open radical hysterectomies,

with superior short-term results and similar oncologic outcomes (Table 10.2). A prospective randomized trial comparing minimally invasive radical hysterectomy (laparoscopic or robotic) with laparotomy is currently underway (252).

Robotic Radical Parametrectomy

Only 2 studies presently report on small series of patients following radical parametrectomy performed using the robot. Ramirez and colleagues reported on 5 cases with squamous cell carcinoma of the cervix (253). None of the patients needed adjuvant treatment following the radical parametrectomy. One patient had an intraoperative cystotomy, and a second patient presented with a vesicovaginal fistula and a lymphocyst. During the short follow-up reported (mean, 7.5 months; range, 1.4–13.8) no recurrences were observed. Vitobello and colleagues recently reported on 11 cases, 5 with squamous cell carcinoma of the cervix, 2 with adenocarcinoma of the cervix, and 4 with a recurrence of endometrial carcinoma (254). One intraoperative cystotomy occurred and one patient suffered an intra-abdominal hemorrhage 15 days after surgery. Three patients required adjuvant treatment. In a median follow-up period of 19 months (8–36), one patient experienced a recurrence. These results are comparable to the reported results of open and laparoscopic radical parametrectomy (255–257). The authors of both robotic reports concluded that this procedure is feasible and can be performed with an acceptable complication rate.

Robotic Radical Trachelectomy

In view of the small number of surgeons mastering the advanced vaginal surgical skills required for performing Dargent's, or the laparoscopic skills required for performing laparoscopic radical trachelectomy, robotic surgery might offer an attractive alternative (258). Nick and colleagues (259) recently compared a series of 12 cases of radical robotic trachelectomy with 25 cases of open radical trachelectomy. Robotic radical trachelectomy was associated with significantly less bleeding and shorter hospital stay. Operative time, rate of serious complications, and histopathologic results were comparable. Four patients of the robotic group required conversion to hysterectomy due to close margins (<5 mm) found on the intraoperative frozen section biopsy. The rate of hysterectomy was significantly higher than in the patients who underwent open surgery.

Endometrial Cancer

In the last 20 years a considerable amount of data supporting the use of laparoscopy rather than laparotomy in the treatment of endometrial cancer were presented, culminating in the LAP2 trial, a large randomized phase III trial performed by the American Gynecologic Oncology Group (101). Despite this compelling evidence, the adoption of laparoscopic surgery for endometrial cancer staging was slow and only a minority of the patients benefitted from its advantages. In a survey taken among members of the Society of Gynecologic Oncologists in 2005, only 8% of responders performed more than 50% of their endometrial cancer staging procedures laparoscopically (234).

Since the approval of the DaVinci surgical system for use in gynecologic surgery in 2005, endometrial cancer has been the most widespread indication for robotic surgery in gynecologic oncology. Several investigators have reported on their experience with the use of the DaVinci system for surgical staging of endometrial cancer (Table 10.3), and compared their results to historic cohorts treated either by laparotomy or laparoscopy. The results were grouped in 2 meta-analyses (260,261) that were published in 2010 (Table 10.3). The results of these meta-analyses are slightly different due to different inclusion criteria.

Overall, in both meta-analyses, when robotic-assisted staging surgery was compared to conventional laparoscopy (Table 10.3), no differences were found in operation time, lymph node yield,

Table 10.2 Comparative Studies Evaluating Radical Hysterectomy in Function of Surgical Approach

Authors	Year of Publication	Method	Methodology	N	Age	BMI
Ko et al. (279)	2008	RRH/ORH	RS, HC	16/32	42.3/41.7	27.6/26.6
Nezhat et al. (250)	2008	RRH/ORH	PNR	13/30	54.8/46.8	NA
Fanning et al. (280)	2008	RRH	RS	20	44	NA
Bogges et al. (284)	2008	RRH/ORH	RS/HC	51/49	47.4/41.9 (S)	28.6/26.1 (NS)
Magrina et al. (251)	2008	RRH/LRH/ORH	CC	27/31/35	50/54.9/50.9	27.2/26.8/27.3
Maggioni et al. (281)	2009	RRH/ORH	CC	40/40	44.1/49.8	24.1/23.6
Oleszczuk et al. (282)	2009	VRARH	PS	12	44	24
Lowe et al. (283)	2009	RRH	PS	42	41	25.1
Halliday et al. (248)	2010	RRH/ORH	PS, HC	16/24	49/47	26/25
Cantrell et al. (249)	2010	RRH/ORH	RS, HC	63/64	43/41.5	28/25

Authors	Mean Operative Time	Lymph nodes	Intraoperative Complications (%)	Postoperative Complications (%)	Estimated Blood Loss (mL)	Transfusion Rate (%)	Conversion Rate (%)	Length of Stay (Days)
Ko et al. (279)	290/219	15.6/17.1 (NS)	0/3.1 (NS)	18.8/21.8	82/665 (S)	6.3/31.2 (NS)	0	1.7/4.9
Nezhat et al. (250)	323/318 (NS)	15.6/17.1 (NS)	15.4/6.66 (NS)	7.7/6.6 (NS)	157/200 (NS)	NA	0/0	27/3.8 (NS)
Fanning et al. (280)	390	18	5	5	300	0	0	1
Bogges et al. (284)	211/248 (S)	33.8/23.3 (S)		7.8/16.3 (NS)	96/416 (S)	0/8 (NS)	0	1/3.2 (S)
Magrina et al. (251)	189/220/166	25.9/25.9/27.7	0/3/6 (NS)	7/6/9 (NS)	133/208/444 (S)	4/0/9 (NS)	0/0	1.7/2.4/3.6
Maggioni et al. (281)	272/200 (S)	20.4/26.2 (S)	5/12.5 (NS)	30/52.5 (NS)	78/222 (S)	7.5/22.5	0	3.7/5 (S)
Oleszczuk et al. (282)	356	40	0	0	123	0	0	4-10
Lowe et al. (283)	215	25	4.8	12	50	0	2.4	1
Halliday et al. (248)	351/283 (S)	15/13 (NS)	6/8 (NS)	0/8 (NS)	106/546 (S)	0/13 (NS)	0	1.9/7.2 (S)
Cantrell et al. (249)	213/240 (S)	29/24 (S)	1.5/1.5	3.1/4.6	50/400 (S)		0	1/4 (S)

RRH, robotic radical hysterectomy; ORH, open radical hysterectomy; LRH, laparoscopic radical hysterectomy; RS, retrospective study; HC, comparison to historic cohort; PNR, prospective nonrandomized study; CC, case control study; PS, prospective study; NS, nonsignificant; S, significant.

or complication rates. The estimated blood loss was lower for robotic-assisted procedures with a lower transfusion rate, reaching statistical significance in one of the meta-analyses. The conversion rate to open surgery was found to be lower in patient operated with the DaVinci system (4.9 vs. 9.9%, $p = 0.06$ in the study by Gaia et al. [260] and OR 0.24; CI, 0.09–0.64 in the study by Reza et al. [261]). The comparison between robotic-assisted and open surgery showed significant prolongation of operation time when the robot was used. However, this was balanced by a reduction in perioperative complications, blood loss, transfusion rate, and length of stay, a motivating trade-off for the longer durations of surgery. The number of dissected lymph nodes was significantly higher in the robotic cases.

These reports support the feasibility and short-term safety of robotic surgery for endometrial cancer staging procedures. In view of the FDA approval in 2005, long-term oncologic outcomes have not yet been published, but short-term outcome with 2-year disease-free survival was reported to be at least as good as open surgery in one recent publication (236).

Ovarian Cancer

Robotic-assisted surgery has been reported to be adequate for surgical treatment and restaging procedures of early ovarian cancer.

However, it remains a challenge for advanced stage disease. The full staging of ovarian cancer requires access to all abdominal quadrants, making it frequently necessary to undock the robot at some stage of the surgery, insert additional trocars, move the robot or the operating table, and re-dock the arms to the trocars, with associated difficulties for anesthesia, the operating team, and arm collisions.

Recently, Magrina et al. (262) retrospectively compared the perioperative outcomes and survival of 25 patients who underwent robotic-assisted primary surgery for ovarian cancer with matched groups of patients that were treated by either laparotomy or laparoscopy. They concluded that laparoscopy or robotic surgery were superior to laparotomy for tumors requiring the excision of the primary tumor alone or with one additional major procedure. When the operation required two or more additional procedures, laparotomy was the preferred method of surgery. In this series, survival was not affected by the type of surgical approach.

A recent update (unpublished) on this patient series reveals a total of 32 patients with invasive epithelial ovarian cancer, 7 patients with stage IV disease, and 18 patients with stage III, half of whom had received neoadjuvant chemotherapy, and 4 patients were above the age of 80. Two patients underwent conversion at the end of the procedure to fully and safely remove

Table 10.3 Comparative Studies Evaluating Hysterectomy and Staging for Endometrial Cancer in Function of Surgical Approach

Authors	Year of Publication	Methodology	Method	N	Age	BMI
Velijovich et al. ^{a,b} (288)	2008	PS HC	RH/LPS/LPT	25/4/131	59/54/63	28/25/32
Boggess et al. ^{a,b} (247)	2008	PS HC	RH/LPS/LPT	103/81/138	62/62/64	33/29/35
Bell et al. ^{a,b} (263)	2008	RS	RH/LPS/LPT	40/30/40	63/68/72	33/32/32
DeNardis et al. ^{a,b} (285)	2008	PS HC	RH/LPT	59/106	59/62	28/34
Seamon et al. ^{a,b} (286)	2009	PS HC	RH/LPS	105/76	59/54	34/29
Lowe et al. (283)	2009	RS	RH	405	62	32
Cardenas-Goicoechea et al. ^a (287)	2010	RS	RH/LPS	102/173	62/60	32/32
Lau et al. (236)	2012	PS HC	RH/LPT+LPS	143/160		
Gaia et al. (260)	2010	Meta-analysis	RH/LPS	424/396	61/60	33.3/31.2
			RH/LPT	333/606	61/63	33.9/35.5
Reza et al. (261)	2010	Meta-analysis	RH/LPS/LPT	329/191/415		

Authors	Method	Operative Time (min)	Lymph Nodes	Intraoperative Complications	Postoperative Complications	Estimated Blood Loss (mL)	Transfusion Rate (%)	Conversion Rate (%)	Length of Stay (Days)
Velijovich et al. ^{a,b} (288)	RH/LPS/LPT	283/255/139 (S)	17.5/20.3/13.1	4/0/3	16/0/ 25 (NS)	66/75/197 (S)	—	1/0	
Boggess et al. ^{a,b} (284)	RH/LPS/LPT	191/213/146	33/23/15	1/3.7/0.7	4.9/9.9/28.9	191/213/146	1/2.5/1.5	2.9/4.9	1/1.2/4.4
Bell et al. ^{a,b} (263)	RH/LPS/LPT	166/253/317	17/17/15	0/3.3/2.5	7.5/23/25	166/250/316	5/10/15	0/0	2.3/2/4
DeNardis et al. ^{a,b} (285)	RH/LPT	177/79 (S)	18.6/18 (S)	—	3.6/20.8 (S)	105/241 (S)	0/8.5 (S)	5.4	1/3.2 (S)
Seamon et al. ^{a,b} (286)	RH/LPS	242/287 (S)	31/33	4/3	7.6/10.3	88/200 (S)	3/10 (S)	12.4/20 (S)	—
Lowe et al. (283)	RH	170	15.5	3.5	14.6	87	—	6.7	1.8
Cardenas-Goicoechea et al. ^a (287)	RH/LPS	237/178 (S)	22/23 (NS)	2/3.5 (NS)	24.5/28.3	109/187 (S)	2.9/1.7 (NS)	1/5.2 (NS)	1.9/2.3 (NS)
Lau et al. (236)	RH/LPT+LPS	241/207 (S)	11.3/11.5 (NS)	2.8/3.1 (NS)	10.5/38.8 (S)	73/266 (S)	1.4/6.3 (NS)	4.2 ^e	1/5 (S)
Gaia et al. (260)	RH/LPS	219/209 (NS)	28.5/25.6 (NS)		Wound ^c 2/2.8 (NS)	91.6/182 (S)	2.6/5 (NS)	4.9/9.9 (p = 0.06)	1.35/1.9 (S)
	RH/LPT	207/130 (S)	27.4/22.2 (NS)		Wound ^c 1.8/13.7 (S)	101/291 (S)	1.7/7.2 (p = 0.06)		1.2/3.9 (S)
Reza et al. (261)	RH/LPS	NS	NS		8.3/13 (NS) ^d	RH < LPS 76 mL p = 0.03	RH < LPS; OR = 0.24 (S)	RH < LPS OR = 0.43 (S)	RH < LPS (S) -0.17
	RH/LPT	RH > LPT (S) 89.25	RH > LPT (S) 5.91		7.1/27 (S) ^d	RH<LPT (S) 152 mL	RH<LPT (S)OR = 0.25		RH < LPT (S) -2.7

PS, prospective study; RS, retrospective study; HC, comparison to historic cohort; RH, robotic hysterectomy; LPT, laparoscopy; LPS, laparoscopy.

^a Data included in the meta-analysis of Gaia et al.^b data included in the meta-analysis of Reza et al.^c Only wound complication reported.^d Overall complication rate.^e Conversions at the end of surgery, only for the removal of specimens too large to be delivered intact via the vagina.

pelvic tumor invading the rectosigmoid. One 88-year-old patient succumbed to sepsis following bowel perforation.

Cost Analysis

The main barrier to the implementation of robotics mentioned repeatedly by health care professionals, administrators, and policymakers concerns the high upfront capital cost, the annual maintenance cost, and the cost of proprietary disposable robotic instruments. Using theoretic decision modeling, some groups found robotics not economically attractive compared to laparoscopy. On the other hand, when compared to laparotomy, the combination of reduced hospital stay and fewer complications in patients undergoing robotics contributes to an overall lower cost for the robotic-assisted procedures, as was demonstrated in patients undergoing radical hysterectomy for cancer of the cervix (248), and in patients undergoing staging procedures for endometrial cancer (236,263). The Canadian Agency for Drugs and Technologies in Health (264) recently published an in-depth economic analysis of robotics, revealing that a robotic surgery program becomes cost-effective once the annual caseload reaches close to 250 hysterectomies (the report is based on data combining hysterectomies for benign and malignant disease); also, the more the robot is utilized, either within a department or across surgical departments, the higher the achieved gains. As expected, the increased annual caseload dilutes the acquisition and maintenance cost, allowing the financial benefits per patient case to reach significant values. Careful selection of patients for whom the robotic approach yields the most prominent improved clinical impact, like the obese and the elderly patient populations, will further improve the economic value of using the robot. Overall, the economic advantages presented in most studies may underestimate the actual value, as only direct and indirect hospital costs were included without calculating the overall gains to the patient and society (i.e., quicker recovery and return to normal activities) (264).

The absence of randomized trials and the retrospective design of most case-control studies warrant cautious interpretation of the results. Despite the inconsistency and the methodological limitations, there is a clear trend indicating the improved perception of security and confidence to manage more complex cases with the robot. This has led to an increase in the proportion of patients benefiting from MIS following the introduction of robotics.

Single-Port Robotic Surgery

The use of a computer, integrated in robotic devices, appears to eliminate most of the ergonomic problems associated with SPLS. Several robotic systems designed specifically for single-port laparoscopy are currently under development and in early clinical trials (265). The present da Vinci system was successfully used for single-port surgery in various urologic procedures. Although technical difficulties were reported, the perioperative outcomes were comparable to conventional laparoscopy (266,267). In a pioneer study by Nam et al. (186), 7 patients underwent robotic total hysterectomy using a single-port transumbilical approach with a home-made multichannel port system and the da Vinci S system. Five patients underwent total hysterectomy for benign reasons; 1 had extra-fascial hysterectomy for carcinoma *in situ* of the cervix and 1 had radical hysterectomy, bilateral pelvic lymph node dissection, and paraaortic lymph node sampling for stage IB1 cervical cancer. One patient had to be converted to a 3-port robotic surgery due to severe pelvic adhesions resulting in significant intraoperative bleeding. Despite this encouraging report, the conventional da Vinci system was clearly not designed to be used as a single-port surgical system. The bulky arms and the

articulating but straight shaft instrument are limiting factors in single port usage.

A prototype single-port robotic system (single-site) was developed by Intuitive Surgical, as an add-on to the da Vinci Si system. The port has 5 channels. One channel is for an 8.5-mm scope, two for the robotic arms via curved crossing cannulae, one for the assistant port, and the fifth for CO₂ insufflation. The surgical instruments used are semi-flexible and cross each other at the insertion point to allow triangulation at the surgical field. At this time, the robotic arms lack the endowrist articulation feature. A uterine manipulator is used to maintain proper exposure (268). The prototype was used by Escobar et al. to perform total hysterectomy and bilateral salpingo-oophorectomy in 8 cadavers, with a success rate of 87.5%. Technical difficulties were noted in one cadaver, with an estimated BMI of 56, including complex docking and exposure problems. A second cadaver with previous midline abdominal surgery also presented problems for docking (269). The safety and feasibility of the single-site system was demonstrated by Konstantinidis et al. who reported the use of the system safely for cholecystectomy in 45 patients (270). The system appears to offer a wide range of motions, instrument and scope stability, improved ergonomics, and minimal instrument clashing.

A different approach is taken with the development of the single-port laparoscopy bimanual robot (SPRINT), which is specifically designed for SPLS (271), but *in vivo* trials are yet to be published.

The Future of Computer Interface

At present the robotic platform confers advantages of increased dexterity of the operating instruments, greatly enhanced three-dimensional immersed visual fields, and improved ergonomics for the surgeon. The introduction of this technology has greatly assisted centers in overcoming the technical challenges of laparoscopy and its steep learning curve, to be able to offer more MIS procedures to their patients. The single-port approach represents one of the new frontiers in MIS. It is facilitated by the computer interface in robotic platforms, and shows promise as a method to reach the various abdominal quadrants without the need for re-docking.

This, however, appears to represent only the tip of the iceberg, as the computer interface has the potential to greatly enhance the surgical capabilities by introducing digital analysis, image integration, feedback controls, surgical algorithms, and other technologies, mixing the power of the computer interface to literally expand surgical abilities beyond the human hand. Although at a different scale, this could be compared to the integration of computers in cars, airplanes, or, for that matter, almost any aspect of our modern life.

CONCLUSION

The movement toward MIS in gynecologic oncology is now irreversible. After the early demonstration of feasibility, it has become evident that magnification, lighting, and reduced capillary vessels bleeding provided a surgical advantage. There has been a growing level-I evidence of the short-term benefits, particularly in terms of patient pain, comfort, quality of life, and return to normal activity (272).

In parallel, a definitive reassurance that laparoscopic surgery does not impair the oncologic long-term outcome, provided that the standards are met, is now available. The patients may even benefit from the fact that postoperative chemotherapy or radiation therapy can be initiated earlier, and that complications arising from bowel adhesions are minimized.

Interestingly, the unequivocal benefit of MIS is in coherence with the trend toward shorter hospital stay imposed by the current financial constraint on health care cost. In the Ghezzi et al. experience (272), length of hospital stay has decreased significantly over time for all disease sites. The final achievement of the effort to reduce hospital stay is day surgery. The Toronto experience of day care major laparoscopic surgeries, including radical hysterectomies and aortic node dissection, shows that 48.5% of

303 patients had same-day discharge (median stay, 295 min). Among outpatients, seven (4.8%) were readmitted within 3 weeks of surgery. No patients with same-day discharge had a major acute postoperative complication (273). Another series of 18 outpatient extraperitoneal aortic dissections has also been reported (274).

Early criticisms that only carefully selected patients may benefit from laparoscopic surgery are now irrelevant. As soon

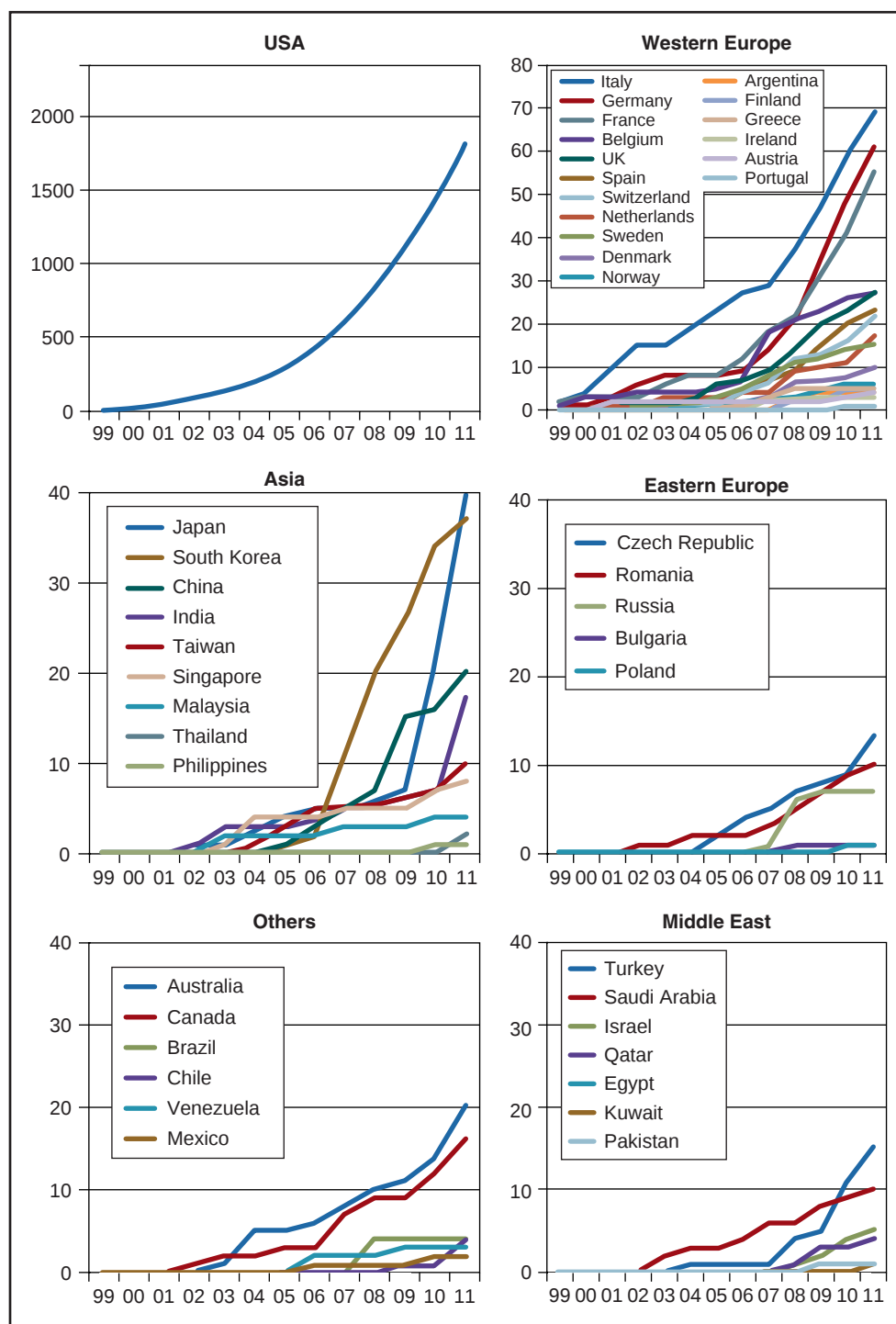


FIGURE 10.1. Global installations of robots, 1999–2011. Countries are represented in the legend in descending order of the number of robots installed (figure prepared based on data obtained from Intuitive Surgical, Sunnyvale, CA).

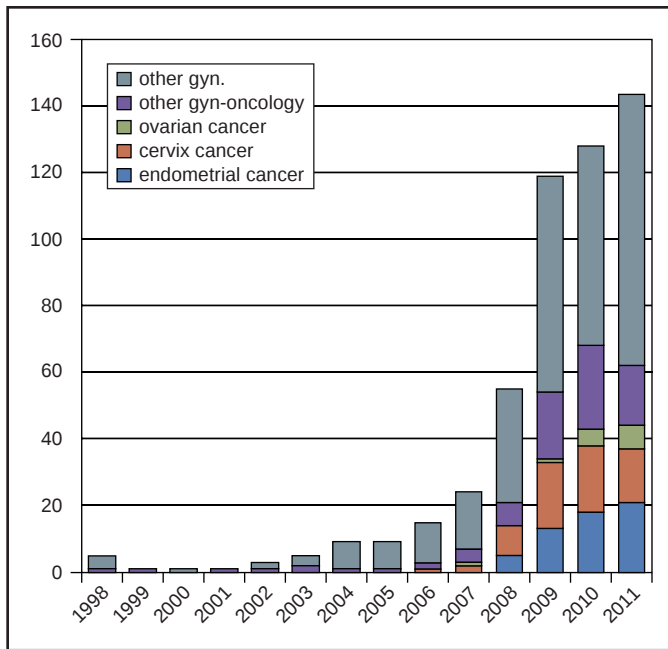


FIGURE 10.2. Number of scientific peer reviewed publications on robotics in the PubMed database.

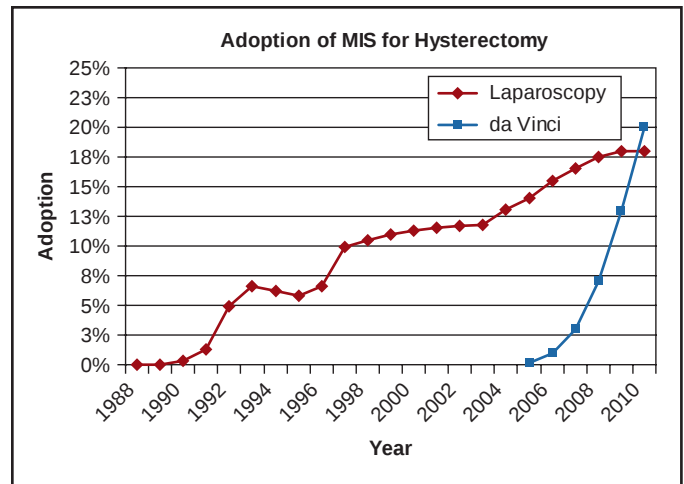


FIGURE 10.3. Adoption of robotic surgery for hysterectomy. MIS, minimal invasive surgery.
Source: Slide obtained from Intuitive Surgical with authorization to be presented.

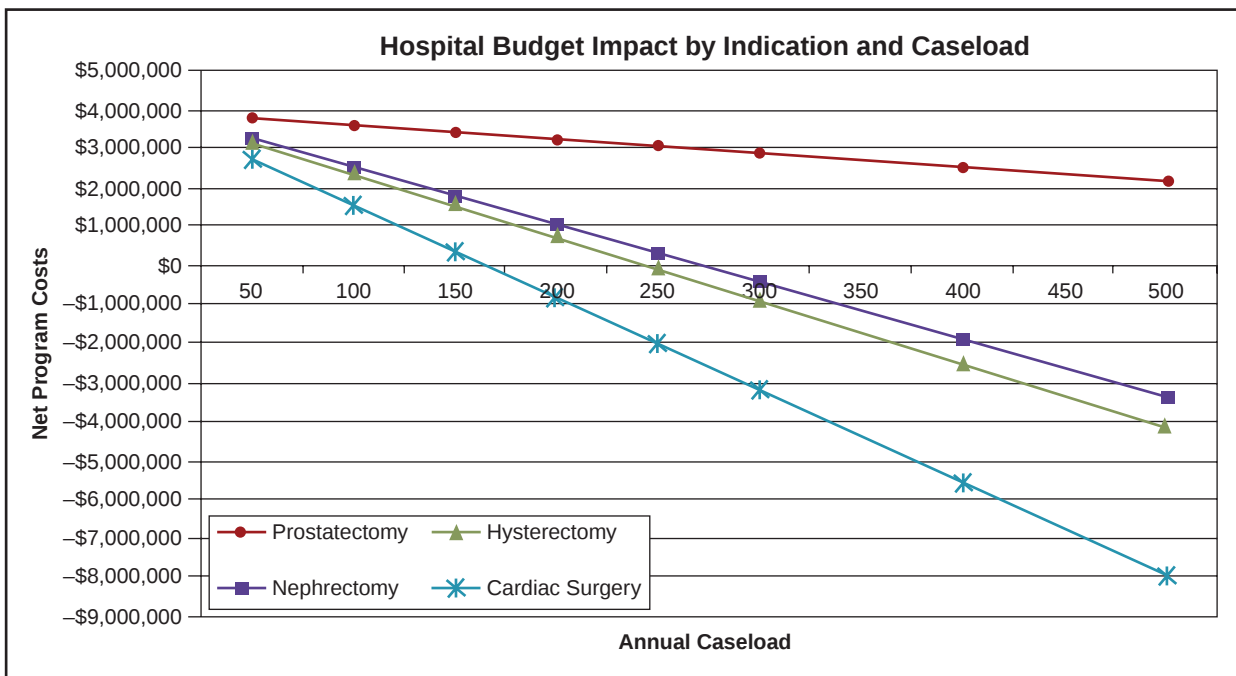


FIGURE 10.4. Hospital budget by caseload.
Source: Reproduced with permission from Fung-Ke-Fung M, Jaworski N, Gotlieb W. CADTH report.

as the senior author implemented a program favoring laparoscopic surgery in a cancer center, over 90% of surgeries for uterine cancer were performed laparoscopically (275). In the Oslo University Hospital, records from all women having a hysterectomy due to premalignant or malignant endometrial changes during the years 2002 to 2009 were examined retrospectively. A total of 521 hysterectomies were performed during the study

period. While laparoscopy was performed in about 20% of the cases in the first 2 years, it increased to 83% in the last year of the period (276). A group in Italy recently reported on 383 consecutive women undergoing surgery for the treatment of an apparently early-stage gynecologic cancer. Integration of minimal access surgery proceeded sequentially to include endometrial, ovarian, and cervical cancer patients. The annual

proportion of laparoscopic cases has increased significantly over the study period from 7.7% in 2001 to 90.9% in 2008 (277). In contrast, only 7.7% of Californian endometrial cancer patients in a recent population-based study (278) were managed laparoscopically. The current place of robotic surgery is to continue to fill the gap and eventually benefit the patient. Ironically, the laparoscopic approach that has been considered for years as “investigational” is now referred to as “conventional laparoscopic surgery” as compared to robotic-assisted laparoscopic surgery. Today it is extremely clear that the 2 variants of laparoscopic approach are complementary, and that the choice between the 2 is mainly driven by surgeon preference generally related to training, and by the availability of the robot generally related to economic reasons. However, specific indications of robotic assistance, such as morbid obesity, are emerging. In the future, further sophistications of the robotic technology will allow for further developments of MIS in gynecologic oncology that will reduce the indications for laparotomy in gynecologic cancer patients.

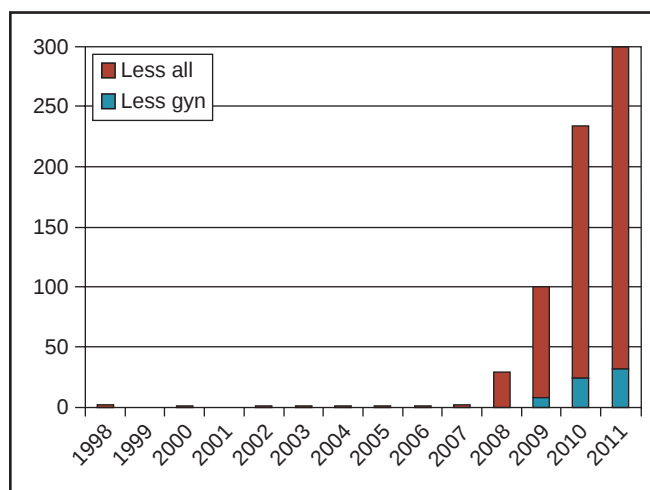


FIGURE 10.5. Scientific peer reviewed publications on LESS in the PubMed database, presented as number per year.
LESS : Laparo-Endoscopic Single-Site

REFERENCES

- Pomel C, Rouzier R, Pocard M, et al. Laparoscopic total pelvic exenteration for cervical cancer relapse. *Gynecol Oncol.* 2003;91(3):616–618.
- Bonjer HJ, Hazebroek EJ, Kazemier G, et al. Open versus closed establishment of pneumoperitoneum in laparoscopic surgery. *Br J Surg.* 1997;84(5):599–602.
- Cogliandolo A, Manganaro T, Saitta FP, et al. Blind versus open approach to laparoscopic cholecystectomy: a randomized study. *Surg Laparosc Endosc.* 1998;8(5):353–355.
- Chapron C, Cravello L, Chopin N, et al. Complications during set-up procedures for laparoscopy in gynecology: open laparoscopy does not reduce the risk of major complications. *Acta Obstet Gynecol Scand.* 2003;82(12):1125–1129.
- Vilos GA, Ternamian A, Dempster J, et al. Laparoscopic entry: a review of techniques, technologies, and complications. *J Obstet Gynaecol Cancer.* 2007;29(5):433–465.
- Ternamian AM, Vilos GA, Vilos AG, et al. Laparoscopic peritoneal entry with the reusable threaded visual cannula. *J Minim Invasive Gynecol.* 2010;17(4):461–467.
- Morice P, Camatte S, Larregain-Fournier D, et al. Port-site implantation after laparoscopic treatment of borderline ovarian tumors. *Obstet Gynecol.* 2004;104(5 Pt 2):1167–1170.
- Ramirez PT, Frumovitz M, Wolf JK, et al. Laparoscopic port-site metastases in patients with gynecologic malignancies. *Int J Gynecol Cancer.* 2004;14(6): 1070–1077.
- Zivanovic O, Sonoada Y, Diaz JP, et al. The rate of port-site metastases after 2251 laparoscopic procedures in women with underlying malignant disease. *Gynecol Oncol.* 2008;111(3):431–437.
- Martinez A, Querleu D, Leblanc E, et al. Low incidence of port-site metastases after laparoscopic staging of uterine cancer. *Gynecol Oncol.* 2010;118(2):145–150.
- Vergote I, Marquette S, Amant F, et al. Port-site metastases after open laparoscopy: a study in 173 patients with advanced ovarian carcinoma. *Int J Gynecol Cancer.* 2005;15(5):776–779.
- Heitz F, Ognjenovic D, Harter P, et al. Abdominal wall metastases in patients with ovarian cancer after laparoscopic surgery: incidence, risk factors, and complications. *Int J Gynecol Cancer.* 2010;20(1):41–46.
- Paulsen T, Kaern J, Tropé C. Improved 5-year disease-free survival for FIGO stage I epithelial ovarian cancer patients without tumor rupture during surgery. *Gynecol Oncol.* 2011;122(1):83–88.
- Odegaard E, Staff AC, Langebrekke A, et al. Surgery of borderline tumors of the ovary: retrospective comparison of short-term outcome after laparoscopy or laparotomy. *Acta Obstet Gynecol Scand.* 2007;86(5):620–626.
- Canis M, Botchorishvili R, Wattiez A, et al. Cancer and laparoscopy, experimental studies: a review. *Eur J Obstet Gynecol Reprod Biol.* 2000;91(1):1–9.
- Lécuru F, Agostini A, Camatte S, et al. Impact of pneumoperitoneum on visceral metastasis rate and survival. Results in two ovarian cancer models in rats. *BJOG.* 2001;108(7):733–737.
- Narducci F, Lanvin D, Ocelli B, et al. No difference found in survival using carbon dioxide laparoscopy, helium laparoscopy, or laparotomy in an adenocarcinoma nude mouse model. *Gynaecol Endosc.* 2000;9:409–415.
- Abu-Rustum NR, Sonoda Y, Chi DS, et al. The effects of CO₂ pneumoperitoneum on the survival of women with persistent metastatic ovarian cancer. *Gynecol Oncol.* 2003;90(2):431–434.
- Mathew G, Watson DI, Ellis TS, et al. The role of peritoneal immunity and the tumour-bearing state on the development of wound and peritoneal metastases after laparoscopy. *Aust N Z J Surg.* 1999;69(1):14–8.
- Matsuzaki S, Jardon K, Maleysson E, et al. Impact of intraperitoneal pressure of a CO₂ pneumoperitoneum on the surgical peritoneal environment. *Hum Reprod.* 2012;27(6): 1613–1623.
- Bouvy ND, Giuffrida MC, Tseng LN, et al. Effects of carbon dioxide pneumoperitoneum, air pneumoperitoneum, and gasless laparoscopy on body weight and tumor growth. *Arch Surg.* 1998;133(6):652–656.
- Agostini A, Robin F, Aggerbeck M, et al. Influence of peritoneal factors on port-site metastases in a xenograft ovarian cancer model. *BJOG.* 2001;108(8):809–812.
- Hoffman MS, Ondrovic LE, Wenham RM, et al. Evaluation of the porcine model to teach various ancillary procedures to gynecologic oncology fellows. *Am J Obstet Gynecol.* 2009; 201(1):116.e1–3.
- Clevin L, Grantcharov TP. Does box model training improve surgical dexterity and economy of movement during virtual reality laparoscopy? A randomized trial. *Acta Obstet Gynecol Scand.* 2008;87(1):99–103.
- Grantcharov TP, Kristiansen VB, Bendix J, et al. Randomized clinical trial of virtual reality simulation for laparoscopic skills training. *Br J Surg.* 2004;91(2):146–150.
- Gurusamy KS, Aggarwal R, Palanivelu L, et al. Virtual reality training for surgical trainees in laparoscopic surgery. *Cochrane Database Syst Rev.* 2009;(1):CD006575.
- Briet JM, Mourits MJ, Kenkhuis MJ, et al. Implementing an advanced laparoscopic procedure by monitoring with a visiting surgeon. *J Minim Invasive Gynecol.* 2010;17(6):771–778.
- Worley MJ Jr, Anwandter C, Sun CC, et al. Impact of surgeon volume on patient safety in laparoscopic gynaecologic surgery. *Gynecol Oncol.* 2012;125(1):241–244.
- Grantcharov TP, Funch-Jensen P. Can everyone achieve proficiency with the laparoscopic technique? Learning curve patterns in technical skills acquisition. *Am J Surg.* 2009;197(4):447–449.
- Blavier A, Gaudissart Q, Caidere GB, et al. Comparison of learning curves and skill transfer between classical and robotic laparoscopy according to the viewing conditions: implications for training. *Am J Surg.* 2007;194(1):115–121.
- Frumovitz M, Soliman PT, Greer M, et al. Laparoscopy training in gynecologic oncology fellowship programs. *Gynecol Oncol.* 2008; 111(2):197–201.
- Öbek C, Hubka M, Poerter M, et al. Robotic versus conventional laparoscopic skill acquisition: implications for training. *J Endourol.* 2005;19(9):1098–1103.
- Lanvin D, Elhage A, Henry B, et al. Accuracy and safety of laparoscopic lymphadenectomy:

- an experimental prospective randomized study. *Gynecol Oncol.* 1997;67(1):83–87.
34. Fowler JM, Carter JR, Carlson JW, et al. Lymph node yield from laparoscopic lymphadenectomy in cervical cancer: a comparative study. *Gynecol Oncol.* 1993;51(2):187–192.
 35. Querleu D, Leblanc E. Laparoscopic infrarenal paraaortic lymph node dissection for restaging of carcinoma of the ovary or fallopian tube. *Cancer.* 1994;73(5):1467–1471.
 36. Querleu D, Leblanc E. Laparoscopic modified radical hysterectomy in laparoscopic surgery. In: Querleu D, Childers J, Dargent D, eds. *Laparoscopic Surg Gynaecol Oncol* Oxford, UK: Blackwell Science; 1999:49–52.
 37. van de Lande J, von Mensdorff-Pouilly S, Lettinga RG, et al. Open versus laparoscopic pelvic lymph node dissection in early stage cervical cancer: no difference in surgical or disease outcome. *Int J Gynecol Cancer.* 2012;22(1):107–114.
 38. Zullo F, Falbo A, Palomba S. Safety of laparoscopy vs laparotomy in the surgical staging of endometrial cancer: a systematic review and metaanalysis of randomized controlled trials. *Am J Obstet Gynecol.* 2012;207(2):94–100.
 39. Panici BP, Plotti F, Zullo MA, et al. Pelvic lymphadenectomy for cervical carcinoma: laparotomy extraperitoneal, transperitoneal or laparoscopic approach? A randomised study. *Gynecol Oncol.* 2006;103(3):859–864.
 40. Ghezzi F, Cromi A, Serati M, et al. Radiation-induced bowel complications: laparoscopic versus open staging of gynecologic malignancy. *Ann Surg Oncol.* 2011;18(3):782–791.
 41. Querleu D, Leblanc E, Carrton G, et al. Audit of preoperative and early complications of laparoscopic lymph node dissection in 1000 gynecologic cancer patients. *Am J Obstet Gynecol.* 2006;195(5):1287–1292.
 42. Köhler C, Klemm P, Schau A, et al. Introduction of transperitoneal lymphadenectomy in a gynecologic oncology center: analysis of 650 laparoscopic pelvic and/or paraaortic transperitoneal lymphadenectomies. *Gynecol Oncol.* 2004;95(1):52–61.
 43. Chi DS, Abu-Rustum NR, Sonoda Y, et al. Ten-year experience with laparoscopy on a gynecologic oncology service: analysis of risk factors for complications and conversion to laparotomy. *Am J Obstet Gynecol.* 2004;191(4):1138–1145.
 44. Ghezzi F, Uccella S, Cromi A, et al. Lymphoceles, lymphorrhea, and lymphedema after laparoscopic and open endometrial cancer staging. *Ann Surg Oncol.* 2012;19(1):259–267.
 45. Köhler C, Tozzi R, Klemm P, et al. Laparoscopic paraaortic left-sided transperitoneal infrarenal lymphadenectomy in patients with gynecologic malignancies: technique and results. *Gynecol Oncol.* 2003;91(1):139–148.
 46. Ocelli B, Narducci F, Lanvin D, et al. *De novo* adhesions with extraperitoneal endosurgical paraaortic lymphadenectomy versus transperitoneal laparoscopic paraaortic lymphadenectomy: a randomized experimental study. *Am J Obstet Gynecol.* 2000;183(3):529–533.
 47. Chen MD, Teigen GA, Reynolds HT, et al. Laparoscopy versus laparotomy: an evaluation of adhesion formation after pelvic and paraaortic lymphadenectomy in a porcine model. *Am J Obstet Gynecol.* 1998;178(3):499–503.
 48. Vasilev SA, McGonigle KF. Extraperitoneal laparoscopic paraaortic lymph node dissection. *Gynecol Oncol.* 1996;61(3):315–320.
 49. Querleu D, Dargent D, Ansquer Y, et al. Extraperitoneal endosurgical aortic and common iliac dissection in the staging of bulky or advanced cervical carcinomas. *Cancer.* 2000;88(8):1883–1891.
 50. Sonoda Y, Leblanc E, Querleu D, et al. Prospective evaluation of surgical staging of advanced cervical cancer via a laparoscopic extraperitoneal approach. *Gynecol Oncol.* 2003;91(2):326–331.
 51. Leblanc E, Gauthier H, Querleu D, et al. Accuracy of 18-Fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. *Ann Surg Oncol.* 2011;18(8):2302–2309.
 52. Leblanc E, Narducci F, Frumovitz M, et al. Therapeutic value of pretherapeutic extraperitoneal laparoscopic staging of locally advanced cervical carcinoma. *Gynecol Oncol.* 2007;105(2):304–311.
 53. Gil-Moreno A, Magrina JF, Perez-Benavente A, et al. Location of aortic node metastases in locally advanced cervical cancer. *Gynecol Oncol.* 2012;125(2):312–314.
 54. Mullins JK, Hyndman ME, Mettee LZ, et al. Comparison of extraperitoneal and transperitoneal pelvic lymph node dissection during minimally invasive radical prostatectomy. *J Endourol.* 2011;25(12):1883–1887.
 55. Pan XY, Lin H, Wang YN, et al. Feasibility of laparoscopic extraperitoneal pelvic lymphadenectomy in gynecologic malignancies. *Gynecol Oncol.* 2011;122(2):281–284.
 56. Querleu D, Ferron G, Rafii A, et al. Pelvic lymph node dissection via a lateral extraperitoneal approach: description of a technique. *Gynecol Oncol.* 2008;109(1):81–85.
 57. Pandit-Taskar N, Gemignani ML, Lyall A, et al. Single photon emission computed tomography SPECT-CT improves sentinel node detection and localization in cervical and uterine malignancy. *Gynecol Oncol.* 2010;117(1):59–64.
 58. Martínez A, Zerdoud S, Mery E, et al. Hybrid imaging by SPECT/CT for sentinel lymph node detection in patients with cancer of the uterine cervix. *Gynecol Oncol.* 2010;119(3):431–435.
 59. Diaz-Feijoo B, Perez-Benavente MA, Cabrera-Diaz S, et al. Change in clinical management of sentinel lymph node location in early stage cervical cancer: the role of SPECT/CT. *Gynecol Oncol.* 2011;120(3):353–357.
 60. van de Lande J, Torrença B, Raijmakers PG, et al. Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. *Gynecol Oncol.* 2007;106(3):604–613.
 61. Rasty G, Hauspy J, Bandarchi B. Assessment of sentinel lymph node in cervical cancer: review of literature. *J Clin Pathol.* 2009;62(12):1062–1065.
 62. Lécuru F, Mathevet P, Querleu D, et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J Clin Oncol.* 2011;29(13):1686–1691.
 63. Ballester M, Dubernard G, Lécuru F, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicenter study (SENTI-ENDO). *Lancet Oncol.* 2011;12(5):469–476.
 64. Roy M, Bouchard-Fortier G, Popa I, et al. Value of sentinel node mapping in cancer of the cervix. *Gynecol Oncol.* 2011;122(2):269–274.
 65. Altgassen C, Pagenstecher J, Hornung D, et al. A new approach to label sentinel nodes in endometrial cancer. *Gynecol Oncol.* 2007;105(2):457–461.
 66. Perrone AM, Casadio P, Formelli G, et al. Cervical and hysteroscopic injection for identification of sentinel lymph node in endometrial cancer. *Gynecol Oncol.* 2008;111(1):62–67.
 67. Canis M, Mage G, Pouly JL, et al. Laparoscopic diagnosis of adnexal cystic masses: a 12-year experience with long-term follow-up. *Obstet Gynecol.* 1994;83(5 Pt 1):707–712.
 68. Leng JH, Lang JH, Zhang JJ, et al. Role of laparoscopy in the diagnosis and treatment of adnexal masses. *Chin Med J (Engl).* 2006;119(3):202–206.
 69. Yuen PM, Yu KM, Yip SK, et al. A randomized prospective study of laparoscopy and laparotomy in the management of benign ovarian masses. *Am J Obstet Gynecol.* 1997;177(1):109–114.
 70. Lehner R, Wenzl R, Heinzl H, et al. Influence of delayed staging laparotomy after laparoscopic removal of ovarian masses later found malignant. *Obstet Gynecol.* 1998;92(6):967–971.
 71. Maiman M, Seltzer V, Boyce J. Laparoscopic excision of ovarian neoplasms subsequently found to be malignant. *Obstet Gynecol.* 1991;77(4):563–565.
 72. Blanc B, Boubli L, D'Ercole C, et al. Laparoscopic management of malignant ovarian cysts: a 78 case national survey. Part 1: preoperative and laparoscopic evaluation. *Eur J Obstet Gynecol Reprod Biol.* 1994;56(3):177–180.
 73. Blanc B, D'Ercole C, Nicoloso E, et al. Laparoscopic management of malignant ovarian cysts: a 78 case national survey. Part 2: follow-up and final treatment. *Eur J Obstet Gynecol Reprod Biol.* 1995;61(2):147–150.
 74. Kindermann G, Maassen V, Kuhn W. Laparoscopic preliminary surgery of ovarian malignancies. Experiences from 127 German gynecologic clinics. *Geburtsilfe Frauenheilk.* 1995;55(12):687–694.
 75. Leminen A, Lehtovirta P. Spread of ovarian cancer after laparoscopic surgery: report of eight cases. *Gynecol Oncol.* 1999;75(3):387–390.
 76. Canis M, Mashiah R, Wattiez A, et al. Frozen section in laparoscopic management of macroscopically suspicious ovarian masses. *J Am Assoc Gynecol Laparosc.* 2004;11(3):365–369.
 77. Geomini PM, Zuurendonk LD, Bremer GL, et al. The impact of size of the adnexal mass on the accuracy of frozen section diagnosis. *Gynecol Oncol.* 2005;99(2):362–366.
 78. Ghezzi F, Cromi A, Uccella S, et al. Laparoscopy versus laparotomy for the surgical management of apparent early stage ovarian cancer. *Gynecol Oncol.* 2007;105(2):409–413.
 79. Havrilesky LJ, Peterson BL, Dryden DK, Soper JT, Clarke-Pearson DL, Berchuck A. *Obstet Gynecol.* 2003 Aug;102(2):243–51.
 80. Lécuru F, Desfeux P, Camatte S, et al. Impact of initial surgical access on staging and survival of patients with stage I ovarian cancer. *Int J Gynecol Cancer.* 2006;16(1):87–94.
 81. Angioli R, Palaia I, Zullo MA, et al. Diagnostic open laparoscopy in the management of advanced ovarian cancer. *Gynecol Oncol.* 2006;100(3):455–461.
 82. Fagotti A, Ferrandina G, Fanfani F, et al. A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. *Ann Surg Oncol.* 2006;13(8):1156–1161.
 83. Brun JL, Rouzier R, Uzan S, et al. External validation of a laparoscopy-based score to evaluate resectability of advanced ovarian cancers: clues for a simplified score. *Gynecol Oncol.* 2008;110(3):354–359.
 84. Fagotti A, Vizzielli G, Costantini B, et al. Learning curve and pitfalls of a laparoscopic score to describe peritoneal carcinosis in advanced ovarian cancer. *Acta Obstet Gynecol Scand.* 2011;90(10):1126–1131.
 85. Fagotti A, Fanfani F, Vizzielli G, et al. Should laparoscopy be included in the work-up of advanced ovarian cancer patients attempting interval debulking surgery? *Gynecol Oncol.* 2010;116(1):72–77.
 86. Husain A, Chi DS, Prasad M, et al. The role of laparoscopy in second-look evaluations for ovarian cancer. *Gynecol Oncol.* 2001;80(1):44–47.

87. Clough KB, Ladonne JM, Nos C, et al. Second look for ovarian cancer: laparoscopy or laparotomy? A prospective comparative study. *Gynecol Oncol.* 1999;72(3):411–417.
88. Littell RD, Hallonquist H, Matulonis U, et al. Negative laparoscopy is highly predictive of negative second-look laparotomy following chemotherapy for ovarian, tubal, and primary peritoneal carcinoma. *Gynecol Oncol.* 2006;103(2):570–574.
89. Abu-Rustum NR, Barakat RR, Siegel PL, et al. Second-look operation for epithelial ovarian cancer: laparoscopy or laparotomy? *Obstet Gynecol.* 1996;88(4 Pt 1):549–553.
90. Hauspy J, Jimenez W, Rosen B, et al. Laparoscopic surgery for endometrial cancer: a review. *J Obstet Gynaecol Can.* 2010;32(6):570–579.
91. Querleu D, Leblanc E, Morice P, Ferron G. *Chirurgie des cancer gynécologiques*. Paris: Elsevier-Masson, 2007.
92. Ghezzi F, Uccella S, Cromi A, et al. Postoperative pain after laparoscopic and vaginal hysterectomy for benign gynecologic disease: a randomized trial. *Am J Obstet Gynecol* 2010;203:118.e1–e8.
93. Drachonovskiy J, Haakova L, Otčenasek M, et al. A prospective randomized comparison of vaginal hysterectomy, laparoscopically assisted vaginal hysterectomy, and total laparoscopic hysterectomy in women with benign uterine disease. *Eur J Obstet Gynecol Reprod Biol.* 2010;148(2):172–176.
94. Marana R, Busacca M, Zupi E, et al. Laparoscopically assisted vaginal hysterectomy versus total abdominal hysterectomy: a prospective, randomized, multicenter study. *Am J Obstet Gynecol.* 1999;180(2 Pt 1):270–275.
95. Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. *Lancet Oncol.* 2010;11(8):763–771.
96. Malur S, Possover M, Michels W, et al. Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer—a prospective randomized trial. *Gynecol Oncol.* 2001;80(2):239–244.
97. Fram KM. Laparoscopically assisted vaginal hysterectomy versus abdominal hysterectomy in stage I endometrial cancer. *Int J Gynecol Cancer.* 2002;12(1):57–61.
98. Zullo F, Palomba S, Russo T, et al. A prospective randomized comparison between laparoscopic and laparotomic approaches in women with early stage endometrial cancer: a focus on the quality of life. *Am J Obstet Gynecol.* 2005;193(4):1344–1352.
99. Tozzi R, Malur S, Koehler C, et al. Laparoscopy versus laparotomy in endometrial cancer: first analysis of survival of a randomized prospective study. *J Minim Invasive Gynecol.* 2005;12(2):130–136.
100. Malzoni M, Tinelli R, Cosentino F, et al. Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early-stage endometrial cancer: a prospective randomized study. *Gynecol Oncol.* 2009;112(1):126–133.
101. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol.* 2009;27(32):5331–5336.
102. Janda M, Gebiski V, Brand A, et al. Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial. *Lancet Oncol.* 2010;11(8):772–780.
103. Tinelli R, Malzoni M, Cicinelli E, et al. Is early stage endometrial cancer safely treated by laparoscopy? Complications of a multicenter study and review of recent literature. *Surg Oncol.* 2011;20(2):80–87.
104. Barnett JC, Havrilesky LJ, Bondurant AE, et al. Adverse events associated with laparoscopy vs. laparotomy in the treatment of endometrial cancer. *Am J Obstet Gynecol.* 2011;205(2):143.e1–6.
105. Palomba S, Ghezzi F, Falbo A, et al. Laparoscopic versus abdominal approach to endometrial cancer: a 10-year retrospective multicenter analysis. *Int J Gynecol Cancer.* 2012;22(3):425–433.
106. Eltabbakh GH, Mount SL. Laparoscopic surgery does not increase the positive peritoneal cytology among women with endometrial carcinoma. *Gynecol Oncol.* 2006;100(2):361–364.
107. Lim S, Kim HS, Lee KB, et al. Does the use of a uterine manipulator with an intrauterine balloon in total laparoscopic hysterectomy facilitate tumor cell spillage into the peritoneal cavity in patients with endometrial cancer? *Int J Gynecol Cancer.* 2008;18(5):1145–1149.
108. Bijen CB, Vermeulen KM, Mourits MJ, et al. Costs and effects of abdominal versus laparoscopic hysterectomy: systematic review of controlled trials. *PLoS.* 4(10):e7340.
109. Bijen CB, Vermeulen KM, Mourits MJ, et al. Cost effectiveness of laparoscopy versus laparotomy in early stage endometrial cancer: a randomized trial. *Gynecol Oncol.* 2011;121(1):76–82.
110. Barnett JC, Judd JP, Wu JM, et al. Cost comparison among robotic, laparoscopic, and open hysterectomy for endometrial cancer. *Obstet Gynecol.* 2010;116(3):685–693.
111. Tozzi R, Malur S, Koehler C, et al. Analysis of morbidity in patients with endometrial cancer: is there a commitment to offer laparoscopy. *Gynecol Oncol.* 2005;97(1):4–9.
112. Siesto G, Uccella S, Ghezzi F, et al. Surgical and survival outcomes in older women with endometrial cancer treated by laparoscopy. *Menopause.* 2010;17(3):539–544.
113. Querleu D, Morrow CP. Classification of radical hysterectomy. *Gynecol Oncol.* 2009;115(2):314–315.
114. Querleu D, Narducci F, Poulard V, et al. Modified radical vaginal hysterectomy with or without laparoscopic nerve-sparing dissection: a comparative study. *Gynecol Oncol.* 2002;85(1):154–158.
115. Spirtos NM, Eisenkop SM, Schlaerth JB, et al. Laparoscopic radical hysterectomy (type III) with aortic and pelvic lymphadenectomy in patients with stage I cervical cancer: surgical morbidity and intermediate follow-up. *Am J Obstet Gynecol.* 2002;187(2):340–348.
116. Pomet C, Atallah D, Le Bouedec G, et al. Laparoscopic radical hysterectomy for invasive cervical cancer: 8-year experience of a pilot study. *Gynecol Oncol.* 2003;91(3):534–539.
117. Xu H, Chen Y, Li Y, et al. Complications of laparoscopic radical hysterectomy and lymphadenectomy for invasive cervical cancer: experience based on 317 procedures. *Surg Endosc.* 2007;21(6):960–964.
118. Puntambekar SP, Palep RJ, Puntambekar SS, et al. Laparoscopic total radical hysterectomy by the Pune technique: our experience of 248 cases. *J Minim Invasive Gynecol.* 2007;14(6):682–689.
119. Chen Y, Xu H, Li Y, et al. The outcome of laparoscopic radical hysterectomy and lymphadenectomy for cervical cancer: a prospective analysis of 295 patients. *Ann Surg Oncol.* 2008;15(10):2847–2855.
120. Pellegrino A, Vizza E, Frusio R, et al. Total laparoscopic radical hysterectomy and pelvic lymphadenectomy in patients with Ib1 stage cervical cancer: analysis of surgical and oncological outcome. *Eur J Surg Oncol.* 2009;35(1):98–103.
121. Lee CL, Wu KY, Huang KG, et al. Long-term survival outcomes of laparoscopically assisted radical hysterectomy in treating early-stage cervical cancer. *Am J Obstet Gynecol.* 2010;203(2):165.e1–7.
122. Yan X, Li G, Shang H, et al. Twelve-year experience with laparoscopic radical hysterectomy and pelvic lymphadenectomy in cervical cancer. *Gynecol Oncol.* 2011;120(3):362–367.
123. Jackson KS, Das N, Naik R, et al. Laparoscopically assisted radical vaginal hysterectomy vs. radical abdominal hysterectomy for cervical cancer: a match controlled study. *Gynecol Oncol.* 2004;95(3):655–661.
124. Steed H, Rosen B, Murphy J, et al. A comparison of laparoscopic-assisted radical vaginal hysterectomy and radical abdominal hysterectomy in the treatment of cervical cancer. *Gynecol Oncol.* 2004;93(3):588–593.
125. Frumovitz M, dos Reis R, Sun CC, et al. Comparison of total laparoscopic and abdominal radical hysterectomy for patients with early-stage cervical cancer. *Obstet Gynecol.* 2007;110(1):96–102.
126. Li G, Yan X, Shang H, et al. A comparison of laparoscopic radical hysterectomy and pelvic lymphadenectomy and laparotomy in the treatment of Ib–IIa cervical cancer. *Gynecol Oncol.* 2007;105(1):176–180.
127. Malzoni M, Tinelli R, Cosentino F, et al. Total laparoscopic radical hysterectomy versus abdominal radical hysterectomy with lymphadenectomy in patients with early cervical cancer: our experience. *Ann Surg Oncol.* 2009;16(5):1316–1323.
128. Ghezzi F, Cromi A, Ciravolo G, et al. Surgicopathologic outcome of laparoscopic versus open radical hysterectomy. *Gynecol Oncol.* 2007;106(3):502–506.
129. Uccella S, Laterza R, Ciravolo G, et al. A comparison of urinary complications following total laparoscopic radical hysterectomy and laparoscopic pelvic lymphadenectomy to open abdominal surgery. *Gynecol Oncol.* 2007;107(suppl. 1):S147–S149.
130. Naik R, Jackson KS, Lopes A, et al. Laparoscopic assisted radical vaginal hysterectomy versus radical abdominal hysterectomy—a randomised phase II trial: perioperative outcomes and surgicopathological measurements. *BJOG.* 2010;117(6):746–751.
131. Chong GO, Park NY, Hong DG, et al. Learning curve of laparoscopic radical hysterectomy with pelvic and/or para-aortic lymphadenectomy in the early and locally advanced cervical cancer: comparison of the first 50 and second 50 cases. *Int J Gynecol Cancer.* 2009;19(8):1459–1464.
132. Raatz D, Börner P. Laparoscopy assisted radical vaginal hysterectomy (LAVRH) for cervical carcinoma—perioperative parameters and complications. *Zentralbl Gynäkol.* 2001;123(3):136–142.
133. Zakashansky K, Chuang L, Gretz H, et al. A case-controlled study of total laparoscopic radical hysterectomy with pelvic lymphadenectomy versus radical abdominal hysterectomy in a fellowship training program. *Int J Gynecol Cancer.* 2007;17(5):1075–1082.
134. Pareja R, Nick AM, Schmeler KM, et al. Quality of laparoscopic radical hysterectomy in developing countries: a comparison of surgical and oncologic outcomes between a comprehensive cancer center in the United States and a cancer center in Colombia. *Gynecol Oncol.* 2012;125(2):326–329.
135. Possover M, Stober S, Plaul K, et al. Identification and preservation of the motoric innervation of the bladder in radical hysterectomy type III. *Gynecol Oncol.* 2000;79(2):154–157.
136. Liang Z, Chen Y, Xu H, et al. Laparoscopic nerve-sparing radical hysterectomy with fascia

- space dissection technique for cervical cancer: description of technique and outcomes. *Gynecol Oncol.* 2010;119(2):202–207.
137. Kavallaris A, Hornemann A, Chalvatzas N, et al. Laparoscopic nerve-sparing radical hysterectomy: description of the technique and patients' outcome. *Gynecol Oncol.* 2010;119(2):198–201.
 138. Park NY, Chong GO, Hong DG, et al. Oncologic results and surgical morbidity of laparoscopic nerve-sparing radical hysterectomy in the treatment of FIGO stage IB cervical cancer: long-term follow-up. *Int J Gynecol Cancer.* 2011;21(2):355–362.
 139. Roy M, Plante M. Place of Schauta's radical vaginal hysterectomy. *Best Pract Res Clin Obstet Gynaecol.* 2011;25(2):227–237.
 140. Possover M. Technical modification of the nerve-sparing laparoscopy-assisted vaginal radical hysterectomy (VRH) type 3 for better reproducibility of this procedure. *Gynecol Oncol.* 2003;90(2):245–247.
 141. Sardi J, Vidaurreta J, Bermudez A, et al. Laparoscopically assisted Schauta operation: learning experience at the Gynecologic Oncology Unit, Buenos Aires University Hospital. *Gynecol Oncol.* 1999;75(3):361–365.
 142. Hertel H, Köhler C, Michels W, et al. Laparoscopy-assisted radical vaginal hysterectomy (LARVH): prospective evaluation of 200 patients with cervical cancer. *Gynecol Oncol.* 2003;90(3):505–511.
 143. Sharma R, Bailey J, Anderson R, et al. Laparoscopically assisted radical vaginal hysterectomy (Coelio-Schauta): a comparison with open Wertheim/Meigs hysterectomy. *Int J Gynecol Cancer.* 2006;16(5):1927–1932.
 144. Pahisa J, Martínez-Román S, Torné A, et al. Comparative study of laparoscopically assisted radical vaginal hysterectomy and open Wertheim–Meigs in patients with early-stage cervical cancer: eleven years of experience. *Int J Gynecol Cancer.* 2010;20(1):173–178.
 145. Leblanc E. How I perform. vaginal preparation for a laparoscopic radical hysterectomy or the “Schautheim” procedure [Article in French]. *Gynecol Obstet Fertil.* 2007;35(3):263–264.
 146. Lanowska M, Mangler M, Spek A, et al. Radical vaginal trachelectomy (RVT) combined with laparoscopic lymphadenectomy: prospective study of 225 patients with early-stage cervical cancer. *Int J Gynecol Cancer.* 2011;21(8):1458–1464.
 147. Plante M, Grogire J, Renaud MC, et al. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. *Gynecol Oncol.* 2011;121(2):290–297.
 148. Xu L, Sun FQ, Wang ZH. Radical trachelectomy versus radical hysterectomy for the treatment of early cervical cancer: a systematic review. *Acta Obstet Gynecol Scand.* 2011;90(11):1200–1209.
 149. Lee CL, Huang KG, Wang CJ, et al. Laparoscopic radical trachelectomy for stage Ib1 cervical cancer. *J Am Assoc Gynecol Laparosc.* 2003;10(1):111–115.
 150. Park NY, Chong GO, Cho YL, et al. Total laparoscopic nerve-sparing radical trachelectomy. *J Laparoendosc Adv Surg Tech A.* 2009;19(1):53–58.
 151. Martin A, Torrent A. Laparoscopic nerve-sparing radical trachelectomy: surgical technique and outcome. *J Minim Invasive Gynecol.* 2010;17(1):37–41.
 152. Kim JH, Park JY, Kim DY, et al. Fertility-sparing laparoscopic radical trachelectomy for young women with early stage cervical cancer. *BJOG.* 2010;117(3):340–347.
 153. Plante M, Roy M. Operative laparoscopy prior to a pelvic exenteration in patients with recurrent cervical cancer. *Gynecol Oncol.* 1998;69(2):94–99.
 154. Köhler C, Tozzi R, Possover M, et al. Explorative laparoscopy prior to exenterative surgery. *Gynecol Oncol.* 2002;86(3):311–315.
 155. Ferron G, Lim TY, Pomel C, et al. Creation of the Miami pouch during laparoscopic-assisted pelvic exenteration: the initial experience. *Int J Gynecol Cancer.* 2009;19(3):466–470.
 156. Martinez A, Filleron T, Vitse L, et al. Laparoscopic pelvic exenteration for gynaecological malignancy: is there any advantage? *Gynecol Oncol.* 2011;120(3):374–379.
 157. Ramirez PT, Dos Reis R. Splenectomy in patients with advanced or recurrent ovarian cancer: open and laparoscopic surgical techniques and clinical outcomes. *Gynecol Oncol.* 2007;104(2 suppl. 1):S29–S32.
 158. Anaf V, Gangji D, Simon P, et al. Laparoscopic insertion of intraperitoneal catheters for intraperitoneal chemotherapy. *Acta Obstet Gynecol Scand.* 2003;82(12):1140–1145.
 159. Ferron G, Gesson-Paute A, Classe JM, et al. Feasibility of laparoscopic peritonectomy followed by intra-peritoneal chemohyperthermia: an experimental study. *Gynecol Oncol.* 2005;99(2):358–361.
 160. Gesson-Paute A, Ferron G, Thomas F, et al. Pharmacokinetics of oxaliplatin during open versus laparoscopically assisted heated intraoperative intraperitoneal chemotherapy (HIPEC): an experimental study. *Ann Surg Oncol.* 2008;15(1):339–344.
 161. Tozzi R, Lavra F, Cassese T, et al. Laparoscopic debulking of bulky lymph nodes in women with cervical cancer: indication and surgical outcomes. *BJOG.* 2009;116(5):688–692.
 162. Martinek IE, Haldar K, Tozzi R. Laparoscopic surgery for gynaecological cancers in obese women. *Maturitas.* 2010;65(4):320–324.
 163. Obermair A, Manolitsas TP, Leung Y, et al. Total laparoscopic hysterectomy versus total abdominal hysterectomy for obese women with endometrial cancer. *Int J Gynecol Cancer.* 2005;15(2):319–324.
 164. O'Hanlan KA, Dibble SL, Fisher DT. Total laparoscopic hysterectomy for uterine pathology: impact of body mass index on outcomes. *Gynecol Oncol.* 2006;103(3):938–941.
 165. Fanning J, Hossler C. Laparoscopic conversion rate for uterine cancer surgical staging. *Obstet Gynecol.* 2010;116(6):1354–1357.
 166. Caquant F, Mas-Calvet M, Turbelin C, et al. Endometrial cancer by laparoscopy and vaginal approach in the obese patient [Article in French]. *Bull Cancer.* 2006;93(4):402–406.
 167. Helm CW, Arumugam C, Gordinier ME, et al. Laparoscopic surgery for endometrial cancer: increasing body mass index does not impact postoperative complications. *J Gynecol Oncol.* 2011;22(3):168–176.
 168. Dowdy SC, Aletti G, Cliby WA, et al. Extra-peritoneal laparoscopic paraaortic lymphadenectomy — a prospective cohort study of 293 patients with endometrial cancer. *Gynecol Oncol.* 2008;111(3):418–424.
 169. Benedetti-Panici P, Perniola G, Pernice M, et al. Laparoscopically guided minilaparotomy: a minimally invasive approach for the treatment of gynaecologic diseases in morbidly obese patients. *Eur J Obstet Gynecol Reprod Biol.* 2012;160(2):210–214.
 170. Moss EL, Balega J, Chan KK, et al. Surgical and oncological outcome of total laparoscopic radical hysterectomy in obese women with early-stage cervical cancer. *Int J Gynecol Cancer.* 2012;22(1):101–106.
 171. Palomba S, Falbo A, Russo T, et al. Updating of a recent meta-analysis of randomized controlled trials to assess the safety and the efficacy of the laparoscopic surgery for treating early stage endometrial cancer. *Gynecol Oncol.* 2009;114(1):135–136.
 172. Zullo F, Palomba S, Falbo A, et al. Laparoscopic surgery vs laparotomy for early stage endometrial cancer: long-term data from a randomized controlled trial. *Am J Obstet Gynecol.* 2009;200(3):296.e1–9.
 173. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. *J Clin Oncol.* 2012;30(7):695–700.
 174. Ghezzi F, Cromi A, Uccella S, et al. Laparoscopic versus open surgery for endometrial cancer: a minimum 3-year follow-up study. *Ann Surg Oncol.* 2010;17(1):271–278.
 175. Zullo F, Palomba S, Russo T, et al. A prospective randomized comparison between laparoscopic and laparotomic approaches in women with early stage endometrial cancer: a focus on the quality of life. *Am J Obstet Gynecol.* 2005;193(4):1344–1352.
 176. Kornblith AB, Huang HQ, Walker JL, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic International Federation of Gynecology and Obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. *J Clin Oncol.* 2009;27(32):5337–5342.
 177. Spirtos NM, Eisekop SM, Boike G, et al. Laparoscopic staging in patients with incompletely staged cancers of the uterus, ovary, fallopian tube, and primary peritoneum: a Gynecologic Oncology Group (GOG) study. *Am J Obstet Gynecol.* 2005;193(5):1645–1649.
 178. Chen Y, Xu H, Li Y, et al. The outcome of laparoscopic radical hysterectomy and lymphadenectomy for cervical cancer: a prospective analysis of 295 patients. *Ann Surg Oncol.* 2008;15(10):2847–2855.
 179. Pellegrino A, Vizza E, Fruscio R, et al. Total laparoscopic radical hysterectomy and pelvic lymphadenectomy in patients with Ib1 stage cervical cancer: analysis of surgical and oncological outcome. *Eur J Surg Oncol.* 2009;35(1):98–103.
 180. Lee CL, Wu KY, Huang KG, et al. Long-term survival outcomes of laparoscopically assisted radical hysterectomy in treating early-stage cervical cancer. *Am J Obstet Gynecol.* 2010;203(2):165.e1–7.
 181. Yan X, Li G, Shang H, et al. Twelve-year experience with laparoscopic radical hysterectomy and pelvic lymphadenectomy in cervical cancer. *Gynecol Oncol.* 2011;120(3):362–367.
 182. Jackson KS, Das N, Naik R, et al. Laparoscopically assisted radical vaginal hysterectomy vs. radical abdominal hysterectomy for cervical cancer: a match controlled study. *Gynecol Oncol.* 2004;95(3):655–661.
 183. Steed H, Rosen B, Murphy J, et al. A comparison of laparoscopic-assisted radical vaginal hysterectomy and radical abdominal hysterectomy in the treatment of cervical cancer. *Gynecol Oncol.* 2004;93(3):588–593.
 184. Li G, Yan X, Shang H, Wang G, Chen L, Han Y, et al. A comparison of laparoscopic radical hysterectomy and pelvic lymphadenectomy and laparotomy in the treatment of Ib–IIa cervical cancer. *Gynecol Oncol.* 2007;105:176–180.
 185. Sobiczewski P, Bidzinski M, Derlatka P, et al. Early cervical cancer managed by laparoscopy

- and conventional surgery: comparison of treatment results. *Int J Gynecol Cancer*. 2009;19(8):1390–1395.
186. Nam JH, Park JY, Kim DY, et al. Laparoscopic versus open radical hysterectomy in early-stage cervical cancer: long-term survival outcomes in a matched cohort study. *Ann Oncol*. 2012;23(4):903–911.
 187. Hong JH, Choi JS, Lee JH, et al. Comparison of survival and adverse events between women with stage IB1 and stage IB2 cervical cancer treated by laparoscopic radical vaginal hysterectomy. *Ann Surg Oncol*. 2012;19(2):605–611.
 188. Ramirez PT, Jhingran A, Macapinlac HA. Laparoscopic extraperitoneal paraaortic lymphadenectomy in locally advanced cervical cancer: a prospective correlation of surgical findings with positron emission tomography/computed tomography findings. *Cancer*. 2011;117(9):1928–1934.
 189. Gil-Moreno A, Diaz-Feijoo B, Pérez-Benavente A, et al. Impact of extraperitoneal lymphadenectomy on treatment and survival in patients with locally advanced cervical cancer. *Gynecol Oncol*. 2008;110(3 suppl 2): S33–S35.
 190. Colombo PE, Bertrand MM, Gutowski M, et al. Total laparoscopic radical hysterectomy for locally advanced cervical carcinoma (stages IIB, IIA and bulky stages IB) after concurrent chemoradiation therapy: surgical morbidity and oncological results. *Gynecol Oncol*. 2009;114(3):404–409.
 191. Iglesias DA, Ramirez PT. Role of minimally invasive surgery in staging of ovarian cancer. *Curr Treat Options Oncol*. 2011;12(3):217–229.
 192. Leblanc E, Sonoda Y, Narducci F, et al. Laparoscopic staging of early ovarian carcinoma. *Curr Opin Obstet Gynecol*. 2006;18(4):407–412.
 193. Spiro NM, Eisekop SM, Boike G, et al. Laparoscopic staging in patients with incompletely staged cancers of the uterus, ovary, fallopian tube, and primary peritoneum: a Gynecologic Oncology Group (GOG) study. *Am J Obstet Gynecol*. 2005;193(5):1645–1649.
 194. Chi DS, Abu-Rustum NR, Sonoda Y, et al. The safety and efficacy of laparoscopic surgical staging of apparent stage I ovarian and fallopian tube cancers. *Am J Obstet Gynecol*. 2005;192(5):1614–1619.
 195. Park J-Y, Bae J, Lim MC, et al. Laparoscopic and laparotomic staging in stage I epithelial ovarian cancer: a comparison of feasibility and safety. *Int J Gynecol Cancer*. 2008;18(6):1202–1209.
 196. Nezhat FR, Ezzati M, Chuang L, et al. Laparoscopic management of early ovarian and fallopian tube cancers: surgical and survival outcome. *Am J Obstet Gynecol*. 2009;200(1):83.e1–e6.
 197. Ghezzi F, Malzoni M, Vizza E, et al. Laparoscopic staging of early ovarian cancer: results of a multi-institutional cohort study. *Ann Surg Oncol*. 2012;19(5):1589–1594.
 198. Tozzi R, Köhler C, Ferrara A, et al. Laparoscopic treatment of early ovarian cancer: surgical and survival outcomes. *Gynecol Oncol*. 2004;93(1):199–203.
 199. Trinh H, Ott C, Fanning J. Feasibility of laparoscopic debulking with electrosurgical loop excision procedure and argon beam coagulator at recurrence in patients with previous laparotomy debulking. *Am J Obstet Gynecol*. 2004;190(5):1394–1397.
 200. Fanning J, Yacoub E, Hojat R. Laparoscopic-assisted cytoreduction for primary advanced ovarian cancer: success, morbidity, and survival. *Gynecol Oncol*. 2011;123(1):47–49.
 201. Nezhat FR, DeNoble SM, Liu CS, et al. The safety and efficacy of laparoscopic surgical staging and debulking of apparent advanced stage ovarian, fallopian tube, and primary peritoneal cancers. *JSLs*. 2010;14(2):155–168.
 202. Camatte S, Morice P, Atallah D, et al. Clinical outcome after laparoscopic pure management of borderline ovarian tumors: results of a series of 34 patients. *Ann Oncol*. 2004;15(4):605–609.
 203. Fauvet R, Boccara J, Dufournet C, et al. Laparoscopic management of borderline ovarian tumors: results of a French multicenter study. *Ann Oncol*. 2005;16(3):403–410.
 204. Maneo A, Vignali M, Chiari S, et al. Are borderline tumors of the ovary safely treated by laparoscopy? *Gynecol Oncol*. 2004;94(2):387–392.
 205. Desfeux P, Camatte S, Chatellier G, et al. Impact of surgical approach on the management of macroscopic early ovarian borderline tumors. *Gynecol Oncol*. 2005;98(3):390–395.
 206. Ødegaard E, Staff AC, Langebrenke A, et al. Surgery of borderline tumors of the ovary: retrospective comparison of short-term outcome after laparoscopy or laparotomy. *Acta Obstet Gynecol Scand*. 2007;86(5):620–626.
 207. Kane A, Uzan C, Gouy S, et al. Fertility results and outcomes after pure laparoscopic management of advanced-stage serous borderline tumors of the ovary. *Fertil Steril*. 2010;94(7):2891–2894.
 208. Querleu D, Papageorgiou T, Lambaudie E, et al. Laparoscopic restaging of borderline ovarian tumors: results of 30 cases initially presumed as stage IA borderline ovarian tumors. *BJOG*. 2003;110(2):201–204.
 209. Darai E, Tulpin L, Prugnotte H, et al. Laparoscopic restaging of borderline ovarian tumors. *Surg Endosc*. 2007;21(11):2039–2043.
 210. Köhler C, Tozzi R, Klemm P, et al. “Schauta sine utero”: technique and results of laparoscopic-vaginal radical parametrectomy. *Gynecol Oncol*. 2003;91(2):359–368.
 211. Leblanc E, Narducci F, Farre I, et al. Radical fibriectomy: a reasonable temporary risk-reducing surgery for selected women with a germ line mutation of BRCA 1 or 2 genes? Rationale and preliminary development. *Gynecol Oncol*. 2011;121(3):472–476.
 212. Shimada M, Kigawa J, Nishimura R, et al. Ovarian metastasis in carcinoma of the uterine cervix. *Gynecol Oncol*. 2006;101(2):234–237.
 213. Pahisa J, Martinez-Roman, Martinez-Zamora MA, et al. Laparoscopic ovarian transposition in patients with early cervical cancer. *Int J Gynecol Cancer*. 2008;18(3):584–589.
 214. Al-Badawi IA, Al-Aker M, AlSubhi J, et al. Laparoscopic ovarian transposition before pelvic irradiation: a Saudi tertiary center experience. *Int J Gynecol Cancer*. 2010;20(6):1082–1086.
 215. Delotte J, Ferron G, Kuei TL, et al. Laparoscopic management of an isolated ovarian metastasis on a transposed ovary in a patient treated for stage IB1 adenocarcinoma of the cervix. *J Minim Invasive Gynecol*. 2009;16(1):106–108.
 216. Spannuth WA, Rocconi RP, Huh WK, et al. A comparison of hand-assisted laparoscopy and conventional laparotomy for the surgical evaluation of pelvic masses. *Gynecol Oncol*. 2005;99(2):443–446.
 217. Krivak TC, Elkas JC, Rose GS, et al. The utility of hand-assisted laparoscopy in ovarian cancer. *Gynecol Oncol*. 2005;96(1):72–76.
 218. Chi DS, Abu-Rustum NR, Sonoda Y, et al. Laparoscopic and hand-assisted laparoscopic splenectomy for recurrent and persistent ovarian cancer. *Gynecol Oncol*. 2006;101(2):224–227.
 219. Panici PB, Palaia I, Bellati F, et al. Laparoscopy compared with laparoscopically guided minilaparotomy for large adnexal masses: a randomized controlled trial. *Obstet Gynecol*. 2007;110(2 Pt 1):241–248.
 220. Ghezzi F, Cromi A, Siesto G, et al. Microlaparoscopy: a further development of minimally invasive surgery for endometrial cancer staging—initial experience. *Gynecol Oncol*. 2009;113(2):170–175.
 221. Ghezzi F, Cromi A, Siesto G, et al. Minilaparoscopic versus conventional laparoscopic hysterectomy: results of a randomized trial. *J Minim Invasive Gynecol*. 2011;18(4):455–461.
 222. Rettenmaier MA, Abaid LN, Erwin MR, et al. A retrospective review of the GelPort system in single-port access pelvic surgery. *J Minim Invasive Gynecol*. 2009;16(6):743–747.
 223. Schill MR, Varela JE, Frisella MM, et al. Comparison of laparoscopic skills performance between single-site access (SSA) devices and an independent-port SSA approach. *Surg Endosc*. 2012;26(3):714–721.
 224. Escobar PF, Haber GP, Kaouk J, et al. Single-port surgery: laboratory experience with the daVinci single-site platform. *JSLs*. 2011;15(2):136–141.
 225. Gouy S, Kane A, Uzan C, et al. Single-port laparoscopy and extraperitoneal paraaortic lymphadenectomy: about fourteen consecutive cases. *Gynecol Oncol*. 2011;123(2):329–332.
 226. Escobar PF, Kebria M, Falcone T. Evaluation of a novel single-port robotic platform in the cadaver model for the performance of various procedures in gynecologic oncology. *Gynecol Oncol*. 2011;120(3):380–384.
 227. Escobar PF, Frumovitz M, Soliman PT, et al. Comparison of single-port laparoscopy, standard laparoscopy, and robotic surgery in patients with endometrial cancer. *Ann Surg Oncol*. 2012;19(5):1583–1588.
 228. Paek J, Kim SW, Lee SH, et al. Learning curve and surgical outcome for single-port access total laparoscopic hysterectomy in 100 consecutive cases. *Gynecol Obstet Invest*. 2011;72(4):227–233.
 229. Yim GW, Jung YW, Paek J, et al. Transumbilical single-port access versus conventional total laparoscopic hysterectomy: surgical outcomes. *Am J Obstet Gynecol*. 2010;203(1):26.e1–6.
 230. LeBrun JF, Ferron G, Vaysse C, et al. Laparoscopic observation of the diaphragm undersurface in the staging of peritoneal carcinomatosis: comparison of three optical systems. *Eur J Obstet Gynecol Reprod Biol*. 2012;164(1):65–68.
 231. Coomber RS, Sodergren MH, Clark J, et al. Natural orifice transluminal endoscopic surgery applications in clinical practice. *World J Gastrointest Endosc*. 2012;4(3):65–74.
 232. Bourdel N, Kondo W, Botchorishvili R, et al. Assessment of sentinel nodes for gynecologic malignancies by natural orifices transluminal endoscopic surgery (NOTES): preliminary report. *Gynecol Oncol*. 2009;115(3):367–370.
 233. Nassif J, Zacharopoulou C, Marescaux J, et al. Transvaginal extraperitoneal lymphadenectomy by Natural Orifices Transluminal Endoscopic Surgery (NOTES) technique in porcine model: feasibility and survival study. *Gynecol Oncol*. 2009;112(2):405–408.
 234. Naumann RW, Coleman RL. The use of adjuvant radiation therapy in early endometrial cancer by members of the Society of Gynecologic Oncologists in 2005. *Gynecol Oncol*. 2007;105(1):7–12.
 235. Barbash GI, Glied SA. New technology and health care costs—the case of robot-assisted surgery. *N Engl J Med*. 2010;363(8):701–704.
 236. Lau S, Vaknin Z, Ramana-Kumar AV, et al. Outcomes and cost comparisons after introducing a robotics program for endometrial cancer surgery. *Obstet Gynecol*. 2012;119(4):717–724.

237. Hoekstra AV, Jairam-Thodla A, Rademaker A, et al. The impact of robotics on practice management of endometrial cancer: transitioning from traditional surgery. *Int J Med Robot.* 2009;5(4):392–397.
238. Peiretti M, Zanagnolo V, Boccione L, et al. Robotic surgery: changing the surgical approach for endometrial cancer in a referral cancer center. *J Minim Invasive Gynecol.* 2009;16(4):427–431.
239. Gaziano JM. Fifth phase of the epidemiologic transition: the age of obesity and inactivity. *JAMA.* 2010;303(3):275–276.
240. Papadia A, Ragni N, Salom EM. The impact of obesity on surgery in gynecological oncology: a review. *Int J Gynecol Cancer.* 2006;16(2):944–952.
241. Hauspy J, Jimenez W, Rosen B, et al. Laparoscopic surgery for endometrial cancer: a review. *J Obstet Gynaecol Can.* 2010;32(6):570–579.
242. Gehrig PA, Cantrell LA, Shafer A, et al. What is the optimal minimally invasive surgical procedure for endometrial cancer staging in the obese and morbidly obese woman? *Gynecol Oncol.* 2008;111(1):41–45.
243. Seamon LG, Bryant SA, Rheume PS, et al. Comprehensive surgical staging for endometrial cancer in obese patients: comparing robotics and laparoscopy. *Obstet Gynecol.* 2009;114(1):16–21.
244. Lau S, Buzaglo K, Vaknin Z, et al. Relationship between body mass index and robotic surgery outcomes of women diagnosed with endometrial cancer. *Int J Gynecol Cancer.* 2011;21(4):722–729.
245. Bernardini MQ, Gien LT, Tipping H, et al. Surgical outcome of robotic surgery in morbidly obese patient with endometrial cancer compared to laparoscopy. *Int J Gynecol Cancer.* 2012;22(1):76–81.
246. Subramaniam A, Kim KH, Bryant SA, et al. A cohort study evaluating robotic versus laparoscopy surgical outcomes of obese women with endometrial carcinoma. *Gynecol Oncol.* 2011;122(3):604–607.
247. Boggess JF, Gehrig PA, Cantrell L, et al. A case-control study of robot-assisted type III radical hysterectomy with pelvic lymph node dissection compared with open radical hysterectomy. *Am J Obstet Gynecol.* 2008;199(4):357 e1–7.
248. Halliday D, Lau S, Vaknin Z, et al. Robotic radical hysterectomy: comparison of outcomes and cost. *J Robot Surg.* 2010;4:211–216.
249. Cantrell LA, Mendivil A, Gehrig PA, et al. Survival outcomes for women undergoing type III robotic radical hysterectomy for cervical cancer: a 3-year experience. *Gynecol Oncol.* 2010;117(2):260–265.
250. Nezhat FR, Datta MS, Liu C, et al. Robotic radical hysterectomy versus total laparoscopic radical hysterectomy with pelvic lymphadenectomy for treatment of early cervical cancer. *JSL.* 2008;12(3):227–237.
251. Magrina JF, Kho RM, Weaver AL, et al. Robotic radical hysterectomy: comparison with laparoscopy and laparotomy. *Gynecol Oncol.* 2008;109(1):86–91.
252. Obermair A, Gebski V, Frumovitz M, et al. A phase III randomized clinical trial comparing laparoscopic or robotic radical hysterectomy with abdominal radical hysterectomy in patients with early stage cervical cancer. *J Minim Invasive Gynecol.* 2008;15(5):584–588.
253. Ramirez PT, Schmeler KM, Wolf JK, et al. Robotic radical parametrectomy and pelvic lymphadenectomy in patients with invasive cervical cancer. *Gynecol Oncol.* 2008;111(1):18–21.
254. Vitobello D, Siesto G, Bulletti C, et al. Robotic radical parametrectomy with pelvic lymphadenectomy: our experience and review of the literature. *Eur J Surg Oncol.* 2012;38(6):548–554.
255. Leath CA, 3rd, Straughn JM, Bhoola SM, et al. The role of radical parametrectomy in the treatment of occult cervical carcinoma after extrafascial hysterectomy. *Gynecol Oncol.* 2004;92(1):215–219.
256. Vignancour S, Narducci F, Collinet P, et al. Laparoscopic management of occult cervical cancer discovered after simple hysterectomy. *Gynecol Obstet Fertil.* 2007;35(4):297–302.
257. Buda A, Pellegrino A, Vitobello D, et al. Total laparoscopic radical parametrectomy, partial colpectomy, and pelvic lymphadenectomy in patients with occult cervical cancer. *Int J Gynaecol Obstet.* 2009;107(1):73–76.
258. Persson J, Kannisto P, Bossmar T. Robot-assisted abdominal laparoscopic radical trachelectomy. *Gynecol Oncol.* 2008;111(3):564–567.
259. Nick AM, Frumovitz MM, Soliman PT, et al. Fertility sparing surgery for treatment of early-stage cervical cancer: open vs. robotic radical trachelectomy. *Gynecol Oncol.* 2012;124(2):276–280.
260. Gaia G, Holloway RW, Santoro L, et al. Robotic-assisted hysterectomy for endometrial cancer compared with traditional laparoscopic and laparotomy approaches: a systematic review. *Obstet Gynecol.* 2010;116(6):1422–1431.
261. Reza M, Maeso S, Blasco JA, et al. Meta-analysis of observational studies on the safety and effectiveness of robotic gynaecological surgery. *Br J Surg.* 2010;97(12):1772–1783.
262. Magrina JF, Zanagnolo V, Noble BN, et al. Robotic approach for ovarian cancer: perioperative and survival results and comparison with laparoscopy and laparotomy. *Gynecol Oncol.* 2011;121(1):100–105.
263. Bell MC, Torgerson J, Seshadri-Kreadon U, et al. Comparison of outcomes and cost for endometrial cancer staging via traditional laparoscopy, standard laparoscopy and robotic techniques. *Gynecol Oncol.* 2008;111(3):407–411.
264. Ho C TE, Tran K, Cimon K. Robot-Assisted Surgery Compared with Open Surgery and Laparoscopic Surgery: Clinical Effectiveness and Economic Analyses. In: OCAfDaTiHCTrn, ed. Available from: <http://www.cadth.ca/en/products/health-technology-assessment/publication/2682>. Accessed December 12, 2012.
265. Tang B, Hou S, Cuschieri SA. Ergonomics of and technologies for single-port laparoscopic surgery. *Minim Invasive Ther Allied Technol.* 2012;21(1):46–54.
266. White MA, Autorino R, Spana G, et al. Robotic laparoscopic single-site radical nephrectomy: surgical technique and comparative outcomes. *Eur Urol.* 2011;59(5):815–822.
267. Kaouk JH, Goel RK. Single-port laparoscopic and robotic partial nephrectomy. *Eur Urol.* 2009;55(5):1163–1169.
268. Escobar PF, Starks D, Fader AN, et al. Laparoendoscopic single-site and natural orifice surgery in gynecology. *Fertil Steril.* 2010;94(7):2497–2502.
269. Escobar PF, Knight J, Rao S, et al. da Vinci® single-site platform: anthropometrical, docking and suturing considerations for hysterectomy in the cadaver model. *Int J Med Robot.* 2012;8(2):191–195.
270. Konstantinidis KM, Hirides P, Hirides S, et al. Cholecystectomy using a novel Single-Site® robotic platform: early experience from 45 consecutive cases. *Surg Endosc.* 2012;26(9):2687–2694.
271. Sanchez LA, Petroni G, Piccigallo M, et al. Real-time control and evaluation of a teleoperated miniature arm for Single Port Laparoscopy. Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society Conference 2011;7049–53.
272. Ghezzi F, Uccella S, Cromi A, et al. Postoperative pain after laparoscopic and vaginal hysterectomy for benign gynecologic disease: a randomized trial. *Am J Obstet Gynecol.* 2010;203(2):118e1–8.
273. Gien LT, Kupets R, Covens A. Feasibility of same-day discharge after laparoscopic surgery in gynecologic oncology. *Gynecol Oncol.* 2011;121(2):339–343.
274. Tillmans T, Lowe MP. Safety, feasibility, and costs of outpatient laparoscopic extra-peritoneal aortic nodal dissection for locally advanced cervical carcinoma. *Gynecol Oncol.* 2007;106(2):370–374.
275. Ngo C. *Thèse de médecine.* Toulouse, France: Université Paul-Sabatier, 2012.
276. Qvigstad E, Lieng M. Surgical treatment of endometrial cancer and atypical hyperplasia: A trend shift from laparotomy to laparoscopy. *Obstet Gynecol Int.* 2011;829425.
277. Ghezzi F, Cromi A, Uccella S, et al. Incorporating laparoscopy in the practice of a gynecologic oncology service: actual impact beyond clinical trials data. *Ann Surg Oncol.* 2009;16(8):2305–2314.
278. Leiserowitz, GS, Xing G, Parikh-Patel A, et al. Laparoscopic versus abdominal hysterectomy for endometrial cancer. comparison of patient outcomes. *Int J Gynecol Cancer.* 2009;19(8):1370–1376.
279. Ko EM, Muto MG, Berkowitz RS, Feltmate CM. Robotic versus open radical hysterectomy: a comparative study at a single institution. *Gynecologic oncology* 2008;111:425–30.
280. Fanning J, Fenton B, Purohit M. Robotic radical hysterectomy. *American journal of obstetrics and gynecology* 2008;198:649 e1–4.
281. Maggioni A, Minig L, Zanagnolo V, et al. Robotic approach for cervical cancer: comparison with laparoscopy: a case control study. *Gynecologic oncology* 2009;115:60–4.
282. Oleszczuk A, Kohler C, Paulick J, Schneider A, Lanowska M. Vaginal robot-assisted radical hysterectomy (VRARH) after laparoscopic staging: feasibility and operative results. The international journal of medical robotics + computer assisted surgery : MRCAS 2009;5:38–44.
283. Lowe MP, Chamberlain DH, Kamelle SA, Johnson PR, Tillmanns TD. A multi-institutional experience with robotic-assisted radical hysterectomy for early stage cervical cancer. *Gynecologic oncology* 2009;113:191–4.
284. Boggess JF, Gehrig PA, Cantrell L, et al. A case-control study of robot-assisted type III radical hysterectomy with pelvic lymph node dissection compared with open radical hysterectomy. *American journal of obstetrics and gynecology* 2008;199:357 e1–7.
285. DeNardis SA, Holloway RW, Bigsby GE, Pikaart DP, Ahmad S, Finkler NJ. Robotically assisted laparoscopic hysterectomy versus total abdominal hysterectomy and lymphadenectomy for endometrial cancer. *Gynecologic oncology* 2008;111:412–7.
286. Seamon LG, Cohn DE, Henretta MS, et al. Minimally invasive comprehensive surgical staging for endometrial cancer: Robotics or laparoscopy? *Gynecologic oncology* 2009;113:36–41.
287. Cardenas-Goicoechea J, Adams S, Bhat SB, Randall TC. Surgical outcomes of robotic-assisted surgical staging for endometrial cancer are equivalent to traditional laparoscopic staging at a minimally invasive surgical center. *Gynecologic oncology* 2010;117:224–8.
288. Veljovich DS, Paley PJ, Drescher CW, Everett EN, Shah C, Peters WA, 3rd. Robotic surgery in gynecologic oncology: program initiation and outcomes after the first year with comparison with laparotomy for endometrial cancer staging. *American journal of obstetrics and gynecology* 2008;198:679 e1–9; discussion e9–10.

Diagnostic Imaging

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INTRODUCTION

The objectives of imaging in gynecologic oncology are primary tumor detection and characterization, image-guided percutaneous biopsy, staging, monitoring treatment response, and detecting tumor recurrence. Comprehensive imaging of the female pelvis can be achieved using a combination of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and combined 2- ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography computed tomography (FDG-PET/CT). The choice of imaging modality depends on the clinical question (Table 11.1). In some instances, more than one modality may be appropriate, and therefore it is best to discuss the clinical question with the radiologist to determine which modality will be most useful. As with any rapidly evolving technology, imaging strategies are not static and require continuous updating and reevaluation.

IMAGING MODALITIES, EXAMINATION TECHNIQUES, AND NORMAL ANATOMY

Ultrasound

Ultrasound (US) is considered the initial imaging modality of choice for evaluation of the female pelvis. Currently, the accepted roles of US in women with suspected gynecologic malignancy include characterization of adnexal masses, identification of endometrial abnormalities in women with intermenstrual or postmenopausal bleeding, and detection of primary or recurrent gestational trophoblastic disease in women with elevated serum beta human chorionic gonadotropin (β -hCG) levels. US is also used to guide biopsy of primary pelvic tumors and/or metastases (1) and to guide drainage of postoperative fluid collections such as lymphoceles, seromas, or abscesses. The role of US in screening high-risk patient populations for ovarian or endometrial carcinoma remains controversial.

US has many advantages in routine pelvic imaging: it is relatively inexpensive, provides multiplanar views, is widely available, and lacks ionizing radiation. Its portability allows it to be used in virtually any setting including the US suite, operating room, patient bedside, or radiation therapy suite. However, US also has a number of limitations: it is operator-dependent, and image quality varies with patient body habitus and presence of overlying bowel gas. Transvaginal ultrasound (TVS) provides the best spatial and soft-tissue resolution, but it comes at the cost of a significant decrease in the size of the field of view.

Sonohysterogram (SHG), which utilizes TVS while distending the endometrial cavity with fluid, can be useful in evaluating the endometrium.

Technique

Adequate US evaluation of the female pelvis requires a transvaginal approach. Placement of the transducer closer to the organs of interest allows use of a higher-frequency (typically 5.0- to 7.5-MHz) transducer. While the use of such a transducer results in significantly improved spatial resolution and fewer imaging artifacts in comparison to transabdominal imaging, it does so at the cost of a smaller field of view. Hence, transabdominal imaging must be considered an important complementary imaging technique if the mass is larger than the TVS field of view, the ovaries are displaced out of the pelvis, the ovaries are not visualized because of the presence of bowel gas, or to evaluate important ancillary findings such as hydronephrosis, ascites, peritoneal deposits, and liver metastases. Transabdominal imaging also provides a better overall view of the pelvis and the relationship of female pelvic organs to the pelvic sidewall and bladder. Transabdominal pelvic imaging is performed with a 3.5- to 5.0-MHz curved array transducer using a distended urinary bladder as an acoustic window to view the female pelvic organs. Three-dimensional US is a relatively new technique that has been shown to decrease scanning time and possibly improve diagnostic confidence in pelvic imaging (2,3). Color, power, and spectral Doppler provide additional information regarding associated vascularity.

SHG is increasingly performed to improve the evaluation of the endometrium. With this technique, sterile saline is infused into the endometrial cavity under continuous TVS guidance. The sterile saline distends the endometrial cavity, separating the anterior and posterior endometrial layers and outlining the endometrial surface (4,5). Contraindications to SHG include hematometra and acute pelvic inflammatory disease. Three-dimensional SHG reduces operator dependence and length of examination time and has been reported to provide significant additional information in a majority of patients (6).

Normal Anatomy

The normal myometrium is homogeneous in echotexture and intermediate in echogenicity. Anechoic tubular structures separating the outer one-third from the inner two-thirds of the myometrium represent the arcuate vessels, which are best seen on color flow imaging. The internal os can be recognized as a slight constriction of the uterine contour.

The endometrium should be measured at the thickest part of the endometrial stripe in the uterine fundus on a midline sagittal image and, by convention, is always reported as a double-layer

Table 11.1 The Choice of Imaging Modality in Endometrial, Cervical, and Ovarian Cancer				
Pathology	Imaging Modalities			
	US (TA/TVS/SHG)	CT	MRI	PET/CT
Endometrial Cancer	Evaluation of the endometrium in patients presenting with postmenopausal bleeding Double-layer endometrial thickness >5 mm on TVS determines the need for endometrial sampling	Detection of enlarged lymph nodes Detection of distant metastases (lung, liver, etc.) Identification of peritoneal nodules in serous papillary and clear cell carcinoma Detection of recurrent pelvic and distant metastatic disease	Delineating the origin of the primary tumor (endometrial vs. cervical) when the biopsy results are inconclusive Assessment of the depth of myometrial invasion and cervical stromal invasion (improves pretreatment risk stratification) Evaluation of disease extent in the pelvis Detection of enlarged lymph nodes Evaluation of surgical resectability, if pelvis is the sole site of recurrence	Detection of extrauterine disease Monitoring treatment response in selected cases Detection of distant metastases in patients with suspected recurrence within the pelvis; detecting unsuspected distant metastases significantly alters treatment choices
Cervical Cancer	No role apart from evaluation of complications such as hydronephrosis and guiding interventional procedures	Evaluation of extent of disease in advanced cases (especially if no access to MRI) Detection of enlarged lymph nodes Detection of distant metastases (lung, liver etc.)	Accurate evaluation of tumor size (particularly important in cases considered for trachelectomy) Evaluation of parametrial invasion Evaluation of pelvic sidewall invasion and bladder/rectal mucosa invasion Detection of enlarged lymph nodes Brachytherapy treatment planning Monitoring response to chemoradiotherapy Evaluation of surgical resectability, if pelvis is the sole site of recurrence May distinguish radiation fibrosis from recurrent disease	Evaluation of patients with advanced cervical cancer, especially the detection of lymph node metastases Radiotherapy field planning Evaluation of response to treatment May distinguish radiation fibrosis from recurrent disease Detection of distant metastases in patients with suspected recurrence within the pelvis; significantly alters treatment choices
Ovarian Cancer	Detection and characterization of adnexal masses Screening of women at high risk for ovarian carcinoma Guide omental/peritoneal biopsy and drainage of ascites	Characterization of ovarian lesions that are detected incidentally on CT Triage patients to primary surgery versus neoadjuvant chemotherapy by accurate evaluation of the extent and anatomical location of peritoneal spread (dictates the feasibility of cytoreductive surgery) Detect enlarged lymph nodes Detect complications such as small bowel obstruction Evaluation of residual disease following surgery Evaluate treatment response and assess suspected relapse with rising CA-125 levels or clinically suspicious symptoms Guide omental/peritoneal biopsy	Characterization of indeterminate adnexal lesions on US Evaluation of disease in situations where CT is contraindicated (contraindications to contrast media, renal insufficiency, and pregnancy) Evaluate resectability of a pelvic recurrence if surgery is planned	May play a role in evaluation of the extent of disease Evaluation of recurrent ovarian cancer especially in patients with elevated CA-125 but negative CT findings

measurement. The normal endometrium is echogenic. However, the thickness and echotexture of the endometrium vary with the hormonal status of the patient. At the end of the menses, the endometrial stripe is highly echogenic and measures approximately 2 to 3 mm (Fig. 11.1). During the secretory stage, the endometrium becomes less echogenic and thickens, reaching

a maximum of 8 mm (Fig. 11.1). Before ovulation, a trilaminar appearance of the endometrium has been described. The central thin echogenic line represents a reflective artifact and/or mucus and secretions between the anterior and posterior layers of the endometrium. Subjacent is the second layer, which is the relatively hypoechoic functionalis layer. The third layer is the surrounding

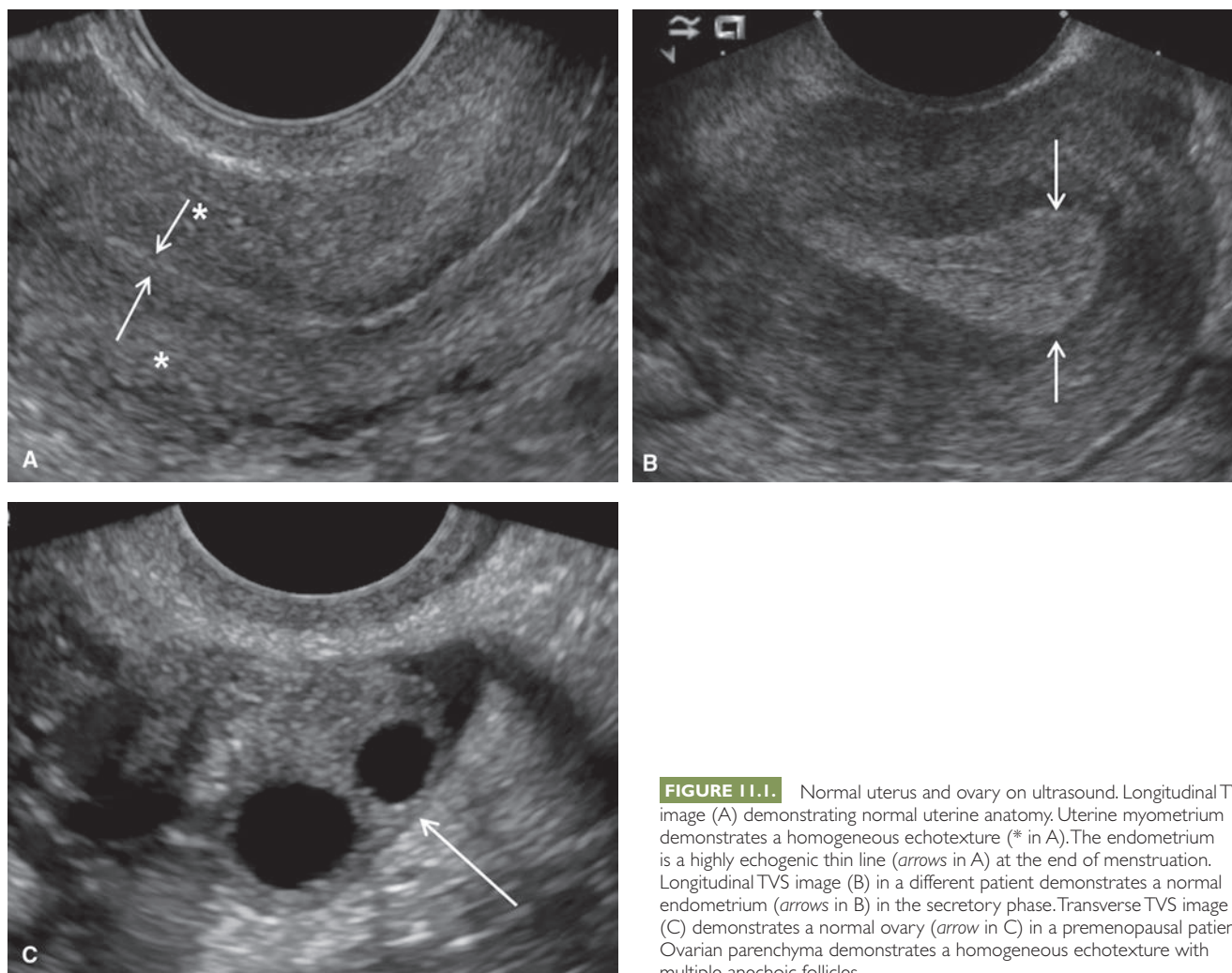


FIGURE 11.1. Normal uterus and ovary on ultrasound. Longitudinal TVS image (A) demonstrating normal uterine anatomy. Uterine myometrium demonstrates a homogeneous echotexture (* in A). The endometrium is a highly echogenic thin line (arrows in A) at the end of menstruation. Longitudinal TVS image (B) in a different patient demonstrates a normal endometrium (arrows in B) in the secretory phase. Transverse TVS image (C) demonstrates a normal ovary (arrow in C) in a premenopausal patient. Ovarian parenchyma demonstrates a homogeneous echotexture with multiple anechoic follicles.

deeper basalis layer, which remains echogenic. Following ovulation, the functionalis layer becomes thicker and more echogenic than during the proliferative phase, and the entire stripe may reach 15 mm in thickness and is more uniformly echogenic just prior to menstruation (7). In some patients, the innermost layer of myometrium is relatively hypoechoic compared to the immediately adjacent endometrium and is termed the subendometrial halo. The subendometrial halo is less commonly visualized in postmenopausal women. Neither the subendometrial halo nor fluid or debris within the endometrial cavity should be included in measurements of the endometrial stripe. At SHG, the endometrium should be homogeneous, symmetric, and regular without mass effect (Fig. 11.2). The sum of the width of the two layers should not exceed the maximum acceptable width for the patient's hormonal status.

In postmenopausal women, the uterine corpus atrophies until it approximates the length of the cervix. Similarly, there is atrophy of the endometrium which appears as a thin, regular echogenic line <5 mm in width (8). In women taking hormonal replacement therapy (HRT), less uterine and endometrial atrophy occurs (9). Women taking sequential HRT are best examined following withdrawal bleeding and the progesterone phase of their cycle when the endometrium is expected to be at the thinnest.

The US appearance of the ovaries also changes with the patient's hormonal status. The premenopausal ovary has a relatively homogeneous outer cortex with a more echogenic central stroma. Small anechoic follicles are commonly seen peripherally (Fig. 11.1). At

ovulation, one follicle becomes dominant, reaching a maximum diameter of 2.0 to 2.5 cm. Following ovulation, the corpus luteum develops. The corpus luteum may contain debris and/or hemorrhage and often involutes, appearing to be crenelated just prior to menstruation. The ovaries atrophy with menopause and contain fewer follicles. Therefore, postmenopausal ovaries are more difficult to visualize with US. In women taking HRT, less ovarian atrophy will occur and follicles will continue to develop.

Doppler evaluation of ovarian blood flow is best performed during days 3 to 7 of the menstrual cycle. The ovary undergoing ovulation in a given cycle demonstrates a relatively high-velocity, low-resistance arterial waveform with continuous forward diastolic flow. The contralateral ovary will typically demonstrate a higher-resistance, low-velocity arterial waveform with either very low or no diastolic flow.

Computed Tomography

CT is the primary imaging modality for staging and treatment follow-up of patients with ovarian cancer. It is also routinely used for detection of distant metastatic disease and lymphadenopathy in patients with advanced endometrial, cervical, and vulvar cancer as well as detection of recurrent gynecologic malignancies. CT rather than US-guided biopsy can be useful masses that are small and/or difficult to access (1,10–12).

Advantages of CT include ready availability, short image acquisition times, large field of view, high spatial resolution, and rapid three-dimensional (3-D) reconstructions. Disadvantages

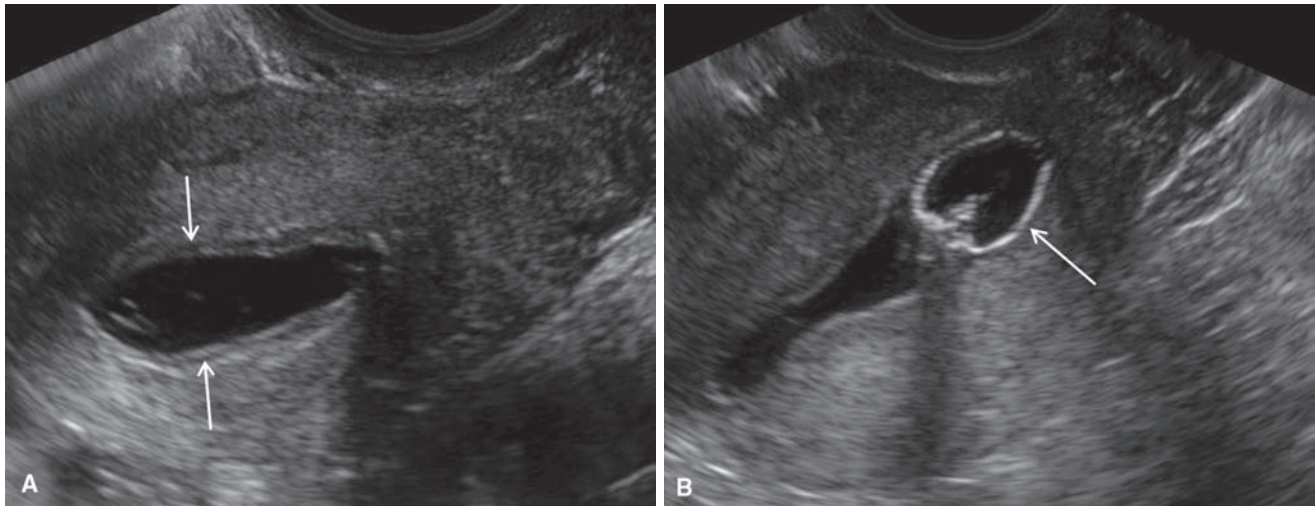


FIGURE 11.2. Normal sonohysterogram. Longitudinal SHG images (A, B) demonstrate a fluid-filled endometrial cavity (arrows in A). Catheter (arrows in B) is seen within the lower uterine segment.

of CT include the use of ionizing radiation, degradation of image quality by patient body habitus or metallic implants, such as a hip prosthesis, and the morbidity and mortality associated with iodinated contrast agents.

Technique

Contrast-enhanced CT of the abdomen and pelvis is performed in the portal venous phase, 70 seconds following an injection of intravenous low osmolar contrast medium; this enhances blood vessels and viscera, allowing easier identification of enlarged lymph nodes and parenchymal lesions, especially in the liver and spleen. Oral contrast medium is utilized to opacify the small and large bowel, which allows detection of bowel serosal deposits. In some centers, patients receive 500 mL of diluted oral contrast medium the evening preceding the examination and an additional 500 mL, 45 minutes before the CT scan. In other protocols, the patient receives 600 to 1,000 mL of dilute oral contrast at least 1 hour before the examination, coupled with a 200-mL dilute contrast enema.

Normal Anatomy

On CT, the vagina, cervix, and uterine corpus can be differentiated based on both morphologic and enhancement characteristics (Fig. 11.3). The uterine corpus appears as a triangular or ovoid soft-tissue mass posterior to the urinary bladder. The cervix is a more rounded structure. At the level of the fornix, the vagina has a flat rectangular or crescentic shape. Following bolus intravenous contrast administration, the myometrium in the uterine corpus enhances to a greater degree than that of the cervix (Fig. 11.3). The endometrium can often be delineated from the enhancing myometrium. The broad and round ligaments can be seen coursing laterally and anteriorly, respectively. Occasionally, the uterosacral ligaments are depicted as arc-like structures extending from the cervix to the sacrum.

In the premenopausal patient, the normal ovaries are routinely seen, usually posterolateral to the uterine corpus and medial to the external iliac vessels (Fig. 11.3). Their uniform soft-tissue density is punctuated by small cystic regions representing follicles. In the postmenopausal patient, the ovaries are small and less readily detected.

Magnetic Resonance Imaging

MRI is the modality of choice for staging of uterine corpus and cervix malignancies. MRI has been shown to be superior to CT

for staging of endometrial and cervical cancers (13,14), and may be useful for staging of ovarian cancer in selected patients. In addition, MRI can often differentiate radiation fibrosis from recurrent tumor (15) and is useful in the detection of recurrent gynecologic malignancies. The accuracy of MRI assessment of lymph node involvement is similar to that of CT; both rely on size criteria to detect lymphadenopathy (16).

Although MRI is still relatively expensive, it minimizes costs in some clinical settings by limiting or eliminating the need for more expensive and/or more invasive diagnostic or surgical procedures (17,18). There are at least three cost-minimizing indications for MRI in the evaluation of women with gynecologic malignancy: (a) staging of invasive cervical carcinoma as an adjunct to clinical examination; (b) the preoperative management of women with endometrial cancer (19-21); and (c) the characterization of indeterminate adnexal lesions on US (18,22).

Advantages of MRI include superior soft-tissue contrast, absence of ionizing radiation, and multiplanar capability. MRI is the modality of choice for patients with allergies to iodinated intravenous contrast media or renal impairment. However, clinicians should be aware that gadolinium contrast agents used in MRI have recently been associated with the development of nephrogenic systemic fibrosis (NSF), a rare progressive connective tissue disease, in patients with end-stage renal disease and/or acute renal failure. One disadvantage of MRI relative to CT is the need for longer acquisition times. In addition, MRI is contraindicated in patients with pacemakers, cochlear implants, certain vascular clips, metallic objects in the eye, and neural stimulators. Furthermore, some patients may experience claustrophobia and may require sedation in order to complete a diagnostic examination.

Technique

Patients are asked to fast for 4-6 hours prior to MRI examination in order to limit motion artifacts from bowel peristalsis (23). An antiperistaltic agent, such as glucagon or hyoscine butyl bromide, is recommended to further reduce motion artifacts (24). The patient is asked to void before the examination, as a full bladder may cause ghosting and motion artifacts that degrade images. Patients are imaged in the supine position using a pelvic surface array multichannel coil (e.g., a cardiac coil usually offers the best image quality) (23,25). Endoluminal coils (endorectal and endovaginal) can provide high-resolution images of small tumors of the cervix and aid detection of early parametrial invasion (26,27). However, their field of view is limited in assessing

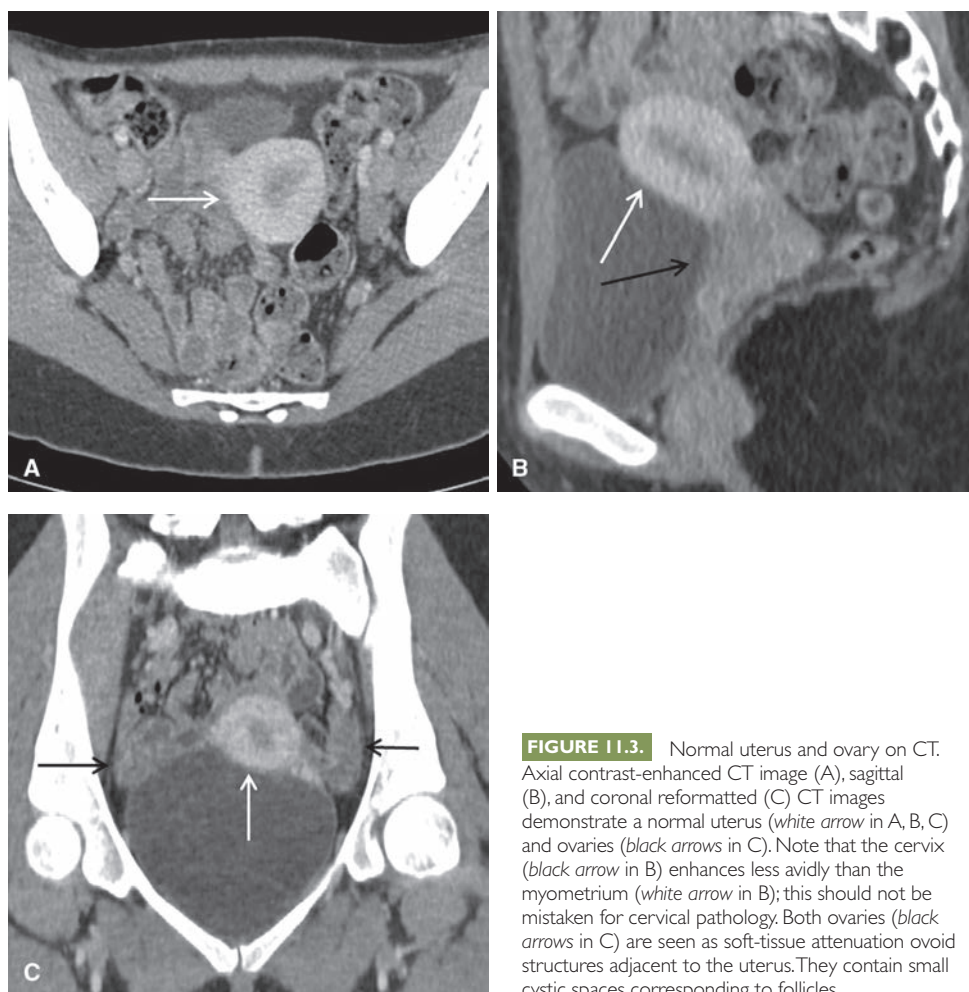


FIGURE 11.3. Normal uterus and ovary on CT. Axial contrast-enhanced CT image (A), sagittal (B), and coronal reformatted (C) CT images demonstrate a normal uterus (white arrow in A, B, C) and ovaries (black arrows in C). Note that the cervix (black arrow in B) enhances less avidly than the myometrium (white arrow in B); this should not be mistaken for cervical pathology. Both ovaries (black arrows in C) are seen as soft-tissue attenuation ovoid structures adjacent to the uterus. They contain small cystic spaces corresponding to follicles.

large tumors, extra-uterine extension to adjacent organs and the pelvic sidewall, and detecting pelvic lymph nodes; consequently, endoluminal coils are not widely used in gynecological imaging. Vaginal opacification with gel, yielding high signal intensity on T2-weighted images (T2WI), may be useful in cases where there is suspected cervical tumor extension into the vagina, particularly into the posterior vaginal fornix (28).

The basic imaging protocol for gynecological MRI includes T1-weighted images (T1WI) of the pelvis in the axial plane and T2WI in the axial and sagittal planes. When T1WI shows high signal intensity within the adnexa, which may represent fat or hemorrhage, fat-saturation T1-weighted images (T1W FS) are mandatory to differentiate between the two. Staging of gynecological malignancies requires large field of view axial T1WI and/or T2WI of the pelvis and abdomen to identify enlarged lymph nodes, hydronephrosis, as well as bone marrow changes (20,29). High resolution, small field of view, axial oblique (short axis) T2W fast spin-echo (T2W FSE) images taken parallel to the short axis of the uterine corpus are essential to accurately evaluate the depth of myometrial invasion in endometrial carcinoma (30). In the assessment of patients with cervical cancer, high resolution small field of view axial oblique (short axis) T2W FSE images parallel to the short axis of the cervix are crucial for identification of parametrial invasion (31).

Dynamic multiphase contrast-enhanced MRI, using 3-dimensional gradient echo T1WI, after intravenous gadolinium administration, is often performed in staging patients with endometrial cancer. It is useful in the characterization of complex adnexal lesions, and can aid detection of small peritoneal

and serosal implants, when ovarian cancer is suspected (32,33). Routine use of dynamic multiphase contrast-enhanced 3D T1-weighted sequences is not recommended for staging patients with cervical carcinoma. However, these sequences may be very useful for accurate delineation of small cervical tumors in patients being considered for fertility sparing surgery (i.e., trachelectomy) (34) and to differentiate tumor recurrence from radiation fibrosis in patients with cervical cancer (15).

Increasingly, diffusion-weighted MRI (DW-MRI) is routinely incorporated in MRI staging protocols for uterine malignancies. DW-MRI can be useful for accurately determining the depth of myometrial invasion in patients with endometrial cancer. It can be particularly helpful for tumors that are either iso- or hyper-intense relative to the myometrium on T2WI or when the use of intravenous contrast medium is contra-indicated, and it may replace dynamic imaging in the future (35,36). DW-MRI may also improve detection of drop metastases in the cervix or metastatic foci outside the uterus, such as in the adnexa or peritoneum (35–37).

Normal Anatomy

Pelvic anatomy is exquisitely depicted on MRI. On T1WI, the normal pelvic musculature and viscera demonstrate homogeneous low to intermediate signal intensity. Cortical bone demonstrates low signal intensity, and fatty marrow is high in signal intensity. Similarly, intrapelvic fat demonstrates high signal intensity. It is the soft-tissue contrast provided by the T2WI, however, that is the basis for the strength of MRI in pelvic imaging. On T2WI, the uterus, cervix, and vagina all exhibit distinct

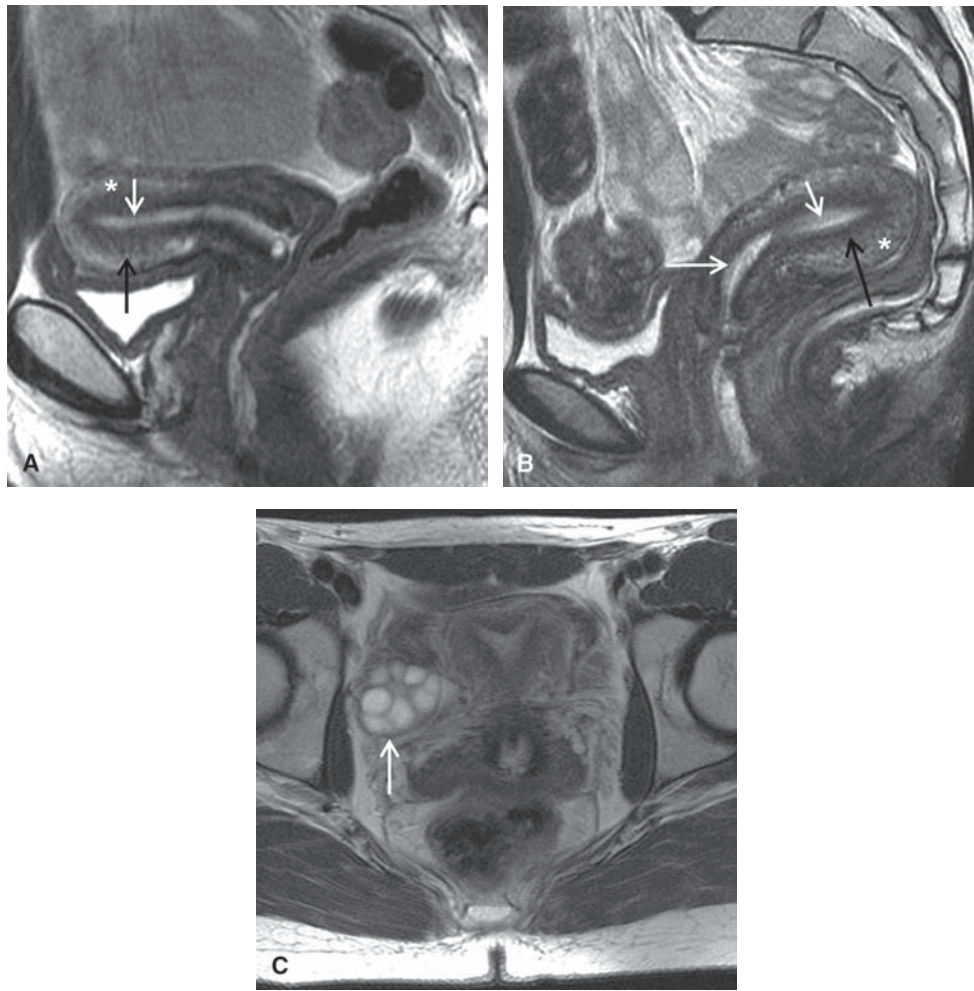


FIGURE 11.4. Normal uterus and ovary on MRI. Sagittal (A, B) and axial (C) T2W FSE MR images through the pelvis demonstrate normal uterus (*anteverted* in A, *retroverted* in B) and ovary. The uterine zonal anatomy is seen with the intermediate signal intensity outer myometrium (* in A, B), low signal intensity junctional zone (*black arrow* in A, B), and high signal intensity endometrium (*short white arrow* in A, B). Plicae palmatis are also elegantly demonstrated (*white long arrow* in B) in the cervix. Normal ovary (*white arrow* in C) demonstrates an intermediate signal intensity stroma and multiple high signal intensity follicles.

layers of different signal intensity—the so-called zonal architecture. The endometrium shows high signal intensity, while the outer myometrium is intermediate in signal intensity, being higher in signal intensity than striated muscle (Fig. 11.4). Interposed between these two layers is a narrow band of lower signal intensity, the junctional zone, which corresponds to the innermost myometrium. The low signal intensity of the junctional zone reflects its low water content relative to the rest of the myometrium, which may be a function of its lesser amount of extracellular matrix per unit volume (38,39). The three zones seen on MR images are not comparable to the different zones seen on US (40). MRI provides good visualization of the endometrium, including the varying width of the endometrium (both leaflets) seen with the menstrual cycle (41). In postmenopausal women not receiving exogenous hormones, uterine zonal anatomy is indistinct, and the endometrium typically measures less than 5 mm (41).

The cervix also demonstrates zonal architecture on T2WI (Fig. 11.4). There is an inner area of high signal intensity, which represents epithelium and mucus, and an outer area of predominantly low signal intensity, which represents fibrous cervical stroma (42,43). Interposed between the high signal intensity endocervical canal and the low signal intensity fibrocervical stroma is a feathery layer of intermediate signal intensity, which

represents the mucosal folds or plicae palmatae. The vagina demonstrates two zones on T2WI, the bright vaginal mucosa and the intermediate signal intensity vaginal wall.

Following the administration of intravenous gadolinium, the zonal anatomy of the uterus is demonstrated on fat-saturated T1W images. The normal endometrium and outer myometrium enhance to a greater extent than the junctional zone. Similarly, in the cervix, the inner cervical mucosa and outer smooth muscle enhance more than the fibrocervical stroma. The parametrial tissues, vaginal wall, and submucosa also enhance after gadolinium administration.

The ovaries display homogeneous low to intermediate signal intensity on T1WI, whereas on T2WI, the follicles appear brighter than the surrounding stroma (Fig. 11.4). The normal fallopian tubes are not routinely seen unless they are dilated.

Positron Emission Tomography/ Computed Tomography

The main applications of FDG-PET/CT in gynecologic oncology are staging of cervical cancer and detection of recurrent ovarian, cervical, and endometrial cancer. FDG-PET/CT is the

only modality that combines the biochemical change (the accelerated rate of glycolysis) associated with malignancy with the structural changes visualized at CT. FDG-PET does not have the same spatial resolution or soft tissue contrast as US or MRI, but image fusion techniques that overlay FDG-PET images onto MR images are available. A disadvantage of FDG-PET/CT is that false negatives can occur with lesions smaller than 0.5 cm and with certain tumor types that demonstrate low metabolic activity. In addition, false-positive results can be seen with inflammatory or infective etiology, postoperative changes, or reactive lymphadenopathy, including chronic inflammatory disorders such as granulomatous disease.

Technique

Patient preparation is crucial to high-quality FDG-PET/CT imaging. Physiologic uptake of tracer is prominently seen in the brain, salivary glands, myocardium, liver, and spleen. The gastrointestinal tract can also show variable uptake which, if prominent, can limit assessment of implants. FDG is excreted by the kidneys, and therefore, intense uptake can be seen in the renal collecting systems, ureters, and bladder that can sometimes limit assessment of disease in the pelvis due to scatter. Bladder catheterization and use of diuretics have been recommended by some, but their use may not be feasible in all cases. Uptake in skeletal muscles may be increased due to physical activity and brown fat, making assessment of lesions difficult. In premenopausal patients, increased physiologic uptake of FDG can occur in the endometrium and ovaries during the menstrual cycle and may cause false positive findings.

The patient is asked to fast for at least 4 hours prior to the FDG-PET/CT examination in order to keep insulin levels low. Elevated insulin levels drive FDG into skeletal muscle, often leading to nondiagnostic examinations. Blood glucose is checked before FDG injection; if the blood glucose is above the recommended level of 200 mg/dL, the study is generally not performed. Specific protocols are used for diabetic patients.

Steps are taken to reduce the amount of bladder activity, including adequate hydration and voiding immediately before imaging. Intravenous hydration may be used, but dextrose should not be given. Patients are asked not to engage in any heavy activity or gum chewing prior to the FDG-PET/CT exam. About 10-20 mCi of FDG is given intravenously, and the patient is asked to lie or sit quietly without talking in order to limit skeletal muscle FDG uptake. Imaging generally commences 45-60 min after FDG injection and lasts 20 to 45 min, depending on the specific protocol.

The amount of FDG uptake in tumors is assessed using a semiquantitative measure called the standardized uptake value (SUV). The SUV is the FDG activity (kBq/ml) divided by the total injected dose (MBq) and multiplied by the body weight. This value represents the metabolic activity of malignant lesions; thus, a change in tumor SUV after treatment reflects metabolic progression or remission. According to the PERCIST criteria for therapy response assessment, a 30% decrease in SUV is considered evidence of partial metabolic response, whereas an increase of 30% is regarded as evidence of progression (44).

Normal Anatomy

In premenopausal patients, uterine and ovarian FDG uptake is related to the menstrual cycle. Ovarian FDG uptake occurs in the late follicular to early luteal phase of the menstrual cycle. The most intense endometrial FDG uptake occurs during the first 3 days of the menstrual cycle (45). Therefore, premenopausal patients should be imaged a week before to a few days after menstruation. There is no physiologic uptake of FDG in the uterus or ovaries of postmenopausal patients (45).

ENDOMETRIAL CANCER

Introduction

Endometrial carcinoma is typically diagnosed by endometrial biopsy, or dilation and curettage (D&C). TVS is the initial imaging modality to evaluate the endometrium, especially in patients presenting with postmenopausal bleeding. MRI is the imaging modality of choice for the evaluation of the extent of disease (36, 46-51). CT is used to identify peritoneal nodules in serous papillary and clear cell carcinoma of the endometrium as well as for evaluation of distant metastatic disease and lymphadenopathy. CT, MRI, and PET/CT, individually or in combination, depending on the clinical question, are useful in the evaluation of recurrent disease.

Primary Diagnosis of Endometrial Cancer

TVS and/or SHG are routinely used to evaluate the endometrium in patients presenting with postmenopausal bleeding (52-55). Double-layer endometrial thickness ≥ 5 mm on TVS is used as the sole US criterion for determining whether endometrial sampling is warranted in postmenopausal patients (54,56,57). However, the specificity of this threshold is low, ranging from 59% to 63% (54,58). In a meta-analysis of 35 studies including 5,892 women, Smith-Bindman et al (54), reported that using a cut-off of 5 mm for endometrial thickness, 96% of women with endometrial cancer had an abnormal TVS. In this series, a woman with a 10% pretest probability of endometrial carcinoma and a negative TVS had a posttest probability of endometrial carcinoma of only 1%. They concluded that TVS is highly accurate in identifying a subgroup of patients at extremely low risk, obviating the need for endometrial sampling in these patients.

In women taking HRT, the specificity of the 5 mm cut-off is even lower, as HRT increases endometrial thickness. However, since the pretest probability of endometrial carcinoma is also likely increased in these patients, the same cut-off value of ≥ 5 mm is generally used. In women on sequential HRT regimens, scanning should be performed after the progesterone part of the cycle when the endometrium is expected to be at its thinnest. Breast cancer patients on tamoxifen treatment can have thickened endometrium with tiny cystic spaces. The risk of endometrial cancer increases with total duration of tamoxifen use and cumulative dose, prior estrogen replacement therapy, etc.

On US, endometrial cancer appears as an irregular, heterogeneous mass with increased vascularity on both Doppler and color flow imaging (Fig. 11.5) (59-61). The most specific and only reliable US finding for endometrial carcinoma is invasion of the myometrium indicated by the disruption of the subendometrial halo by an endometrial mass. On SHG, endometrial carcinoma is most commonly depicted as a broad-based, irregular mass (Fig. 11.5) (56). Difficulty in distending the endometrial cavity has also been described (62). Three-dimensional SHG has been reported to be more accurate than either TVS or two-dimensional (2-D) SHG for the diagnosis of endometrial carcinoma, but is rarely used.

Staging Endometrial Cancer

Staging of endometrial carcinoma is performed using the International Federation of Gynecology and Obstetrics (FIGO) surgical-pathological staging system, revised in 2009 (63). Full FIGO staging comprises a total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), peritoneal washings, and retroperitoneal lymph node dissection. Imaging is not part

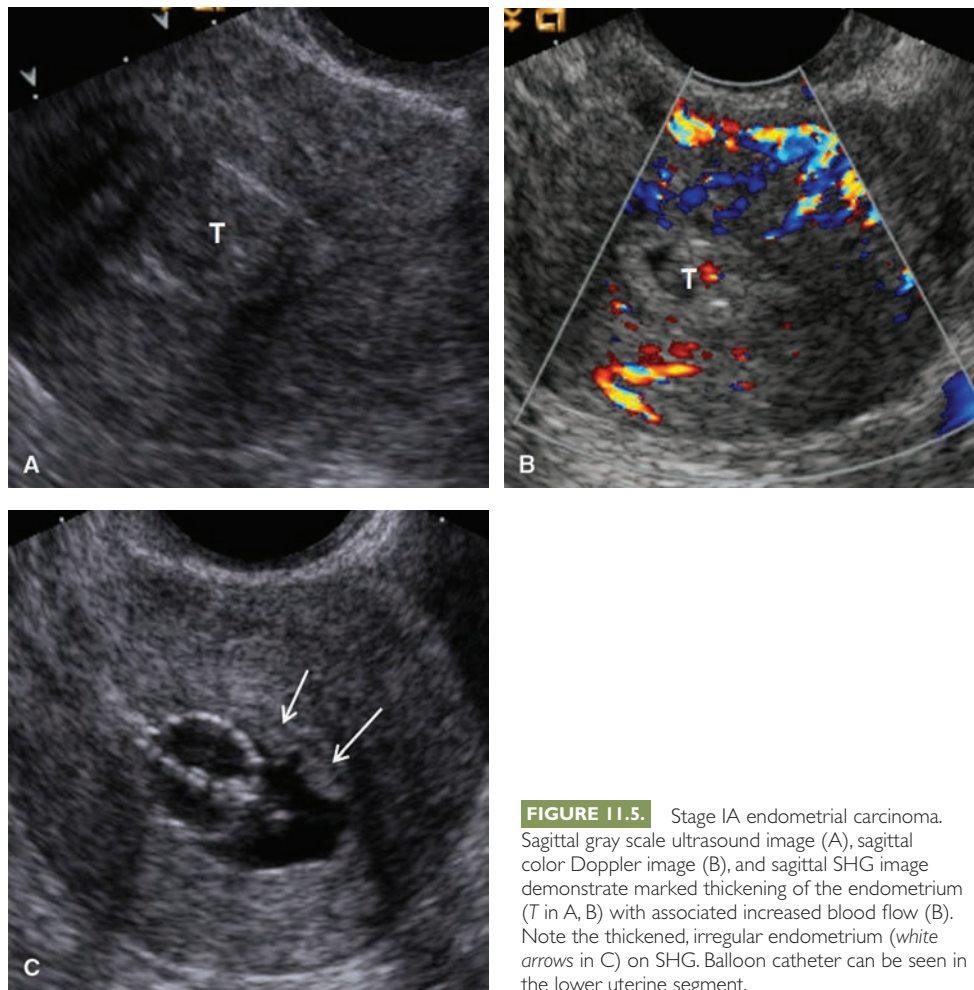


FIGURE 11.5. Stage IA endometrial carcinoma. Sagittal gray scale ultrasound image (A), sagittal color Doppler image (B), and sagittal SHG image demonstrate marked thickening of the endometrium (T in A, B) with associated increased blood flow (B). Note the thickened, irregular endometrium (white arrows in C) on SHG. Balloon catheter can be seen in the lower uterine segment.

of the FIGO staging system for endometrial cancer, but both MRI and CT are increasingly playing a crucial role in risk stratification and surgical treatment planning (64).

Ultrasound

US has little role in staging endometrial carcinoma. However, in centers with no access to MRI, US may be of value for assessing the presence of myometrial invasion in stage I disease. Myometrial invasion is documented when the tumor mass disrupts the subendometrial halo and/or extends into the subjacent myometrium. TVS has been reported to have a sensitivity of 77% to 100%, a specificity of 65% to 93%, and an overall accuracy of 60% to 76% in assessing the degree of myometrial invasion (65). Assessment of myometrial invasion is more difficult when the myometrium is thinned or distorted by fibroids (66). Three-dimensional SHG has been reported to be more accurate than TVS in detecting myometrial and cervical invasion by endometrial carcinoma (67).

Computed Tomography

CT is most commonly used in the assessment of advanced disease and performs as good as MRI in identifying extrauterine spread and enlarged lymph nodes (65). On contrast-enhanced CT, endometrial cancer is usually of slightly lower attenuation than the myometrium, but delineation of the tumor is difficult as there is relatively little contrast difference between tumor and the myometrium (68). CT is not sensitive or specific enough

to assess the depth of myometrial invasion or cervical stroma involvement (69). For detection of deep myometrial invasion, the sensitivity and specificity are 83% and 42%, respectively (69), with an overall staging accuracy of 58% to 76% (70).

Magnetic Resonance Imaging

Almost all patients with endometrial cancer undergo surgery as their primary treatment, during which the FIGO staging information is obtained. Therefore, the role of pretreatment MRI in endometrial cancer continues to be debated (21). However, only a relatively small percentage of patients have disease beyond the uterus (71). There is considerable controversy regarding systematic lymphadenectomy, with conflicting evidence regarding the survival benefits associated with the procedure (72–75). In addition, many patients with endometrial cancer have high surgical risks secondary to obesity, diabetes, and cardiovascular disease. Due to these factors, the extent of surgery is individualized in clinical practice: (a) Patients with a low risk of disease beyond the uterus may undergo more limited surgery, possibly involving minimally invasive surgical techniques and avoiding lymphadenectomy, thus reducing the risk of complications, particularly in high surgical risk cases; and (b) patients with a risk of disease beyond the uterus undergo complete surgical staging.

Prognostic features that predict disease beyond the uterus include the tumor histology and the presence of lymphovascular space invasion, deep myometrial invasion, and cervical involvement. Assessment of these factors together allows preoperative risk stratification for surgical planning. Of these four important

prognostic factors, only one is available preoperatively without the help of imaging: tumor histology, including grade and cell type, is available following pipelle or hysteroscopic sampling, although sampling error results in approximately 15% of cases being up-graded at the final histology (76). Lymphovascular space invasion is the single best predictor of nodal involvement, but its presence can only be determined after hysterectomy.

MRI can accurately assess the depth of myometrial invasion and cervical stromal invasion, which in turn correlate with the likelihood of lymph node metastasis and overall patient survival (50,77). Hence, in combination with tumor histology and grade, MRI aids the patient's preoperative risk stratification and ultimately guides treatment planning. The National Cancer Institute in France has recently incorporated MRI into the standard preoperative assessment of patients with endometrial carcinoma (78). The European Society for Urogenital Imaging (ESUR) also recommends MRI for staging of high-grade endometroid adenocarcinomas (type I histology) as well as serous papillary and clear cell adenocarcinomas (type II histology) (20).

MRI can be also very useful in patients with low-grade endometrial carcinoma who wish to preserve their fertility. The goal is to exclude any myometrial invasion so these patients can undergo treatment with high-dose progesterone and endometrial re-sampling. Finally, MRI is valuable in determining the site of origin of newly diagnosed uterine adenocarcinoma (corpus vs. cervix) when clinical and/or histologic evaluation is indeterminate (79).

Criteria for MRI interpretation according to tumor stage

MRI criteria for evaluation of endometrial cancer follow the FIGO staging system (Table 11.2) (63). Endometrial cancer is usually isointense to the myometrium on T1WI and of lower

signal intensity than the endometrium on T2WI. On dynamic multiphase contrast-enhanced 3D T1WI, the tumor enhances homogeneously, more slowly, and less avidly than the adjacent myometrium. On DW-MRI, the tumor is of high signal intensity with corresponding low signal intensity (restricted diffusion) on the apparent diffusion coefficient (ADC) maps.

Stage I tumors are confined to the uterine corpus and account for more than 80% of cases. Stage IA includes disease involving the endometrium, seen as focal or diffuse thickening of the endometrium as well as disease which invades less than 50% of the myometrium. Tumor that invades more than 50% of myometrium represents stage IB disease (Fig. 11.6). Delayed postcontrast 3D T1W images (2-5 minutes post gadolinium injection) facilitate evaluation of deep myometrial invasion, since these images provide maximum tumor-to-myometrium contrast (Fig. 11.6). This increases staging accuracy in cases where the tumor signal intensity is isointense to normal myometrium on T2WI or where tumor extends into the uterine cornu, when it can be difficult to accurately evaluate the depth of myometrial invasion on T2WI alone due to myometrial thinning (46,49,51,80-84). However, one must be cautious as peritumoral inflammation can lead to overestimation of the depth of invasion on contrast-enhanced images. Other reported pitfalls in assessing the depth of myometrial invasion in endometrial carcinoma include leiomyomas, adenomyosis, loss of junctional zone definition, and myometrial compression by polypoid tumor. These can also be minimized by the addition of dynamic multiphase contrast-enhanced 3D T1WI and DWI to T2WI (36,48,83-85). For assessing the depth of myometrial invasion, reported sensitivities of MRI range from 70% to 95%, while reported specificities range from 80% to 95% (36,50,51,83,86).

Stage II disease is characterized by direct invasion of the cervical stroma. On T2WI, cervical stromal invasion is represented by intermediate to high signal intensity tumor disrupting the normal low

Table 11.2 FIGO Staging of Endometrial Carcinoma with Corresponding MRI Findings

FIGO Stage	Description of Stage	MRI Findings
Stage I	Tumor confined to the corpus uteri	
IA	Tumor extending to <50% of myometrial depth	Abnormal signal intensity extends into the <50% of myometrium
IB	Tumor extending to ≥50% of myometrial depth	Abnormal signal intensity extends into >50% of myometrium
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus	Disruption of low signal intensity cervical stroma by tumor. A widened internal os with tumor protruding into the endocervical canal does not represent stromal invasion
Stage III	Local and/or regional spread of the tumor	
IIIA ^a	Tumor invades the serosa of the corpus uteri and/or adnexae	Disruption of continuity of outer myometrium. Irregular uterine configuration
IIIB	Vaginal and/or parametrial involvement	Segmental loss of hypointense vaginal wall
IIIC	Metastases to pelvic and/or paraaortic lymph nodes	Regional or paraaortic nodes >1 cm in short axis diameter. Additional suspicious features include: multiple small rounded lymph nodes, irregular lymph node contour, abnormal signal intensity similar to that of the primary tumor, presence of necrosis
IIIC1	Positive pelvic nodes	
IIIC2	Positive paraaortic lymph nodes +/- positive pelvic lymph nodes	
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases	
IVA	Tumor invasion of bladder and/or bowel mucosa (biopsy proven)	Abnormal signal intensity disrupts normal low signal intensity bladder/rectal mucosa. Note that bullous edema does not indicate stage IVA
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes	Tumor in distant sites or organs

^aPositive cytology obtained at peritoneal washings should be recorded, but does not alter any stage.

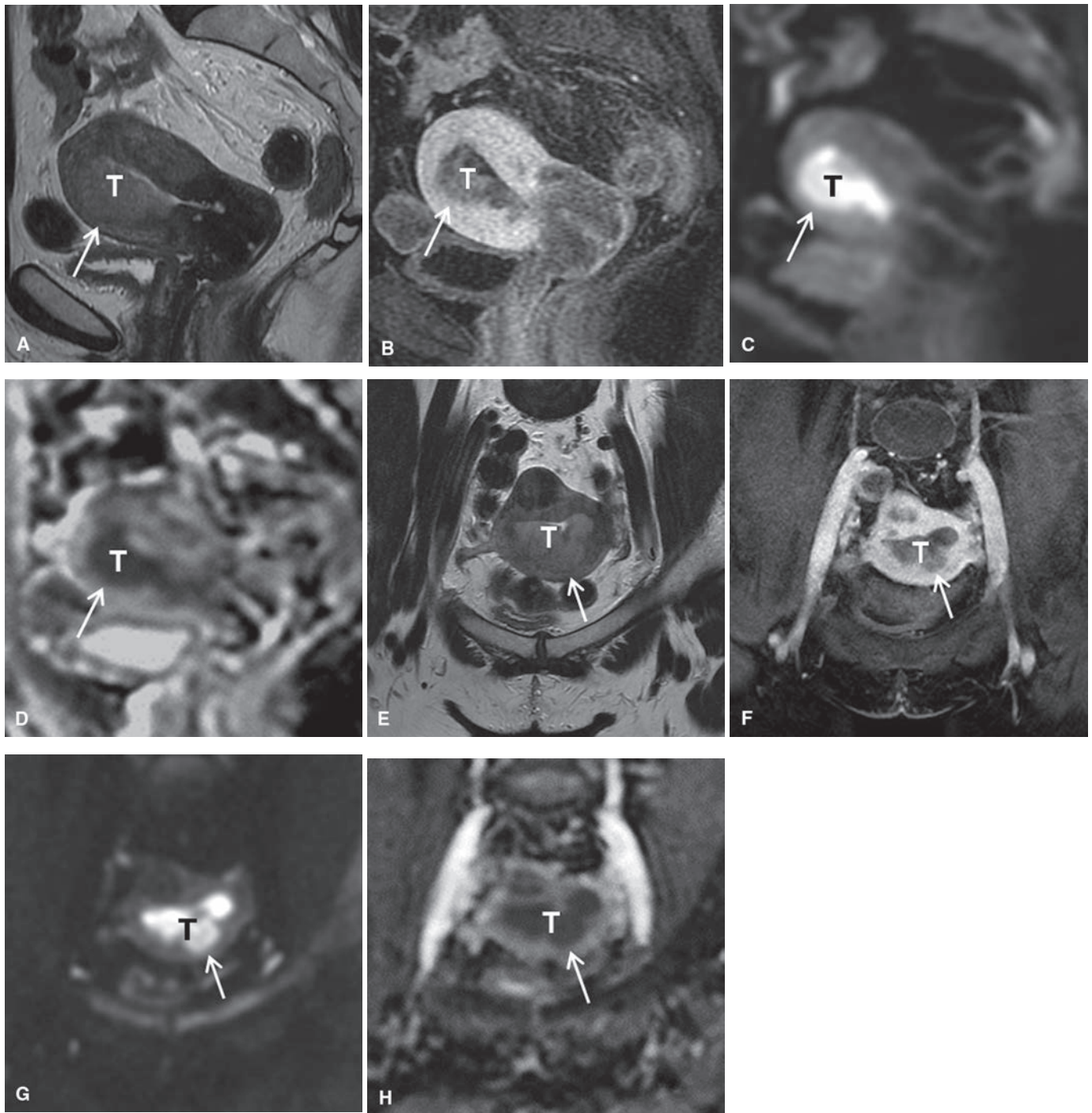


FIGURE 11.6. Stage IB endometrial carcinoma. Sagittal and axial T2W FSE (A, E), sagittal and axial gadolinium-enhanced 3D T1W GRE (B, F), DW (C, G) MR images and the corresponding ADC maps (D, H) show an endometrial carcinoma (T in A-H) which extends into the outer myometrium (arrow in A-H). Deep myometrial invasion was confirmed at histopathology.

signal intensity cervical stroma. The enhancement of cervical mucosa on the delayed phase (2-5 minutes) can confidently exclude cervical stroma invasion (68). In detecting invasion of the cervical stroma, MRI has overall accuracy of 90% to 92% with sensitivity and specificity of 75% to 80%, and 94% to 96%, respectively (49–51).

Stage III is classified as locoregional spread of disease. In stage IIIA disease, there is invasion of uterine serosa or adnexa (Fig. 11.7). Disruption of the low signal intensity uterine serosa and/or irregular uterine contour on T2WI (Fig. 11.7) and the loss of the normal rim of brightly enhancing myometrium on dynamic multiphase contrast-enhanced 3D T1WI indicate

serosal involvement. Tumor deposits may be identified in the adnexa, even in the absence of serosal invasion, especially with high-grade, clear cell or serous papillary tumors (Fig. 11.7); DWI can aid detection in these cases (36). In stage IIIB disease, tumor extends into the upper vagina or parametria (Fig. 11.8), either directly or as metastatic disease. It is of paramount importance that the surgeon is made aware of parametrial invasion, as in its presence, a simple hysterectomy will not be possible and a more radical surgical approach will be required. The presence of enlarged regional lymph nodes indicates stage IIIC disease (IIIC1 involving pelvic nodes; IIIC2 involving paraaortic nodes with or

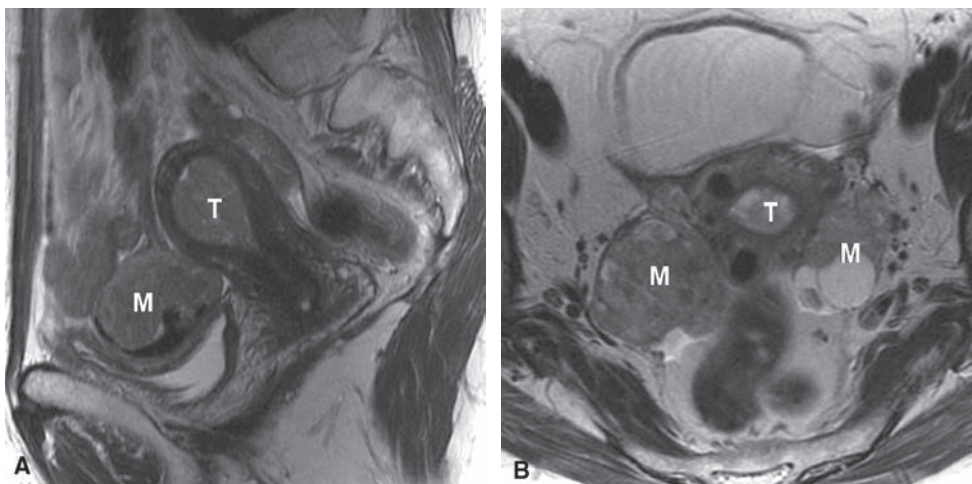


FIGURE 11.7. Stage IIIA endometrial carcinoma. Sagittal T2W FSE MR image (A) shows a tumor deposit on the serosa of the sigmoid colon (M in A) from a grade 3 endometrioid endometrial carcinoma (T in A). Axial T2W FSE MR image (B) in a different patient shows a clear cell endometrial carcinoma (T in B) with metastases to both ovaries (M in B).

without pelvic nodal involvement). A short-axis diameter of 1 cm or greater is used to diagnose nodal involvement on MRI (49,87).

Stage IV is defined by tumor extension beyond the true pelvis or invasion of the bladder or rectal mucosa. On MRI, loss of low signal intensity of the bladder or rectal wall and tumor invading the mucosa indicate stage IVA disease. Bullous edema of the bladder is a frequent sign of tumor in the subserosal or muscular layer of the bladder, but does not qualify for stage IVA disease. In stage IVB disease, distant metastases (including nodal enlargement above renal veins or in the inguinal region), malignant ascites, or peritoneal deposits are present. The latter are more common with high-grade, clear cell or serous papillary tumors, as clinically, they behave like ovarian cancer with a propensity to spread along the serosal and peritoneal surfaces. Distant metastases (lung, liver, and bone) is rare at presentation.

Positron Emission Tomography/ Computed Tomography

For initial staging, FDG-PET/CT has a limited role in assessing primary tumor extension within the pelvis (88). The primary role for FDG-PET/CT in staging of endometrial carcinoma is

detection of nodal disease. Direct comparison of MRI with FDG-PET/CT has demonstrated no statistically significant difference in the detection of lymph node metastases in patients with endometrial cancer (89). The added value of FDG-PET/CT is the detection of distant metastatic deposits, for which it has been found to have sensitivity of 100% and specificity of 94% (89). Kitajima et al. demonstrated that the sensitivity of FDG-PET/CT in detecting involved nodes of 4 mm or less was 16.7%; for nodes measuring 5 to 9 mm, the sensitivity was 66.7%; and for nodes 10 mm or greater, it rose to 93.3% (90). For nodal metastases, a sensitivity of 50% and a specificity of 86% have been reported, on a per patient basis. Overall, the sensitivity of FDG-PET/CT for preoperatively predicting nodal metastasis is not optimal for guiding lymphadenectomy.

Detecting Recurrent Endometrial Cancer

Endometrial cancer has a low rate of recurrence of 4% to 16% (75). Factors that predict relapse include advanced stage at presentation, high tumor grade, type II histology, age over 60 years, and lymphovascular invasion (91). Following primary surgery, 64% of recurrences occur within 2 years and 87% within 3 years,

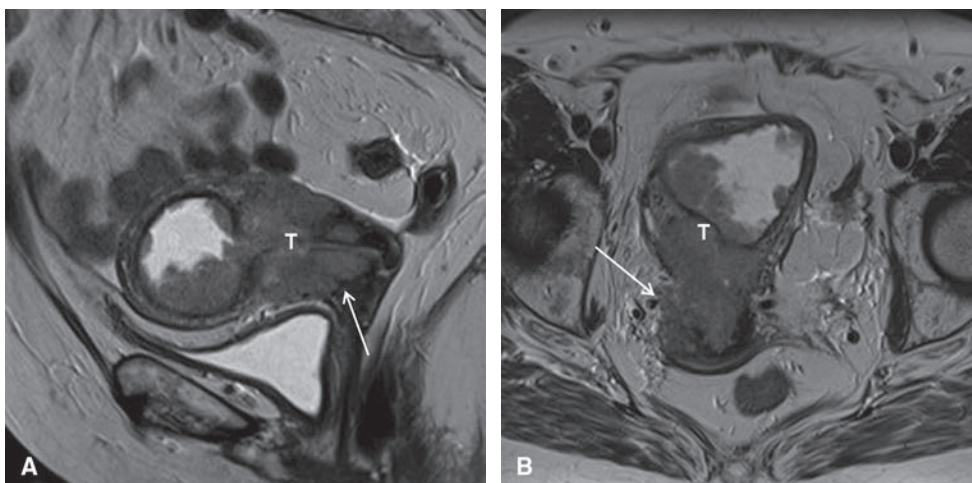


FIGURE 11.8. Stage IIIB endometrial carcinoma. Sagittal (A) and axial (B) T2W FSE MR images show an endometrial carcinoma (T in A, B) which invades the cervical stroma (arrow in A) and extends into the right parametrium (arrow in B).

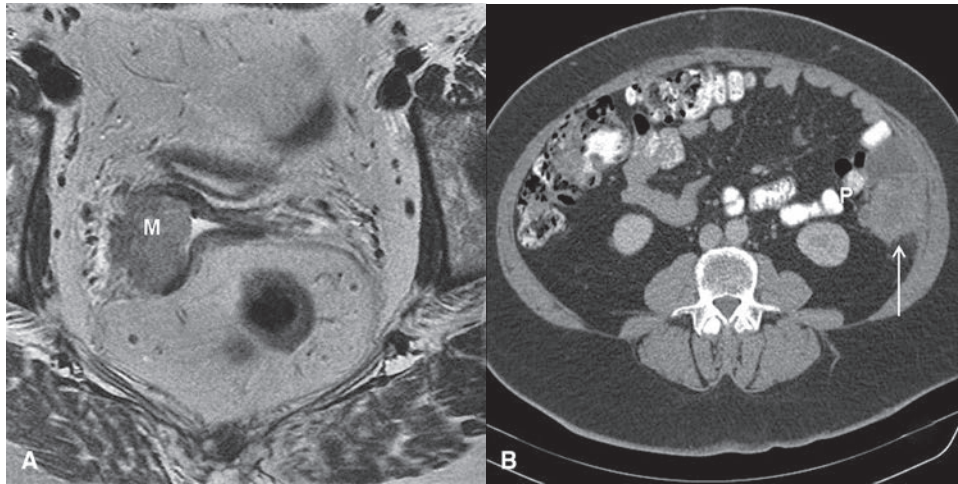


FIGURE 11.9. Recurrent endometrial carcinoma. Axial T2W FSE MR image (A) shows a mass of intermediate signal intensity in the vaginal vault on the right (M in A) in keeping with tumor recurrence from a serous papillary carcinoma of the endometrium. CT image (B) of the same patient shows a peritoneal deposit (arrow in B) in the right paracolic gutter.

the most common sites being lymph nodes (46%) and the vaginal vault (42%) (92). Less frequently, recurrent disease may manifest as peritoneal carcinomatosis (28%) or distant metastases in liver, lung, or bone (92). Routine follow-up has a poor yield in detecting recurrence in the asymptomatic patient, but recognizing those patients who are at an increased risk of recurrence and the likely time scale for recurrence can help in selecting a suitable approach for follow-up imaging.

At present, follow-up of patients treated for endometrial cancer usually consists of regular clinical evaluation. The use of imaging and its impact on the management of these patients is not well defined. CT performs well in the detection of recurrent pelvic and distant metastatic disease (Figs. 11.9 and 11.10), with an overall accuracy of 92% (93). MRI has a role in the evaluation of surgical resectability, if the pelvis is the sole site of recurrence. On T2WI, vaginal vault recurrence is seen as loss of the linear, low signal intensity of the vaginal vault and an associated soft tissue mass of high signal intensity, similar to that of the primary tumor (Fig. 11.9). FDG-PET/CT is helpful in assessing patients with suspected disease recurrence within the pelvis, by detecting

unsuspected distant metastases, the presence of which significantly alters treatment options (94,95). A recent study compared PET integrated with low-dose, unenhanced CT to PET integrated with contrast-enhanced CT (95). It concluded that PET with contrast-enhanced CT is an accurate imaging modality for the assessment of endometrial cancer recurrence and the use of contrast reduces the frequency of equivocal interpretations (95). FDG-PET/CT resulted in a change of management in 42% of patients (95). PET is reportedly useful in posttherapy evaluation and surveillance of patients with suspected recurrence, but it does not have any proven value in asymptomatic patients (96,97).

UTERINE SARCOMA

Uterine sarcomas are rare, aggressive tumors of mesenchymal origin that account for 2% to 3% of all uterine malignancies. They differ from endometrial carcinomas with regard to their

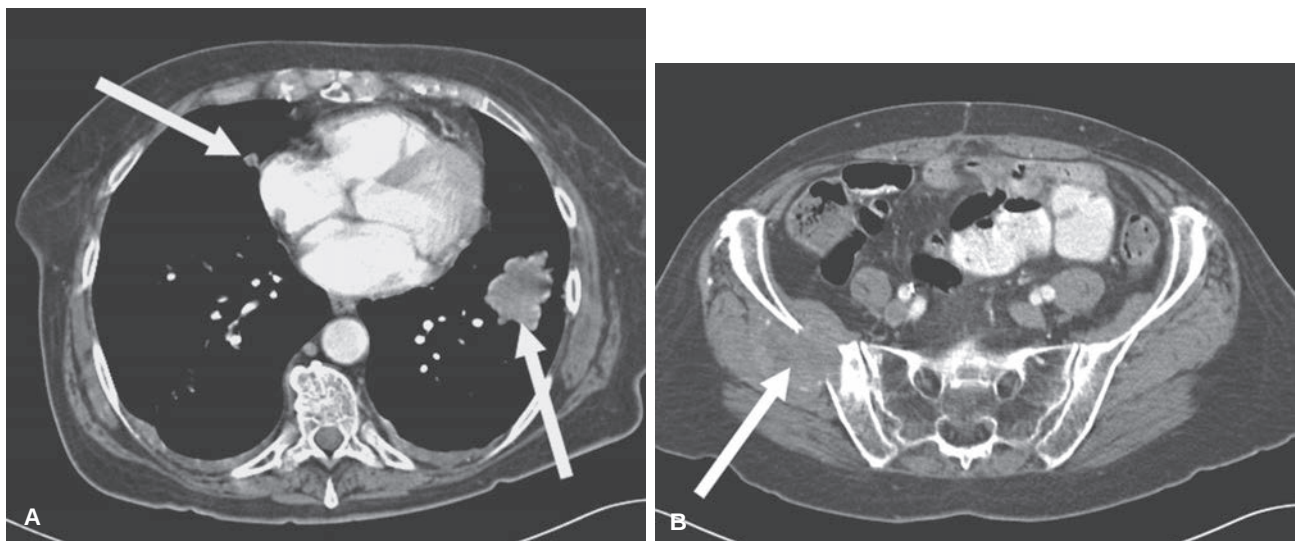


FIGURE 11.10. Recurrent endometrial carcinoma. Axial contrast-enhanced CT images through the lower chest (A) and pelvis (B) demonstrate lung nodules (white arrows in A) and a soft tissue mass with osseous destruction (white arrow in B), both proven to be recurrent endometrial cancer.

clinical behavior, pattern of spread, and management. Although there are no specific imaging findings for uterine sarcomas, imaging (MRI) can be useful to make a correct preoperative diagnosis and evaluate the extent of disease (CT). On MRI, cases that arise within the endometrium may be indistinguishable from endometrial carcinoma, whereas those that arise from the myometrium, usually leiomyosarcomas, may be indistinguishable from degenerating leiomyomas. However, if there are features suggesting the diagnosis preoperatively, alerting the surgeon can alter management by changing the extent of primary surgery or by indicating that surgical management is preferable to embolization or high-intensity focused US. CT can be a very helpful adjunct for detection of distant metastatic disease (usually in the lungs) and recurrence.

Uterine sarcomas are divided into three main subtypes: carcinosarcoma, endometrial stromal sarcoma (ESS), and leiomyosarcoma (LMS). Carcinosarcoma accounts for approximately 50% of all uterine sarcomas (98) and can arise anywhere along the Müllerian axis. Risk factors include a previous history of radiotherapy for an unrelated pelvic malignancy and long-term tamoxifen use (99,100). Carcinosarcomas do not have a pathognomonic appearance on MRI and may be indistinguishable from endometrial carcinomas (101,102). However, when compared with endometrial carcinoma of a similar size, carcinosarcomas are heterogeneous tumors with areas of hemorrhage and necrosis, and enhance more avidly than the adjacent normal myometrium. They demonstrate deep myometrial invasion, cervical stromal invasion, and metastatic nodal disease (101,103,104) more often than do endometrial carcinomas and hence have a poorer prognosis (105-107).

ESS accounts for 10% of primary uterine sarcomas (98). It can be subdivided into low- and high-grade categories, which have distinctly different presentations and outcomes (108). A preoperative diagnosis of high-grade ESS is readily established at histopathology whereas low-grade ESS may be difficult to distinguish from benign endometrial stromal cells in a small sample obtained at curettage. As low-grade ESS usually occurs in young women in whom malignancy is not suspected, the role of MRI is important in providing a clue for preoperative diagnosis.

On MRI, ESS commonly appears as a polypoid mass of homogeneous high signal intensity on T2WI, although areas of necrosis or hemorrhage may also be seen (102,108). The low-grade ESS may be a mimicker of adenomyosis; however, the presence of multiple intra-tumoral flow voids due to neovascularity, multiple marginal tumor nodules, continuous tumor extension along vessels, ligaments, and fallopian tubes due to

marked vascular and lymphatic invasion, with separate myometrial tumor nodules within invaded vessels, are highly suggestive of ESS (102,108,109). Intravenous leiomyomatosis is also in the differential diagnosis if there is involvement of periuterine vessels.

LMS account for approximately one-third of primary uterine sarcomas (98). Most arise *de novo*, but they may rarely (0.2%) result from sarcomatous transformation within a benign leiomyoma. On MRI, in contrast to benign leiomyomas, which have a well-defined margin, LMS are usually irregular and ill-defined. They commonly cause massive uterine enlargement with areas of heterogeneous enhancement, extensive necrosis (>50%) and hemorrhage as well as extrauterine tumor nodules (Fig. 11.11) (102). LMS demonstrate early hematogenous spread to the lungs and liver. Although MRI cannot reliably differentiate most cases of sarcomatous transformation of a leiomyoma from a benign degenerating leiomyoma, features most suggestive of sarcomatous transformation include irregular margins, necrosis, and rapid growth.

GESTATIONAL TROPHOBLASTIC DISEASE

Introduction

Gestational trophoblastic disease (GTD) encompasses a spectrum of placental lesions including hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumor. The role of imaging in GTD is to distinguish benign disease from retained products of conception, and to document metastatic disease or to evaluate for persistent disease. No specific imaging findings allow differentiation between the different GTD lesions (110-112).

Primary Detection, Characterization, Staging, and Monitoring for Recurrence of Gestational Trophoblastic Disease

Ultrasound

TVS is considered the study of choice in the evaluation of suspected GTD. In patients with GTD, TVS examination most commonly demonstrates a soft-tissue mass distending the

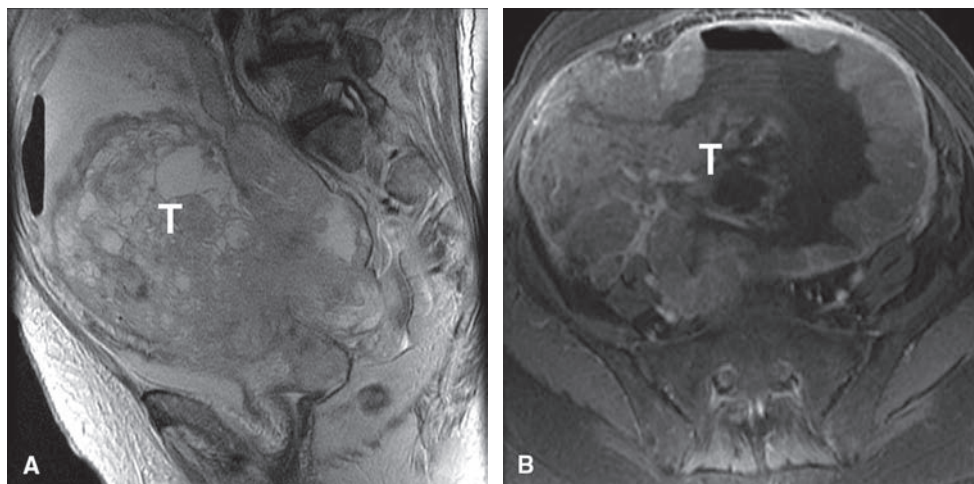


FIGURE 11.11. Leiomyosarcoma. Sagittal T2W FSE (A) and axial gadolinium-enhanced 3D T1W GRE (B) MRI images show an enlarged heterogeneous uterus (T in A, B) with areas of necrosis in keeping with a leiomyosarcoma.

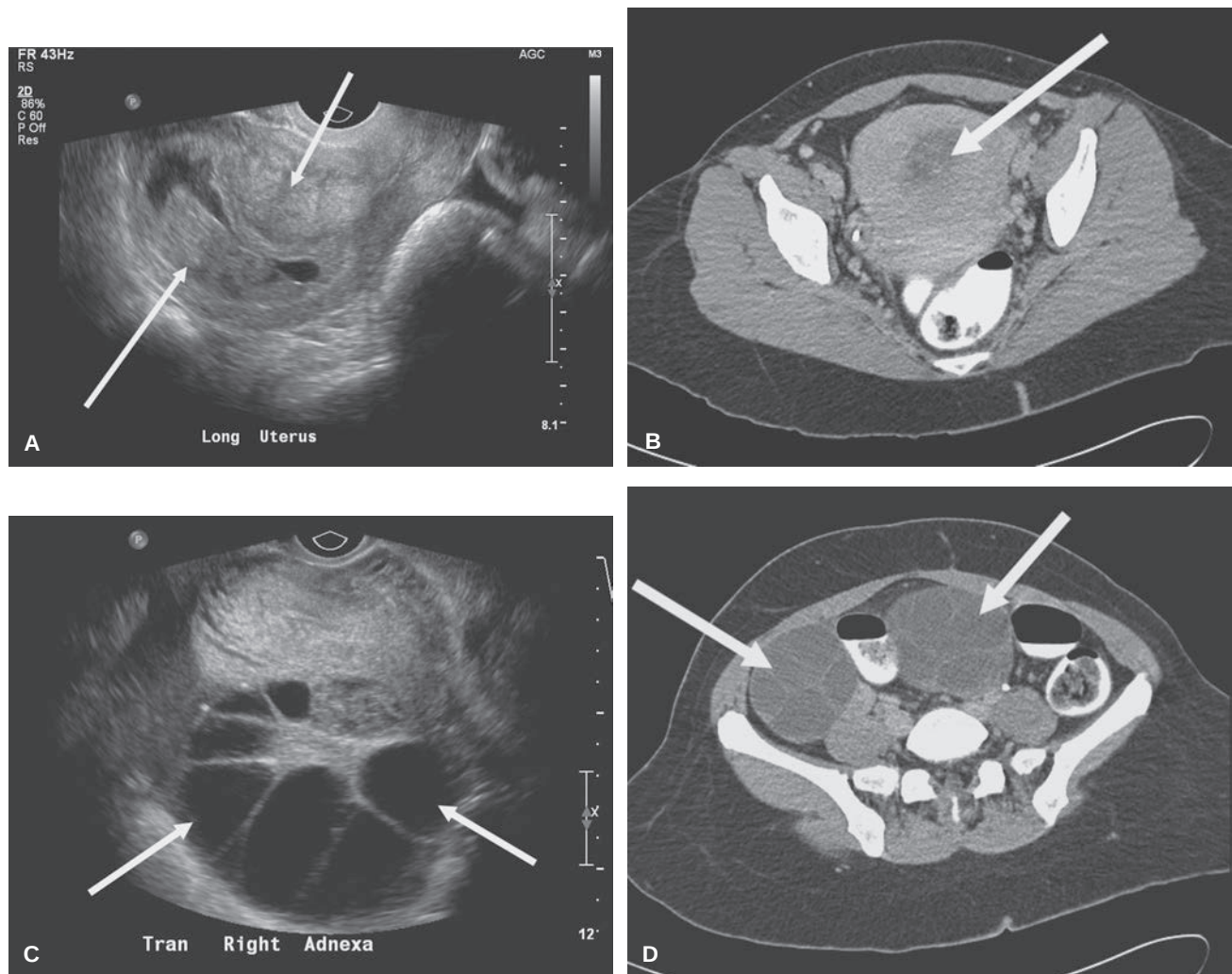


FIGURE 11.12. Hydatidiform mole. Gray scale sagittal ultrasound image of the uterus (A) demonstrates an echogenic, heterogeneous mass within the endometrial canal (white arrows in A). Axial contrast-enhanced CT image (B) in the same patient demonstrates enhancing soft-tissue distending the endometrial canal (white arrow in B). Gray scale ultrasound image (C) of the right ovary and contrast-enhanced CT image (D) through the pelvis in the same patient demonstrate bilateral enlarged ovaries with innumerable theca lutein cysts (white arrows in C, D).

endometrial cavity. Typically, the mass is echogenic and heterogeneous, containing numerous cystic spaces (Fig. 11.12) (110,113, 114). In the case of complete hydatidiform mole, the small cystic spaces correspond to the hydropic villi (110). Hydropic degeneration of the placenta may have a similar US appearance. The mass is usually extremely vascular, demonstrating increased vessel density and an abnormal uterine arterial waveform characterized by high peak systolic velocity and high diastolic blood flow (low resistance index [RI]) compared to the normal uterine arterial waveform (115). Irregularity of the border of the mass or asymmetric extension of the mass into the myometrium suggests myometrial invasion.

The ovaries may become enlarged with numerous theca lutein cysts (Fig. 11.12). This ovarian enlargement can result in symptomatic ovarian torsion or hemorrhage (116). However, theca lutein cysts may not be detected in the early stages of the disease (114).

US can be helpful in assessing for persistent or recurrent disease by documenting an endometrial mass (117). GTD is the most common cause of uterine vascular malformations. These vascular malformations usually present after treatment is complete and can be easily diagnosed with US. They can be treated with uterine artery embolization under fluoroscopic guidance (118).

Computed Tomography

The role of CT in the evaluation of GTD is primarily limited to the detection of metastatic disease. Uterine enlargement is the most common CT feature of GTD. Following administration of intravenous contrast, uterine enhancement is typically heterogeneous with focal enlargement or irregular hypodense regions within the myometrium (Fig. 11.12) (116). These low-attenuation areas correspond to foci of hemorrhage and/or necrosis (116). Contrast-enhanced CT often demonstrates vascular uterine lesions and dilated uterine vessels in the broad ligaments (116).

Locoregional spread is characterized by avidly enhancing soft-tissue nodules in the parametria and/or obliteration of the pelvic fat and/or muscle planes. GTD spreads hematogenously, with the lungs being the most common site of metastatic disease. Metastases to the lung, liver, and brain are vascular and prone to hemorrhage (116). CT detects these metastatic lesions in the usual manner. Trophoblastic emboli to the lungs may produce symptoms of acute pulmonary embolism and occasionally result in large intravascular masses (116).

Magnetic Resonance Imaging

MRI is primarily used for staging and detecting recurrent disease. On T2WI, GTD is seen as a heterogeneous, predominantly

high signal intensity mass that obliterates the normal uterine zonal anatomy (Fig. 11.13) (119). On T1WI, the mass may be isointense or hyperintense compared to the adjacent normal myometrium. The tumors are hypervascular, and enlarged vessels in the broad ligament and the uterus are depicted as signal voids on both T1W and T2WI. Following gadolinium contrast administration, the tumors avidly enhance, and multiple enlarged vessels are often seen. MRI is able to depict tumors that invade the myometrium but spare the endometrium, a cause of nondiagnostic and/or false-negative D&Cs.

MRI is also useful in the identification of extrauterine pelvic spread to the parametria, adnexa, and vaginal fornices (119). Parametrial involvement is seen on MRI as high T2W signal masses within the parametria that avidly enhance after gadolinium contrast. MRI is better at detecting parametrial involvement than US. MRI is the preferred method for determining vaginal spread of tumor. Vaginal involvement is identified on MRI as a high-T2W-signal-intensity mass within the vagina with associated gadolinium contrast enhancement. Metastatic disease is usually hypervascular and is detected in the usual manner.

Another role of MRI is to monitor patient's response to therapy. MRI findings of regression of vascular abnormalities, development of intralesional hemorrhage, and return of normal uterine zonal anatomy parallel a favorable response to chemotherapy (119). Normal uterine zonal anatomy should be seen 6 to 9 months after treatment (119).

Positron Emission Tomography/Computed Tomography

The very limited data available on the use of FDG-PET in patients with GTD show that FDG-PET may be helpful in the detection of metastatic disease and recurrent disease. One study found that FDG-PET might be useful in the detection of metastatic disease (120). Another study demonstrated that FDG-PET/CT was helpful in 43.8% of patients when compared with CT alone (121). More research into the use of FDG-PET is needed before the clinical utility of this modality for evaluation of GTD can be established.

CERVICAL CANCER

Introduction

The role of imaging in patients with cervical cancer includes evaluation of extent of disease, monitoring treatment response, and detecting tumor recurrence. MRI is the modality of choice for evaluating disease extent and monitoring treatment response; CT and PET/CT are utilized in the evaluation of distant metastatic disease or when MRI is contraindicated. CT, MRI, and PET/CT are useful in the evaluation of recurrent disease.

Primary Detection and Characterization of Cervical Cancer

Cervical cancer is usually detected at Pap smear test or by physical examination. Imaging plays no role in the detection and characterization of cervical cancer.

Staging Cervical Cancer

FIGO classification is the most widely used staging system for cervical carcinoma (63,122). FIGO staging of cervical carcinoma is clinical and does not rely on surgico-pathological findings.

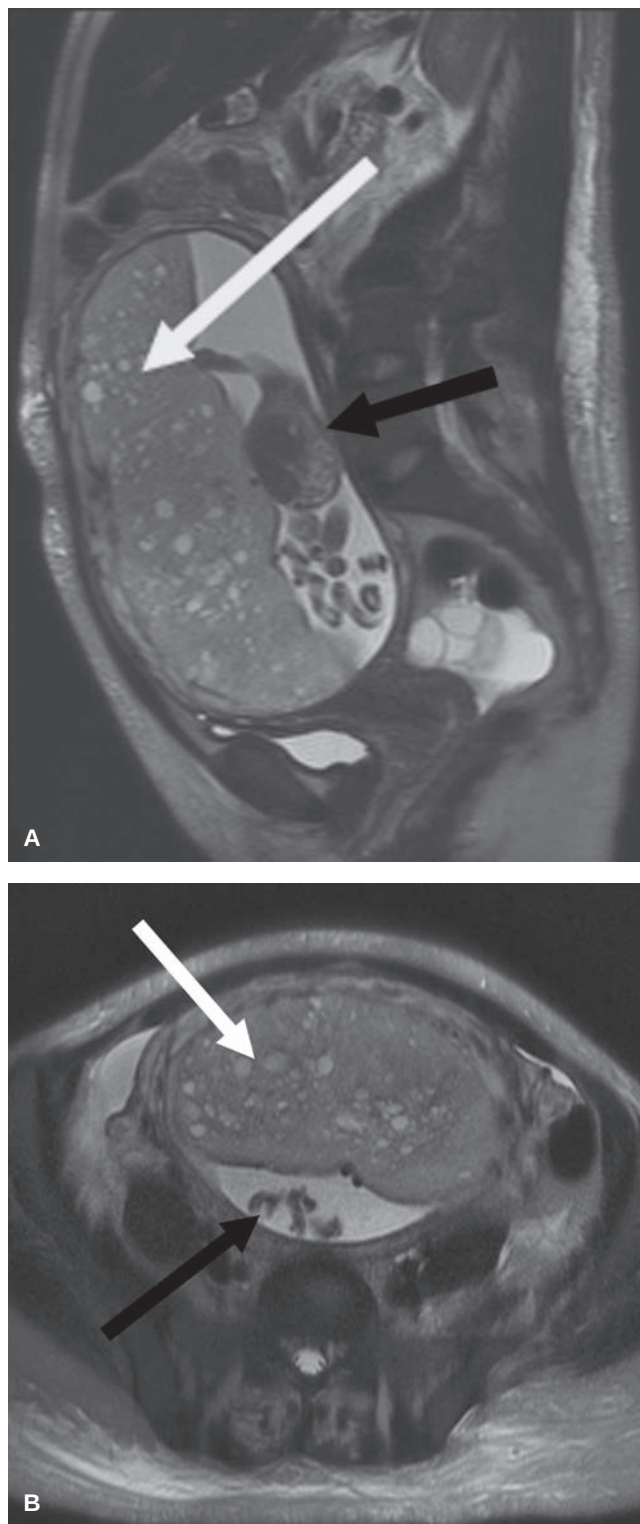


FIGURE 11.13. Partial mole. Sagittal (A) and axial (B) T2W FSE MR images demonstrate a heterogeneous mass within the uterus (white arrows). Fetal abdomen (black arrow in A) and umbilical cord (black arrow in B) can be seen adjacent to the mass.

Thus, it allows uniformity of staging for all patients worldwide; this is particularly important because cervical carcinoma is most prevalent in countries where surgical and diagnostic resources are limited.

Clinical staging of cervical cancer has inherent deficiencies in evaluating several important prognostic factors including

tumor size, parametrial and pelvic sidewall invasion, and nodal metastasis. When compared with surgical staging, clinical FIGO staging can be erroneous in up to 32% of patients with stage IB disease and up to 65% of patients with stage III disease (123,124). This is problematic, as accurate pretreatment evaluation of these prognostic factors determines the appropriate choice of initial treatment for ensuring the best possible patient outcome.

There are two standard primary treatment options for cervical cancer: (a) radical surgery in early-stage disease (IA, IB1 and IIA1) or (b) primary radical radiotherapy with concurrent administration of platinum-based chemotherapy for patients with bulky IB2/IIA2 disease (tumors larger than 4 cm) or locally advanced disease (stage IIB or greater). Therefore, the FIGO staging committee has acknowledged that clinical staging errors occur with reasonable frequency and the 2009 revision has, for the first time, encouraged the incorporation of cross-sectional imaging techniques (MRI/CT) into the evaluation and treatment planning of patients with cervical cancer, where available (63,122).

Ultrasound

Transabdominal sonography plays a limited role in the staging of cervical cancer and is inferior to other cross-sectional modalities in this role. Although the improved spatial resolution achieved with TVS and TRUS is helpful in the evaluation of tumor size and locoregional extent, poor soft-tissue contrast impedes differentiation between tumor and normal adjacent cervical, uterine, parametrial, and vaginal tissue (125). In addition to the limited soft-tissue contrast offered by US, the small field of view leads to suboptimal evaluation of parametrial invasion. Therefore, US plays no significant role in staging of patients with cervical cancer.

Computed Tomography

CT is often used for the staging of advanced cervical carcinoma (Fig. 11.14) because of its large field of view, widespread availability, and large numbers of experienced readers. However, CT has many limitations including poor detection of small primary tumors, parametrial invasion, and early invasion of the rectum and bladder mucosa. A prospective multicenter study conducted jointly by the American College of Radiology Imaging Network (ACRIN) and the Gynecologic Oncology Group (GOG)

compared MRI, CT, and FIGO clinical staging in the pretreatment assessment of early invasive cervical cancer (126,127). The study found that MRI was equivalent to CT for overall preoperative staging. However, MRI performed significantly better than CT for tumor visualization (127) and determination of parametrial invasion (128). Reader agreement was higher for MRI than for CT (126). In this study, the sensitivity, specificity, and negative predictive value (NPV) of CT in staging cervical carcinoma of stage IIB or greater were 42%, 82%, and 84%, respectively (126). Despite its limitations, CT is a valuable complement to clinical staging because of its accuracy in detecting advanced disease (129,130).

Magnetic Resonance Imaging

MRI is considered the best single imaging study for cervical cancer and can accurately determine tumor location (exophytic or endocervical) and size; presence of invasion into the parametria, pelvic sidewall, or adjacent organs; and the presence of nodal enlargement (131,132). Clinical evaluation of tumor size is inaccurate, reported to be as low as 60%, as it may underestimate tumors with an endophytic component (131,132). Conversely, MRI is very accurate for the evaluation of tumor size, providing estimates within 5 mm of the histological size in 93% of cases (133,134). This is particularly important in young women with small-volume invasive disease who wish to preserve fertility, in whom a more conservative surgical procedure can be performed; this involves resection of the cervix together with 2 cm of the parametrium (radical trachelectomy) and lymphadenectomy (135–137). MRI is mandatory in order to determine eligibility for fertility-sparing surgery in terms of tumor size (<2 cm), cervical length (>2.5 cm), distance of tumor from the internal cervical os (>1 cm), and presence of deep cervical stromal invasion (136,137).

Clinical assessment of parametrial and pelvic sidewall invasion is also problematic, with reported accuracy of 29% to 53% (133,138). While an experienced clinician can usually detect gross parametrial invasion, early invasion invariably goes undetected. MRI is very accurate (accuracy of 88% to 97%, specificity of 93%) in evaluating parametrial invasion (25,139). The high NPV (94%) of MRI in excluding parametrial invasion is important clinically, allowing correct selection of patients suitable for radical surgery (134,137,140,141). MRI has also been shown to have a very high NPV (up to

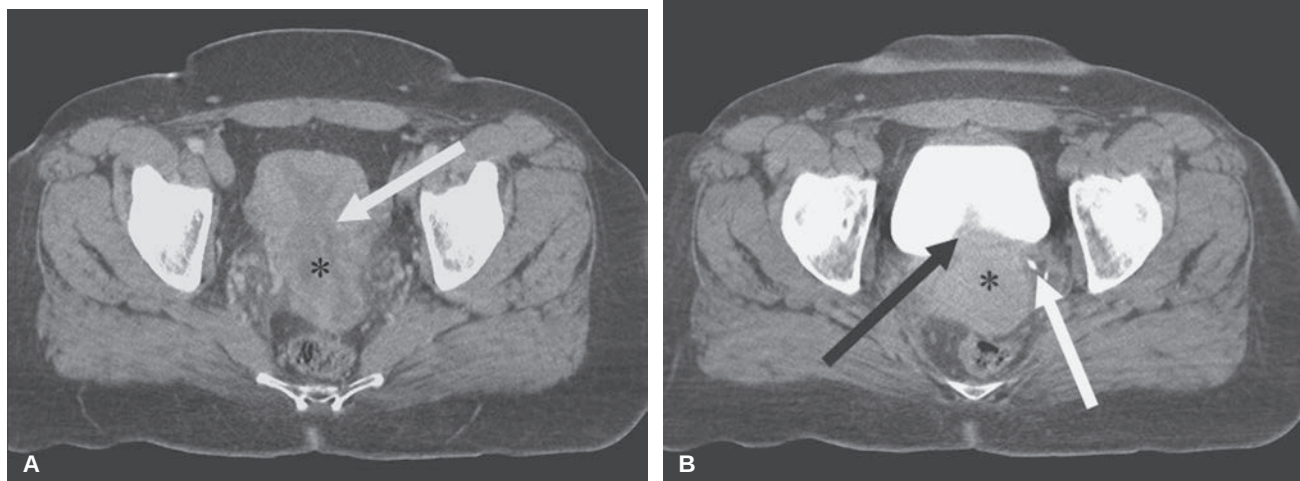


FIGURE 11.14. Stage IVA cervical carcinoma. Contrast-enhanced CT images at two levels (A, B) demonstrate a heterogeneous mass arising in the cervix (black asterisk) with extension into the uterus (white arrow in A) and bladder (black arrow in B). Note the loss of the normal periureteral fat plane around the left ureter (white arrow in B).

100%) for excluding bladder and rectal invasion, thereby negating the need for cystoscopic or endoscopic staging procedures (17,128,142).

MRI is highly accurate for detecting nodal enlargement, which is crucial for treatment planning (143,144). Surgically treated stages IB and IIA survival rates decrease from 85%–90% to 50%–55%, respectively, in the presence of pelvic nodal metastases (141). Although FIGO staging does not include surgical lymph node assessment (122), nodal metastases are an important factor in the choice of adjuvant radiotherapy. Surgical lymphadenectomy is the gold standard in the diagnosis of nodal metastases, but it carries a risk of complications. Therefore, preoperative assessment of nodes with imaging is important (145). Finally, MRI is also routinely used in monitoring treatment response, detection of recurrence, identifying complications of the disease and its treatment (146), and planning radiotherapy (147,148).

Criteria for MRI Interpretation According to Tumor Stage

MRI is complementary to clinical assessment in staging cervical carcinomas of FIGO stage IB1 or greater. In single-institution studies, MRI has been shown to be better than either CT or physical examination in demonstrating parametrial invasion. The staging accuracy of MRI ranges from 85% to 96% (132,139,149). Recommendations for diagnostic evaluation of tumor staging are derived from the FIGO clinical staging system (Table 11.3).

Stage I tumors are confined to the cervix. In stage IA, disease is microinvasive and cannot be seen on MRI. Stage IB is defined as clinically visible tumor limited to the cervix and is subdivided by size into IB1 (<4 cm in greatest dimension) (Fig. 11.15) and IB2 (>4 cm in greatest dimension). The tumor appears as intermediate signal intensity mass in contrast to the low signal intensity cervical stroma on T2WI (132).

Table 11.3 FIGO Staging of Cervical Carcinoma with Corresponding MR Findings

FIGO Stage	Description of Stage	MRI findings
Stage I	The carcinoma is strictly confined to the cervix	
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion <5 mm and largest extension >7 mm	MRI is not indicated in stage IA as tumor not seen (except cases considered for fertility-sparing surgery such as trachelectomy)
IA1	Measured stromal invasion of <3 mm in depth and extension <7 mm	
IA2	Measured stromal invasion of >3 mm and not >5 mm with an extension of not >7 mm	
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage 1A	Mass of intermediate signal intensity on T2WI. MRI can accurately delineate the tumor and its location and provide accurate size measurement (including distance from the internal os and cervical length in cases considered for trachelectomy)
IB1	Clinically visible lesions <4 cm in greatest dimension	
IB2	Clinically visible lesions >4 cm in greatest dimension	
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina	Accurate evaluation of tumor location and tumor size. Invasion of the upper two-third of vagina is indicated by disruption of the low SI vaginal wall by high SI tumor on T2WI
IIA	Without parametrial invasion	
IIA1	Clinically visible lesion <4 cm in greatest dimension	
IIA2	Clinically visible lesion >4 cm in greatest dimension	
IIB	With obvious parametrial invasion	Parametrial invasion is indicated by disruption of the low SI stromal ring and presence of a spiculated tumor/parametrium interface, gross nodular tumor extension into the parametrium, or encasement of the uterine vessels by tumor
Stage III	The tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney	
IIIA	Tumor involves lower third vagina, no extension to pelvic wall	Invasion of the lower one-third of vagina is indicated by disruption of the low SI vaginal wall by high SI tumor on T2WI
IIIB	Extension to the pelvic wall and/or hydronephrosis/nonfunctioning kidney	Pelvic sidewall invasion is indicated by tumor extension within 3 mm of pelvic sidewall. Hydronephrosis is an indication of ureteral and/or bladder invasion
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum	Bladder or rectal invasion is indicated by loss of perivesical/perirectal fat planes and disruption of the normal low signal intensity bladder/rectal mucosa. Note that bullous edema doesn't indicate stage IVA
IVA	Spread to adjacent organs	
IVB	Distant metastases (including intra-abdominal metastases) and/or inguinal lymph nodes	Tumor in distant sites or organs

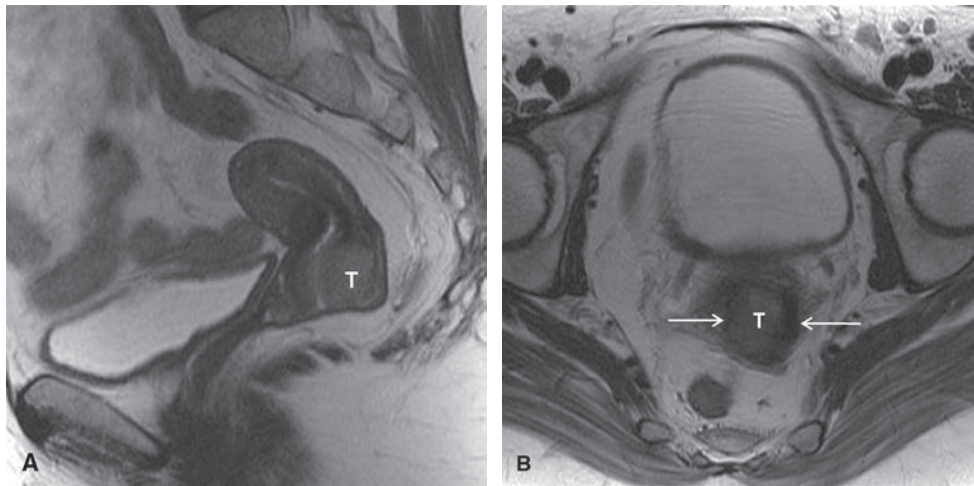


FIGURE 11.15. Stage IB1 cervical carcinoma. Sagittal (A) and axial oblique (B) T2W FSE MR images show a cervical cancer measuring < 4 cm (T in A, B). The low signal intensity cervical stroma is intact (arrows in B) confidently excluding presence of parametrial invasion. Histopathology confirmed a stage IB1 squamous carcinoma of the cervix.

Stage II is defined as tumor growth beyond the cervix but without extension to the pelvic sidewall or the lower third of the vagina. In stage IIA, there is invasion of the upper two-thirds of the vagina without parametrial invasion. Segmental disruption of the hypointense vaginal wall is demonstrated on T2WI. Stage IIA is again subdivided by size into stage IIA1 (<4 cm in greatest dimension) and stage IIA2 (>4 cm in greatest dimension); this subdivision reflects a difference in prognosis similar to that observed between stages IB1 and IB2, which is in turn reflected in differing treatment strategies (122). On MRI, stage IIB disease is seen as disruption of the low signal intensity stromal ring on T2WI; a spiculated tumor to parametrium interface, overt soft tissue extension into the parametria (Fig. 11.16) and encasement of the peri-uterine vessels are additional signs of stage IIB that enhance diagnostic confidence (131). If the intact peripheral low signal intensity stromal rim of the cervix is greater than 3 mm (“hypointense rim sign”), parametrial invasion can almost be excluded with specificity of 96% to 99% and NPV of 94% to 100% (25,138,139). An important pitfall is the overestimation of parametrial invasion on T2WI with large tumors (accuracy of 70%) compared to smaller tumors (accuracy 96%) (132,138,141). Large tumors can cause stromal edema, from

tumor compression or inflammation, which can obscure the real tumor boundary. False positive parametrial invasion can also occur due to postbiopsy hemorrhage. These factors must be considered when making treatment decisions (138,141).

Stage III cervical cancer is defined as tumor extension into the lower third of the vagina and/or pelvic sidewall. In stage IIIA, there is invasion of the lower third of the vagina without extension to the pelvic sidewall. When the tumor extends to the pelvic sidewall or causes hydronephrosis, it is stage IIIB. Tumor visualized within 3 mm of the obturator internus, levator ani, and piriformis muscles or the iliac vessels is suggestive of stage IIIB disease (138).

Stage IV indicates adjacent organ invasion and/or distant metastatic disease. Disruption of low signal intensity bladder mucosa (Fig. 11.17) or rectal wall by high signal intensity tumor on T2WI with tumor involving the mucosa constitutes stage IVA disease. Direct invasion of the rectum is uncommon, as the Pouch of Douglas separates the posterior fornix from the rectum, making the uterosacral ligaments the preferred route for rectal invasion. By adopting a low threshold for invasion, the absence of bladder or rectal invasion can be diagnosed with sufficient confidence using MRI (NPV = 100%) to safely obviate

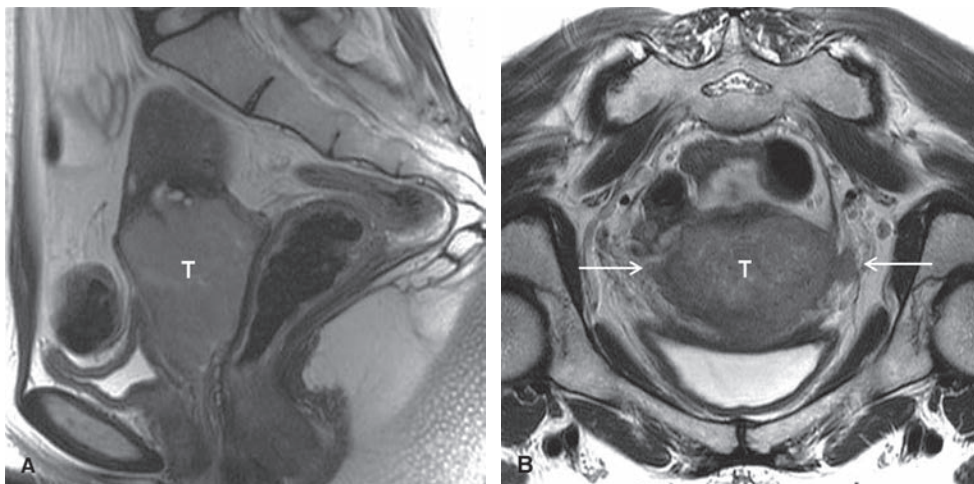


FIGURE 11.16. Stage IIB cervical carcinoma. Sagittal (A) and axial oblique (B) T2W FSE MR images show a large cervical cancer (T in A, B). On the axial oblique image there is a spiculated tumor to parametrium interface on the right and a tumor nodule present in the left parametrium in keeping with bilateral parametrial invasion (arrows in B).

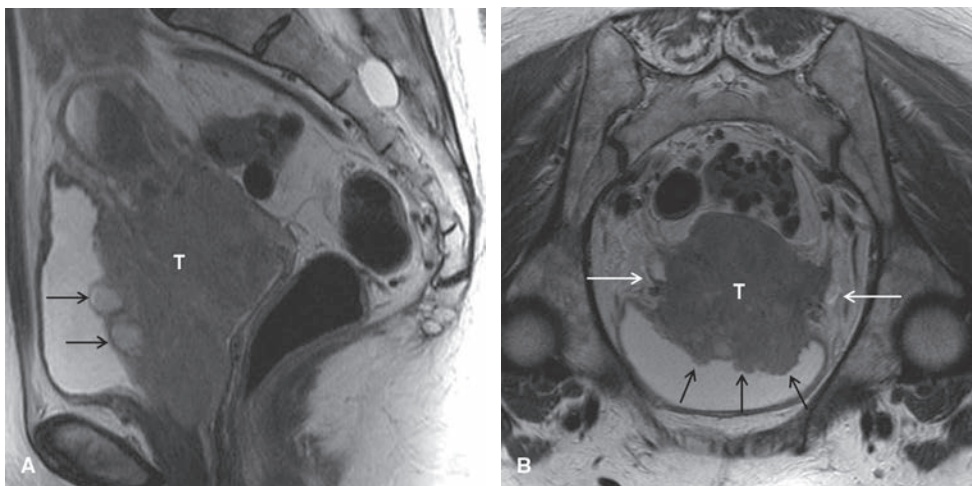


FIGURE 11.17. Stage IVA cervical carcinoma. Sagittal (A) and axial oblique (B) T2V FSE MR images show a large cervical cancer (T in A, B) that invades the cervical stroma and extends into both parametria as indicated by a spiculated tumor to parametrium interface. Tumor also invades the bladder mucosa (black arrows in A, B) and both distal ureters (white arrows in B) causing bilateral hydronephrosis.

the need for invasive cystoscopic or endoscopic staging in the majority of patients with cervical cancer (142). In stage IVB, distant metastatic disease is present.

Positron Emission Tomography/Computed Tomography

FDG-PET is useful in staging patients with advanced cervical cancer, especially in the detection of lymph node metastases (Fig. 11.18). Although lymphadenopathy is not part of the FIGO staging system, it is considered stage IVB disease and knowledge of its presence is therefore crucial when developing a treatment plan. Conventional cross-sectional imaging modalities rely on size criteria for the diagnosis of lymphadenopathy, and, therefore, microscopic disease often goes undetected. FDG-PET is better than the conventional imaging modalities in the detection of lymphadenopathy in patients with cervical cancer, with sensitivities of 75% to 100% and specificities of 87% to 100% (150–153). Reinhardt et al. (154) found that in the detection of involved lymph nodes, sensitivity, specificity, and positive predictive value (PPV) were 91%, 100%, and 100%, respectively, for FDG-PET, as compared to 73%, 83%, and 67%, respectively, for MRI. Another study demonstrated that the accuracy of FDG-PET in the detection of lymph node metastasis was 88%, compared to 75% with MRI (155). FDG-PET also improves initial staging in cases of advanced disease by demonstrating unexpected sites of disease beyond the pelvis or retroperitoneum, such as supraclavicular nodal metastases (156). PET or PET/CT has been found to alter management in a significant number of patients with advanced disease (FIGO IIB–IVB) at presentation (157). In contrast, the value of FDG-PET in early-stage disease (FIGO I to IIA) is questionable. Many studies have reported low sensitivities for the detection of nodal metastases, ranging from 25% to 73%. Chao et al. concluded that PET/CT has a limited role in staging for patients with early-stage disease and should not replace lymphadenectomy for the detection of lymph node metastases (157).

FDG-PET has prognostic value in patients with cervical cancer (158). Kidd et al. found that the maximum SUV (SUV_{max}) of the primary cervical tumor at diagnosis was a sensitive biomarker of treatment response and prognosis for patients with cervical cancer (159). Recently, the same group (160) reported that the SUV_{max} of pelvic lymph nodes is a prognostic

biomarker, predicting treatment response, pelvic recurrence risk, and disease-specific survival in patients with cervical cancer. Increasingly, FDG-PET/CT is being advocated to aid delivery of intensity-modulated radiation therapy (IMRT) (161,162). In a study on 452 patients treated with curative intent (135 with IMRT) based on FDG-PET/CT, the IMRT group showed better overall survival, although recurrence-free survival did not reach statistical significance (161).

Monitoring Treatment Response and Detecting Recurrent Cervical Cancer

Recurrent cervical cancer typically occurs early in the course of disease (60% to 70% percent of cases occur within two years of starting treatment) (163). Salvage treatment may prolong survival, particularly when the recurrence is detected at an early stage. Location of the recurrent disease and initial therapy will determine the course for subsequent treatment. Recurrent disease restricted to the vaginal vault or pelvic sidewalls may be treated with chemoradiotherapy, if this has not been given previously. Patients previously treated with chemoradiotherapy who develop central recurrence may be suitable for pelvic exenteration. Distant metastatic disease may be treated with chemotherapy, and the patient may be offered clinical trial entry. It is imperative to accurately identify those patients deemed suitable for such radical steps as pelvic exenteration, which is associated with considerable morbidity (164). There is, however, no consensus regarding routine follow-up imaging. Imaging is only undertaken if indicated by clinical symptoms or signs, or in cases treated with fertility-preserving radical trachelectomy.

Ultrasound

Currently, there is no role for US in the evaluation of cervical cancer response to chemoradiotherapy or in the detection of recurrent disease.

Computed Tomography

CT is useful for the detection of tumor recurrence in the pelvis following hysterectomy as well as the assessment of metastases

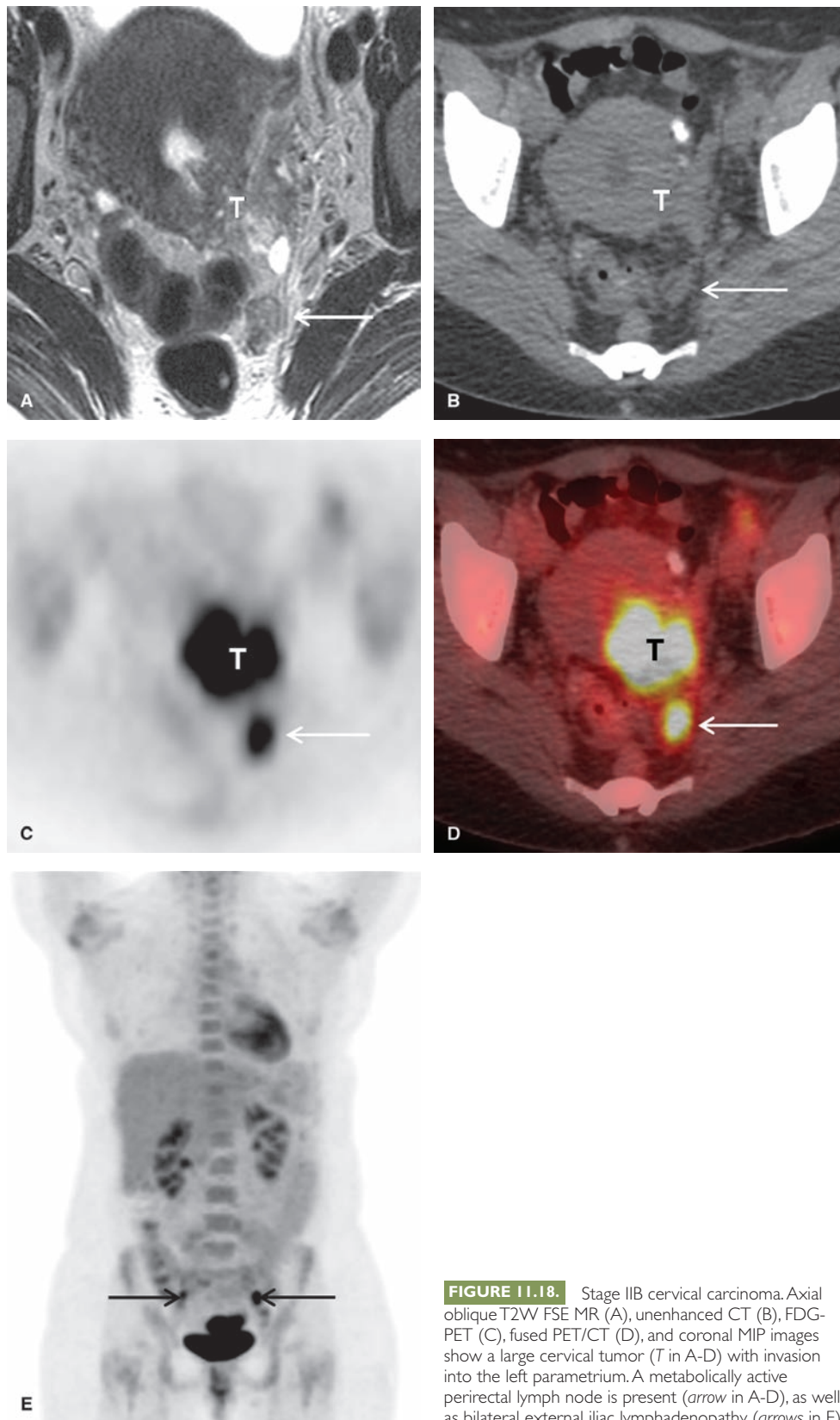


FIGURE 11.18. Stage IIB cervical carcinoma. Axial oblique T2W FSE MR (A), unenhanced CT (B), FDG-PET (C), fused PET/CT (D), and coronal MIP images show a large cervical tumor (*T* in A-D) with invasion into the left parametrium. A metabolically active perirectal lymph node is present (*arrow* in A-D), as well as bilateral external iliac lymphadenopathy (*arrows* in E).

to the peritoneum and solid organs (particularly the liver, lungs, and adrenal glands) (93), but it has limited value for detecting recurrent tumor after chemoradiotherapy, because of poor soft-tissue contrast between the recurrent tumor and the irradiated cervix (93,130). CT features of recurrent pelvic tumor include

soft-tissue asymmetry, soft-tissue mass, compression and invasion of adjacent organs, tumor extension to the pelvic sidewall, and hydronephrosis (165). Pelvic and paraaortic nodal metastases are also often present in patients with recurrent disease and are well depicted by CT (93).

Magnetic Resonance Imaging

In patients treated with primary chemoradiotherapy, MRI is routinely used to monitor response during and at the completion of treatment (29). Change in tumor size on sequential MRI is the standard method for evaluating response to chemoradiotherapy in patients with advanced cervical carcinoma. Decrease in tumor volume can be seen as early as 2 months after treatment and predicts a good prognosis (166). The reconstitution of the normal low signal intensity cervical stroma is the most reliable indicator of a tumor-free postradiation cervix (167,168). If a small area of residual tumor is detected at the completion of treatment, there is a window of opportunity to offer exenterative surgery. These patients should undergo FDG-PET/CT before surgery to exclude distant spread of disease. If, after chemoradiation, the patient is found to have a complete response, no further routine imaging is required.

Physiological imaging with DW-MRI and DCE-MRI are complementary to standard morphological response assessment by MRI. Pretreatment DCE-MRI parameters can predict response to chemoradiotherapy and may enable alteration of treatment strategy in patients with advanced cervical cancer (169–172). DW-MRI has the potential to be used as a response biomarker, to provide a surrogate end-point in the assessment of treatment response in advanced cervical cancers. Measurement of ADC values has been shown to have potential for monitoring early response to chemoradiotherapy (173–176).

MRI plays an important role in evaluation of recurrent cervical cancer. It is useful in the evaluation of surgical resectability, if the

pelvis is the sole site of recurrence. On T2WI, vaginal vault recurrence is seen as loss of the linear, low signal intensity of the vaginal vault and an associated soft tissue mass of high signal intensity, similar to that of the primary tumor. MRI is superior to CT in distinguishing radiation fibrosis from recurrent disease. On MRI, tumor recurrence appears as a region of intermediate to high signal intensity on T2WI compared to the low signal intensity irradiated cervix (Fig. 11.19). However, the appearance of recurrence can be indeterminate, particularly within the first six months after treatment (177). In patients with a history of remote radiation therapy (>1 year), the difference in signal intensity between posttreatment fibrosis and recurrent tumor is statistically significant, and a sensitivity of 86% and a specificity of 94% have been reported for detection of recurrent cervical cancer by MRI (178).

Recurrent tumor is more reliably identified on dynamic contrast-enhanced images, as an area showing increased enhancement, than on T2WI (15). The accuracy of dynamic contrast-enhanced MRI for identifying recurrent disease approaches 85% compared to 64% to 68% for unenhanced T2W images (15,179). On DW-MRI, hyperintense signal on high-b-value images associated with lower ADC values suggests active tumor (180).

Positron Emission Tomography/Computed Tomography

In patients with cervical cancer, there is a role for FDG-PET in treatment response assessment, where findings of residual

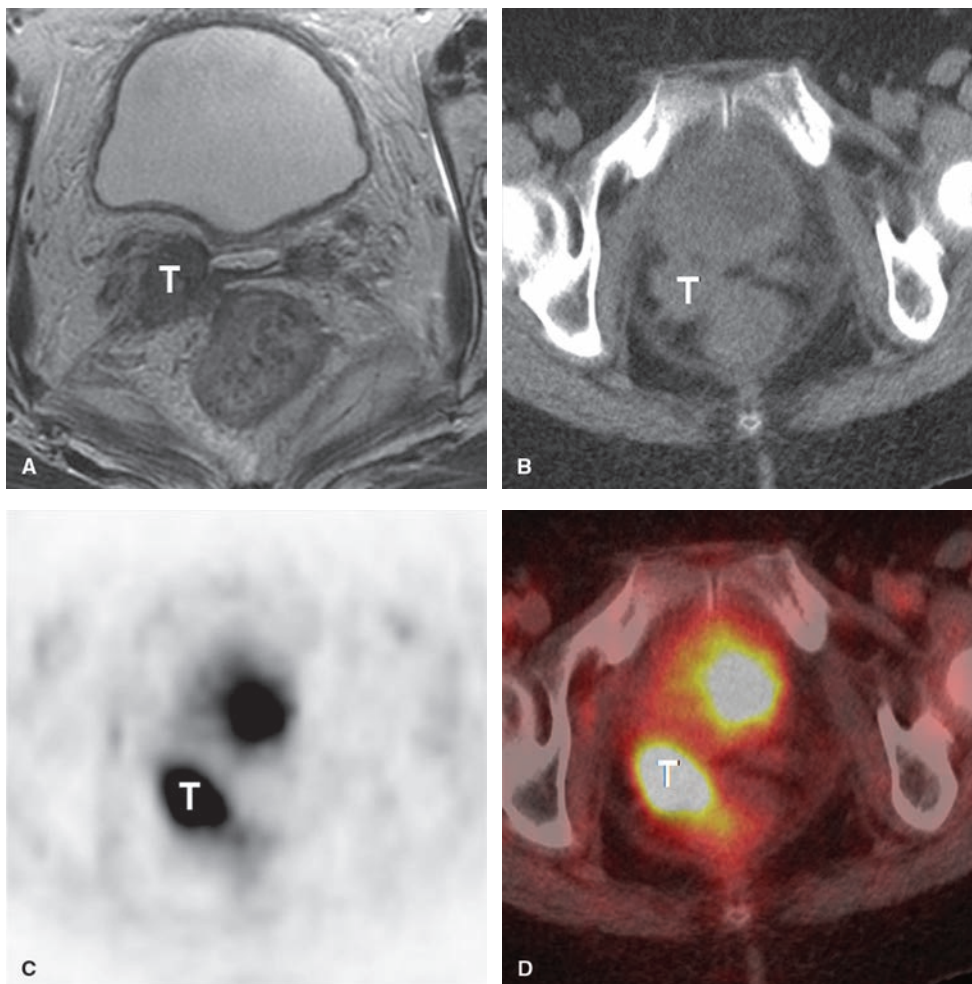


FIGURE 11.19. Recurrent cervical carcinoma. Axial oblique T2W FSE MR (A), unenhanced CT (B), FDG-PET (C), and fused PET/CT (D) images show cervical cancer recurrence in the vaginal vault (T in A–D).

metabolically active disease, 3 months after completion of treatment, may be used to guide additional therapy (181).

PET/CT plays an important role in the management of patients with suspected recurrent cervical cancer. In this context, the applications of PET/CT include detection of recurrent disease (Fig. 11.19) at the primary site, assessment of nodal disease, and detection of distant metastases and radiotherapy field planning (88,182). FDG-PET/CT is increasingly used in identifying pelvic recurrence with sensitivity, specificity, and accuracy of 92.0%, 92.6%, and 92.3%, respectively (183). In addition to local recurrence, FDG-PET/CT is able to detect peritoneal dissemination, paraaortic lymph node metastasis, pelvic lymph node metastasis, and lung metastases. Mittra et al. showed that posttreatment surveillance with PET/CT is highly effective in identifying both residual/recurrent disease and distant metastases. All 30 patients in the study had a change in their management on the basis of the PET/CT findings (184). Similarly, Pallardy et al. found that the use of FDG-PET/CT in patients suspected cervical cancer recurrence modified treatment in more than 50% of patients with negative conventional imaging (185).

FDG-PET/CT is also promising in asymptomatic patients. In a series of 103 patients, FDG-PET/CT detected recurrence in nine of 78 (11.5%) asymptomatic patients and 21 of 25 symptomatic patients at 13 months (186). In 100 women, a study examining the use of unenhanced versus contrast-enhanced CT with integrated FDG-PET/CT showed no significant difference in sensitivity or specificity for detecting recurrence, although the latter was helpful in correctly interpreting a few equivocal findings on unenhanced CT (95).

OVARIAN CANCER

Introduction

The detection of early ovarian cancer is difficult for a variety of reasons and currently involves a combination of physical examination, CA-125 levels, and TVS. At present, there is no screening strategy that reliably detects early ovarian cancer. Because of this, ovarian cancer is often not diagnosed until it has spread to other organs. Imaging by means of US, CT, MRI, and FDG-PET/CT plays a crucial role in detection, characterization, staging, and follow-up of patients with ovarian cancer.

Primary Detection and Characterization of Ovarian Cancer

The 5-year survival rates for stage I and stage II ovarian cancer are 90% and 70%, respectively (187,188); however, the 5-year survival rate for stages III and IV ranges from 5% to 30% (188). Therefore, if more ovarian cancers were detected as stage I disease rather than stage III or IV disease, 5-year survival would dramatically improve. Unfortunately, there are no good screening methods for ovarian cancer at present; most use a combination of physical examination, CA-125 levels, and TVS.

Ultrasound

US plays a crucial role in the detection and characterization of adnexal masses, and is an important component of screening programs for women at high risk for ovarian carcinoma. US is the initial imaging modality of choice for characterization of ovarian masses.

The early diagnosis of ovarian carcinoma, when cure is possible but tumors are clinically asymptomatic (silent), is made difficult by the low prevalence of ovarian carcinoma in the

general population. Therefore, efforts at screening patients for ovarian carcinoma have focused on high-risk populations. Risk factors include older age, high socioeconomic status, factors that increase the number of ovulatory cycles such as early menarche, nulliparity, and late-onset menopause, and having a first-degree relative with ovarian carcinoma (189,190). Approximately 10% of ovarian carcinomas are believed to be due to an inherited susceptibility. Three syndromes have been described: the breast/ovarian cancer syndrome; the Lynch 2 syndrome, or the hereditary nonpolyposis colorectal cancer syndrome; and hereditary site-specific ovarian cancer. In 1994, a National Institutes of Health (NIH) consensus conference (191) recommended that screening be offered to women with two or more first-degree relatives with ovarian carcinoma. It is also recommended that women with an inherited predisposition to ovarian cancer be screened (191–193). In practice, many women with a single first-degree relative are enrolled in screening programs.

Most screening programs for ovarian cancer rely on a combination of physical examination, serologic markers, and TVS. The results of these screening trials have consistently demonstrated that US detects more stage I ovarian carcinomas than CA-125 levels and physical examination (194). Nonetheless, very few stage I carcinomas have been found in such screening programs (195). The data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (196) demonstrated that the PPV for invasive cancer was 1.0% for an abnormal TVS, 3.7% for an abnormal CA-125 and 23.5% if both tests (CA-125 and TVS) were abnormal. Only one study has demonstrated ovarian cancer screening trials to have a survival benefit. Van Nagell et al. (197), reported a decrease in case-specific ovarian cancer mortality with 89.9% 2-year and 77.2% 5-year survival in women with US-detected ovarian carcinoma.

Ultrasound is considered as the initial imaging modality of choice to differentiate a benign from a malignant ovarian mass (Fig. 11.20). Although a likely benign mass can be followed or removed by a general gynecologist, suspicion of a malignant ovarian mass initiates referral to a gynecologic oncologist who can better perform the more complex therapeutic and staging cytoreductive surgery for ovarian carcinoma. Morphologic features remain the primary criteria for differentiating complex ovarian masses as benign or malignant on US. Hence, TVS is the critical US imaging approach because of the improved spatial and soft-tissue resolution afforded by the higher frequency endovaginal probe. Nonetheless, transabdominal US remains an important, complementary component of the US examination when a larger field of view is required—for example, if a mass is displaced out of the pelvis or is so large that it is incompletely visualized by TVS. In addition, transabdominal imaging is required for evaluation of secondary findings in ovarian cancer, such as ascites, peritoneal implants, or hydronephrosis. Such findings can be important not only to confirm the impression of malignancy but also for staging.

Numerous studies have reported that when strict US criteria and a pattern recognition approach for identification of benign ovarian masses are used, US examination has a near 95% to 99% NPV in excluding malignancy (198–200). US features consistent with benign etiology include smooth, thin walls; few, thin septations; absence of solid components or mural nodularity; as well as pattern recognition for certain benign diagnoses. Simple cysts will be anechoic with a smooth, thin wall and posterior acoustic enhancement. Endometriomas may contain uniform low-level echoes (Fig. 11.20) but should still demonstrate a smooth, thin wall, increased through transmission. Hemorrhagic cysts may contain complex internal echoes; however, the appearance of the internal echoes should change over time and should never demonstrate internal vascularity. Several US patterns associated with dermoid cysts have been described including uniform increased echogenicity (Fig. 11.20) with or without posterior acoustic attenuation, echogenic mural nodules, and layering with or without floating debris.

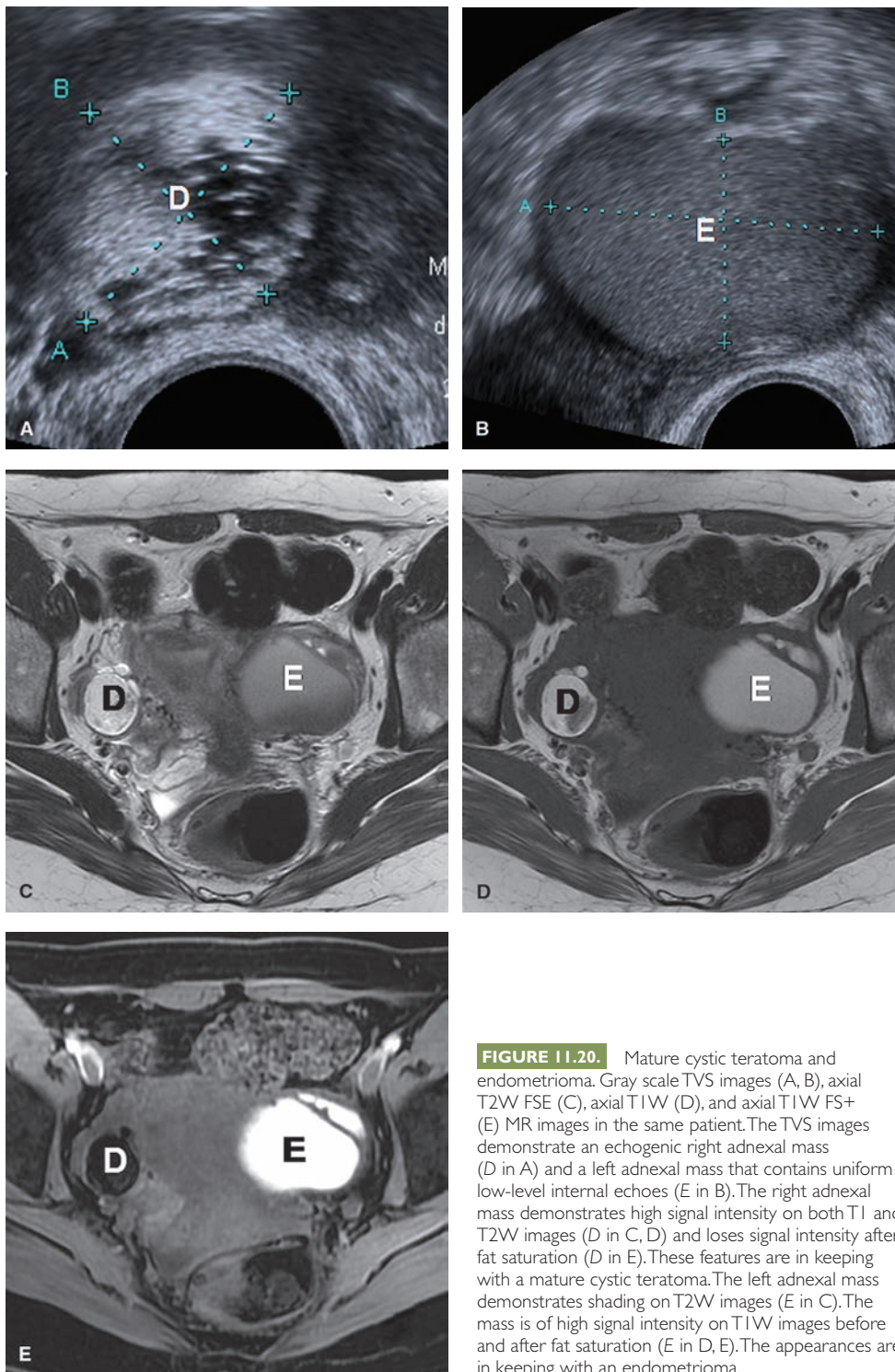


FIGURE 11.20. Mature cystic teratoma and endometrioma. Gray scale TVS images (A, B), axial T2W FSE (C), axial T1W (D), and axial T1W FS+ (E) MR images in the same patient. The TVS images demonstrate an echogenic right adnexal mass (D in A) and a left adnexal mass that contains uniform low-level internal echoes (E in B). The right adnexal mass demonstrates high signal intensity on both T1 and T2W images (D in C, D) and loses signal intensity after fat saturation (D in E). These features are in keeping with a mature cystic teratoma. The left adnexal mass demonstrates shading on T2W images (E in C). The mass is of high signal intensity on T1W images before and after fat saturation (E in D, E). The appearances are in keeping with an endometrioma.

Conversely, mural nodules, mural thickening or irregularity (Fig. 11.21), solid components, thick septations (>3 mm), and associated findings such as ascites, peritoneal implants, and/or hydronephrosis, suggest malignancy. Such US descriptors have been reported to have a high sensitivity but lower specificity for malignancy (197,199,200). The lower specificity reflects overlap in the imaging appearance of benign, borderline, and malignant lesions. For example, benign lesions such as hemorrhagic cysts, cystadenomas, or cystadenofibromas may have thick septations and apparent mural nodules; borderline tumors may have minimal findings; and Brenner's tumors, fibromas, and

fibrothecomas are solid but benign. Furthermore, pedunculated fibroids, dermoids, and endometriomas can masquerade as solid ovarian lesions.

The use of color and pulse Doppler in the evaluation of ovarian masses is controversial, with some investigators considering blood flow characteristics to be merely confirmatory, but others considering the Doppler examination to be a helpful discriminator (201–203). Malignant lesions more often demonstrate increased vessel density and tortuosity than benign lesions, but significant overlap exists. Malignant ovarian lesions also tend to demonstrate higher peak systolic velocities and lower

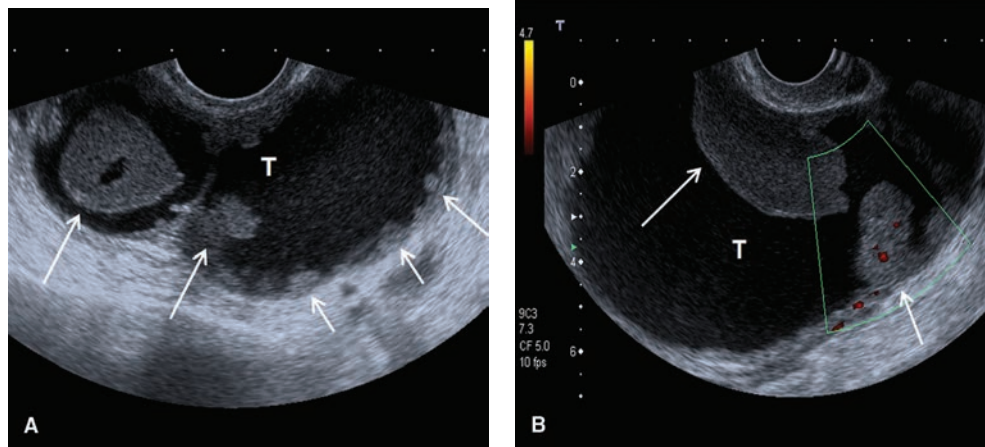


FIGURE 11.21. Ovarian carcinoma. Gray scale TVS image (A) and color Doppler TVS image (B) demonstrate a complex adnexal mass (T in A, B). Note the presence of multiple soft tissue components in the wall of the mass (white arrows in a, b). Increased blood flow is seen in the soft tissue components on the color Doppler image.

resistive indices than benign masses, but again, considerable overlap exists and no discriminatory cut-off values are accepted (201–203).

Scoring systems have been proposed to standardize evaluation of ovarian masses in an attempt to improve specificity (204,205). Using a stepwise logistic regression analysis to determine the most discriminating gray-scale and Doppler sonographic features of malignancy, Brown et al. (204), reported that a multiparameter approach, which assessed for nonhyperechoic solid components, central blood flow on color Doppler, ascites, and thick septations, had 93% sensitivity and specificity for malignancy. To achieve 100% sensitivity, specificity was dropped to 86% in this study (204). However, Timmerman et al. (206) have reported similar results and interobserver variability when readers used subjective criteria for evaluating ovarian masses. Combining Doppler with gray-scale imaging improves the diagnostic assessment of ovarian lesions (Fig. 11.21). A meta-analysis of 46 studies compared the relative utility of gray-scale imaging, color Doppler, and Doppler flow analysis for interrogating adnexal masses, and found that the combination of these methods was more powerful than their individual use (207).

Three-dimensional US may improve characterization of adnexal masses. In one study of 71 pelvic masses, 3-D power Doppler US improved the specificity and PPV compared to conventional 2-D US from 54% to 75% and from 35% to 50%, respectively (208). Contrast-enhanced US has also been used for characterization of adnexal masses. Malignant ovarian lesions show a slower washout of contrast medium than do benign lesions (209–211). The development of diagnostic criteria for the kinetics of contrast enhancement may increase the specificity of US for adnexal malignancies (209).

Computed Tomography

CT is not the study of choice to evaluate a suspected ovarian lesion; however, on CT, ovarian lesions may be detected incidentally and characterized. The sensitivity, specificity, and accuracy of CT for distinguishing benign versus malignant lesions are reported to be 89%, 96% to 99%, and 92% to 94%, respectively (212,213).

On CT, ovarian cancer demonstrates varied morphologic patterns, including a multilocular cyst with thick internal septations and solid mural or septal components (Fig. 11.22), a partially cystic and solid mass, and a lobulated, papillary solid mass (Fig. 11.23). The outer border of the mass may be irregular

and poorly defined, and amorphous, coarse calcifications and contrast enhancement may be seen in the cyst wall or soft-tissue components. In a study of 143 patients with CT and histopathology, features suspicious for malignancy in cystic lesions included multilocularity, irregular wall thickening, and soft tissue nodules, while unilocular homogeneous lesions with thin walls and smooth contours tended to be benign (214). Secondary findings of peritoneal deposits, ascites, and other metastases also aid in distinguishing malignant from benign lesions (Figs. 11.22 and 11.23). Since the CT appearance of ovarian metastases is indistinguishable from a primary ovarian neoplasm, the stomach and colon should be carefully examined as potential primary tumor sites when an ovarian mass is detected on CT (215).

Magnetic Resonance Imaging

MRI is the modality of choice for characterization of adnexal lesions which are indeterminate on US (Fig. 11.20). Ovarian masses at times can grow large, and it can be difficult to determine the organ of origin on US and/or CT. Uterine fibroids and other pelvic masses can also grow to a large size and mimic ovarian tumors. The multiplanar capabilities of MRI are helpful in this situation and often help to delineate the organ of origin of a large pelvic mass and characterize its nature.

It is important to recognize that as there are no MRI signal intensity characteristics that are specific for malignant epithelial tumor; such tumors must be distinguished based on morphologic criteria. Primary and ancillary criteria have been proposed for characterizing an adnexal mass as malignant on MRI. A study of 60 lesions (216) established five primary criteria for malignancy: size greater than 4 cm; solid mass or large solid component; wall thickness greater than 3 mm; septal thickness greater than 3 mm; and/or the presence of vegetations or nodularity and necrosis (Fig. 11.24). Four ancillary criteria of malignancy were also established: involvement of pelvic organs or pelvic sidewall; peritoneal, mesenteric, or omental disease; ascites; and adenopathy. The presence of one or more of the five primary criteria, coupled with a single criterion from the ancillary group, correctly characterized 95% of malignant lesions (216).

Dynamic multiphase contrast-enhanced MRI is useful for the evaluation of adnexal cystic lesions, as it may help differentiate solid components or papillary projections (Fig. 11.24) from clots and debris (32,217). Semiquantitative analysis of enhancement curves shows that early initiation and high rate and magnitude of enhancement are associated with malignancy (32). Dynamic contrast-enhanced MRI (DCE-MRI) can help distinguish among

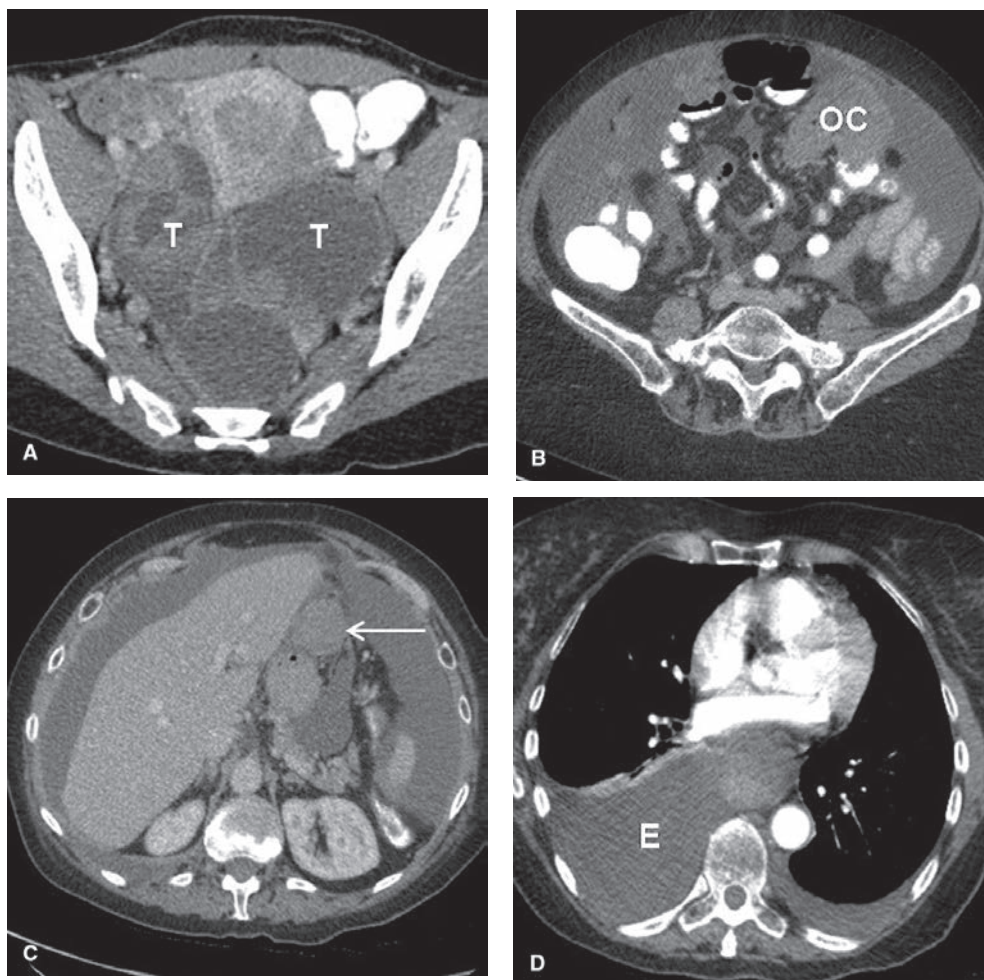


FIGURE 11.22. Ovarian carcinoma. Axial contrast-enhanced CT images demonstrate bilateral complex cystic and solid adnexal lesions (T in A), omental cake (OC in B), a peritoneal deposit in the gastrohepatic ligament (arrow in C), as well as ascites and bilateral pleural effusions largest on the right (E in D).

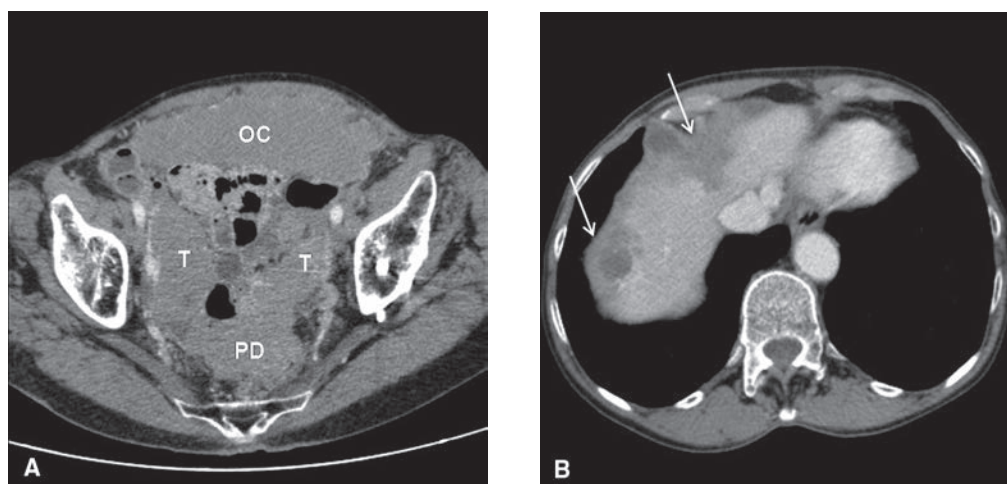


FIGURE 11.23. Ovarian carcinoma. Axial contrast-enhanced CT images demonstrate bilateral solid adnexal lesions (T in A), omental cake (OC in B), peritoneal deposits in the pouch of Douglas (PD in A) and subcapsular liver deposits (arrows in B).

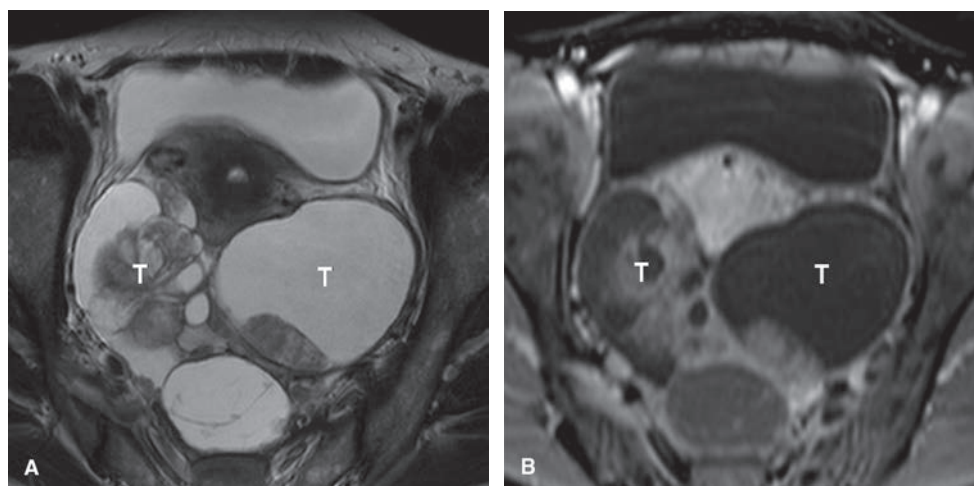


FIGURE 11.24. Ovarian carcinoma. Axial T2W FSE (A) and T1W contrast-enhanced fat-saturated (B) MR images show bilateral solid and cystic adnexal masses (T in A, B). Note the avid enhancement of solid components (B) after administration of intravenous gadolinium.

benign, borderline, and invasive tumors. Amplitude and maximal slope of enhancement reportedly achieve 100% sensitivity with 72% and 92% specificity, respectively, in identifying histological invasion (33). A recent study suggested threshold criteria for presence of malignancy; maximum solid tumor enhancement of more than 250 had 100% sensitivity, specificity, and accuracy for prediction of malignancy in preoperative indeterminate adnexal masses (281).

A controversy remains regarding the utility of DW-MRI for differentiating benign from malignant ovarian tumors. Nakayama et al. (219) found no significant difference in ADC values between the benign and malignant cystic ovarian lesions. There was a wide variation in the ADC values of malignant ovarian tumors, which was related to their morphological heterogeneity. Recently, Thomasin-Naggara et al. (220) found that the presence of low-signal-intensity solid components on high-b-value DW images was the most significant criterion for predicting a benign lesion. In their study, all masses that displayed low signal intensity within the solid components on both T2WI and DW-MRI were benign. However, ADC values do not contribute in differentiating benign from malignant adnexal lesions owing to a considerable overlap of mean and lowest ADC values between the two groups (219–221). These findings reflect the histological heterogeneity of ovarian neoplasms, as high ADC values in malignant lesions may arise from desmoplastic stroma, whereas low ADC values in benign lesions, such as fibromas, result from compact cellular organization (220). More recently, the same group reported that the addition of DCE-MRI and DW-MRI to conventional MRI improved diagnostic accuracy in the characterization of complex adnexal masses, allowing accuracy of 95% (222).

Positron Emission Tomography/Computed Tomography

Currently, FDG-PET has little role in the primary detection of ovarian cancer. A study by Hubner et al. (223) found good correlation between FDG-PET and histologic findings in women with suspected ovarian cancer imaged prior to laparotomy. Specifically, the sensitivity, specificity, accuracy, PPV, and NPV of FDG-PET were 83%, 80%, 82%, 86%, and 76%, respectively. A further study found that PET-CT imaging had a sensitivity of 100% and a specificity of 92.5% for the detection of malignant masses (224). Castelluci et al. (225) compared the accuracy of 18F-FDG PET/CT and TVS in distinguishing malignant from benign pelvic lesions in 50 consecutive patients. The sensitivity,

specificity, NPV, PPV, and accuracy of 18F-FDG PET/CT were 87%, 100%, 81%, 100%, and 92%, respectively, compared with 90%, 61%, 78%, 80%, and 80%, respectively, for TVS. The investigators concluded that FDG-PET/CT provided additional value to TVS for the differentiation of benign from malignant pelvic lesions. However, the major pitfall of the study was the lack of comparison with MRI, which remains the modality of choice for characterizing adnexal lesions. Therefore, currently, there is no convincing evidence or justification to suggest the use of PET/CT for characterization of indeterminate adnexal lesions; instead, PET/CT should be reserved for staging and follow-up of patients with ovarian carcinoma.

Staging Ovarian Cancer

The FIGO staging system for ovarian cancer is surgically based. It does not formally include imaging, but the FIGO committee encourages the use of imaging techniques, if available, to assess the important prognostic factors such as disease resectability and lymph node status. The standard of care for patients with newly diagnosed advanced ovarian cancer has been comprehensive staging laparotomy and primary optimal surgical cytoreduction followed by adjuvant chemotherapy (226,227). However, the use of neoadjuvant chemotherapy followed by interval debulking surgery (IDS) as a suitable alternative (228,229) is supported by recent multicenter randomized controlled trials (230,231). Imaging is therefore of paramount importance in helping triage patients for appropriate management by accurately evaluating the extent of anatomical location of peritoneal spread, which in turn dictates the feasibility of cytoreductive surgery and predicts the likelihood of optimal primary cytoreduction. Imaging by US and CT is also used to guide ovarian mass/omental biopsy, which is needed prior to neoadjuvant chemotherapy.

Ultrasound

US has a limited role in the staging of ovarian cancer except in detecting the presence of ascites. Transabdominal US is an excellent modality not only for identifying ascites, but also for guiding paracentesis as well as omental/peritoneal biopsy. However, the detection of stage II and III disease by US is limited. Peritoneal implants can sometimes be documented on careful US examination. The specificity of US examination in documenting abdominal spread of disease has been reported to be slightly

higher than that of CT or MRI (232). However, the sensitivity of US for the detection of implants less than 2 cm (stage IIIB) is lower than that of CT or MRI owing to a limited field of view and decreased spatial and soft-tissue resolution (232,233). US, therefore, should only be used for specific indications.

Computed Tomography

CT is the primary cross-sectional imaging modality used to stage ovarian cancer. It is complimentary to surgical staging identifying possible sites of unsuspected disease, which include the pelvic peritoneum, paraaortic nodes, diaphragm, and chest (234,235). Several clinical studies have demonstrated that the thorax frequently harbors undiagnosed pleural disease at the time of the initial diagnosis, and that this is likely to affect survival even in cases of optimal debulking (236–238). In addition, a recent study found that moderate-to-large pleural effusion on preoperative CT was associated with a decrease in overall survival in patients with stage III or IV ovarian cancer after controlling for age, preoperative CA-125, surgical stage, ascites, and cytoreductive status (239).

Cytoreductive surgery is the treatment of choice for patients with ovarian cancer. “Optimal” cytoreductive surgery (residual disease <1 cm) is a very strong predictor of survival, (240) and even after the threshold for optimal cytoreduction has been reached, it is important to remove as much of the residual tumor as possible (241). Accurate imaging will help guide the surgeon to areas of disease that may be difficult to identify surgically,

and describe the volume and extent of disease for optimal cytoreductive surgery. Relative criteria for “nonoptimally resectable disease” have been developed (242). They include: lymph node enlargement above the renal hilum; presence of abdominal wall invasion; parenchymal liver metastases and subcapsular liver metastases; peritoneal implants of >2 cm along the diaphragm, lesser sac, porta hepatis, intersegmental fissure, and gall bladder fossa; gastrosplenic; gastrohepatic ligament; and small bowel mesentery. However, it is important to realize that these criteria may vary and will depend on the aggressiveness of the surgical procedure and on the performance status of the patient. Therefore, the criteria should only be used as a basis for a multidisciplinary consensus. It is important to note that upper abdominal disease and pleural metastases can be surgically resected, but this requires careful planning as it involves a team of surgeons (e.g., liver surgeons for hepatic resection, and thoracic surgeons for video-assisted thoracoscopic resection of pleural disease).

Criteria for CT Interpretation According to Tumor Stage

CT staging of ovarian cancer should be performed after administration of both intravenous and oral contrast medium, the latter being crucial for detection of tumor deposits along the small and large bowel serosa. Recommendations for diagnostic evaluation of tumor staging are derived from the FIGO surgical staging system (Table 11.4).

Table 11.4 FIGO Staging of Ovarian Carcinoma with Corresponding CT Findings

FIGO Stage	Description of Stage	CT Findings
Stage I	Tumor limited to ovaries (one/both)	
IA	Tumor limited to one ovary, capsule intact, no tumor on ovarian surface, no malignant cells in ascites or peritoneal washings ^a	Enlarged or normal ovary, ascites may be present
IB	Tumor limited to both ovaries, capsule intact, no tumor on ovarian surface, no malignant cells in ascites or peritoneal washings ^b	Enlarged or normal ovaries, ascites may be present
IC	Tumor limited to one or both ovaries with any of the following: capsular rupture, tumor on ovarian surface, malignant cells in ascites or peritoneal washings ^a	Unilateral or bilateral mixed cystic/solid or solid adnexal mass with irregular contour, heterogeneous enhancement of solid components and thick septa. Ascites.
Stage II	Tumor involves one or both ovaries with pelvic extensions or implants	
IIB	Tumor extension and/or implants on uterus/fallopian tube(s), no malignant cells in ascites or peritoneal washings ^a	Irregularity or obliteration of the fat plane between the uterus and the adnexal mass. Dilated fallopian tubes which may contain enhancing soft tissue nodules. Ascites.
IIB	Tumor extension and/or implants on other pelvic tissue, no malignant cells in ascites or peritoneal washings	Loss of the normal fat plane around the rectum or bladder, less than 3 mm between the tumor and the pelvic sidewall, and/or displacement or encasement of the iliac vessels. Ascites.
Stage III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis.	
IIIA	Microscopically confirmed peritoneal metastasis ^b outside the pelvis (no macroscopic tumor).	Microscopic extra-pelvic peritoneal implants are not detectable with CT
IIIB	Macroscopically peritoneal metastasis outside the pelvis 2 cm or less in dimension.	Omental cake. Peritoneal/serosal deposits <2 cm outside the pelvis.
IIIC	Macroscopically peritoneal metastasis outside the pelvis >2 cm and/or enlarged regional lymph nodes.	Peritoneal implants of >2 cm. Note that subcapsular liver implants and those along the diaphragm, lesser sac, porta hepatis, intersegmental fissure, gall bladder fossa; gastrosplenic, gastrohepatic ligament and small bowel mesentery are “difficult to resect.”
Stage IV	Distant metastasis beyond the peritoneal cavity. Enlarged lymph nodes above the level of the renal hilum	Liver parenchymal metastases, pleural effusion. ^c Enlarged lymph nodes above the level of the renal hilum

^aThe presence of ascites does not affect staging unless malignant cells are present.

^bLiver capsule metastasis are Stage III, liver parenchymal metastasis are stage IV.

^cStage IV: Pleural effusion must have positive cytology.

Stage I ovarian cancer is limited to either one (stage IA) or both (stage IB) ovaries; no tumor is present on the ovarian surface, and no malignant cells in the ascites or peritoneal washings. In stage IC the tumor is still limited to one or both ovaries but there is a capsular rupture, tumor is present on the ovarian surface, and/or malignant cells are present in the ascites or peritoneal washings. Ascites on CT is easily identified; however, the distinction between stage IC and stage III, or subtle peritoneal disease, is often difficult to make out and has significant clinical implications. In one series of patients, the presence of ascites on CT had a PPV of 72% to 80% as a sign of peritoneal metastasis (235).

Stage II disease is characterized by local extension of tumor confined to the pelvis but with no upper abdominal involvement. In stage IIA disease there is extension and/or tumor implants are found in the uterus or fallopian tube(s), but there are no malignant cells in the ascites or peritoneal washings. Stage IIB disease is characterized by extension into and/or implants on other pelvic tissues, with no malignant cells in the ascites or peritoneal washings. Irregularity or obliteration of the fat plane between the uterus and the ovarian mass indicates stage IIA disease. Loss of the normal fat plane around the rectum or bladder, less than 3 mm between the tumor and the pelvic sidewall, and/or displacement or encasement of the iliac vessels, indicates stage IIB disease (243).

Stage III disease is defined as the presence of extra-pelvic peritoneal and/or lymph node metastasis. Microscopic extra-pelvic peritoneal implants are stage IIIA disease and are not detectable with CT. Stage IIIB, extra-pelvic peritoneal implants less than 2 cm and stage IIIC extra-pelvic peritoneal implants larger than 2 cm or lymph node metastasis can easily be detected with CT (Figs. 11.22 and 11.23).

Approximately 70% of patients have peritoneal metastases at staging laparotomy (244). Peritoneal fluid flows from the Pouch of Douglas, along the paracolic gutters to the diaphragm, and hence these are the key areas where peritoneal seeding and deposits occur. There is preferential flow along the right paracolic gutter, and hence the right side of the peritoneum and diaphragm should be especially closely scrutinized on CT for the presence of metastatic disease (245). CT detection of peritoneal implants depends on several factors including location, the presence or absence of surrounding ascites, and size. The three sites most commonly involved are the right subphrenic space, the greater omentum, and the Pouch of Douglas (244). The presence of surrounding ascites aids in the detection of small peritoneal implants by increasing their conspicuity. Size plays an important role in the reliable detection of peritoneal implants. CT has a sensitivity of 14% to 27% for detection of peritoneal implants smaller than 1 cm, especially in the absence of ascites (246,247). However, the use of coronal and sagittal reformatted images improves sensitivity and allows for better detection of smaller lesions (248).

Mesenteric metastases appear as either round or ill-defined soft-tissue masses surrounded by small-bowel loops and mesenteric fat, or as thickened leaves of the mesentery caused by tumor coating the peritoneal surfaces (233). Omental metastases are characterized as stranding or soft tissue nodules embedded in omental fat or the replacement of the omental fat with thick, nodular tumor ("omental cake") along the greater curvature of the stomach, in the gastrosplenic ligament, or anterior to the transverse colon and small bowel in the lower abdomen (249) (Figs. 11.22 and 11.23). The sensitivity of CT for detection of omental metastasis is reported to be 80% to 86% (243,247).

Care must be taken when assessing the liver and spleen. Peritoneal metastasis implanted on the liver surface (liver capsular deposits) is the most common type of liver involvement in ovarian cancer. Sometimes a peritoneal metastasis on the liver surface can invade into the liver parenchyma (subcapsular liver deposits) (Fig. 11.23) (250). Less commonly, direct intrahepatic

metastasis can occur by hematogenous dissemination. Distinction between these different types of liver metastases is important for the selection of an appropriate treatment approach. Perihepatic metastases without parenchymal invasion can be resected directly. However, surgical removal of perihepatic metastases with parenchymal invasion requires liver resection. Information obtained from CT about liver involvement (including involvement of liver regions that are difficult or impossible to explore surgically) is very useful to the gynecologic surgeon, who can obtain appropriate hepatobiliary surgical consultation and necessary equipment in the surgical room. Knowledge of the extent of liver involvement is also important in surgical planning. The presence of multiple perihepatic metastases with parenchymal invasion in multiple regions of both lobes of the liver precludes surgical resection.

Capsular implants on the surface of the liver/spleen are seen as well-defined, biconvex and peripheral soft-tissue nodules studded along the peritoneal surface of the liver. They may indent the liver. Subcapsular liver deposits cause scalloping of the liver surface with an irregular, enhancing interface between the deposit and the liver parenchyma. They can be difficult to differentiate from intraparenchymal liver lesions. The latter are usually less well defined and circular, and partially or completely surrounded by liver tissue (250). Hematogenous spread to the liver can occur in ovarian cancer but it is unusual and should raise the suspicion of a gastrointestinal primary tumor. Tumor extending into the falciform ligament (stage III) can also be mistaken for intraparenchymal disease on axial images, and multiplanar reformatted images can be helpful.

Subcapsular scalloping of the liver can also occur in pseudomyxoma peritonei. This is a rare condition characterized by metastatic thick mucinous or gelatinous material on the surfaces of the peritoneal cavity causing mass effect. Bowel loops are matted posteriorly rather than floating anteriorly and freely within fluid; ascites and fine septae may be visualized. Surgical resection of the insidious mucin is very difficult and repeated laparotomies may be needed (251). Peritoneal mucinous carcinomatosis can arise from mucinous carcinoma of the ovary, gastrointestinal tract, or pancreas with peritoneal spread and is characterized by invasive, high-grade, poorly differentiated mucinous carcinoma with large extracellular pools of mucin. However, it is now widely accepted that the majority of cases of classic pseudomyxoma peritonei develop from low-grade mucinous carcinomas that arise in the appendix, and that penetrate or rupture into the peritoneal cavity (252). Both serous and mucinous cystadenocarcinomas produce unilocular/multilocular fluid-filled masses. Both the primary tumor and the metastatic peritoneal deposits can contain microcalcifications; in serous tumors, these are known as psammoma bodies, and in mucinous tumors they are known as nonpsammoma calcifications. Both types of tumor calcification can be seen on CT (253–255).

Ovarian cancer can also metastasize through the lymphatic system. Lymph node involvement follows the ovarian veins to the paraaortic and aortocaval nodes at the level of the renal hilum; these are the most common sites for metastatic lymphadenopathy. In general, lymph nodes are defined as enlarged if the short axis diameter is greater than 1 cm; pericardiophrenic nodes are an exception, as they are considered suspicious if greater than 5 mm. Tangjitgamol et al. studied 104 ovarian carcinoma patients and demonstrated that the sensitivity for nodal involvement, identified by a nodal size of 1 cm, was 45%, while the specificity was 81%. They concluded that size alone may not reflect nodal disease (256). Lymph vessels also pass through the broad ligament and involve the external iliac, hypogastric, and obturator. Lymph nodes above the renal hilum and those in the inguinal region represent stage IV disease.

There is increasing evidence that primary surgical evaluation of the lymph nodes by extensive systemic lymphadenectomy

at the time of surgical staging is associated with an improved 5-year disease-specific survival rate, even when adjusted for age, stage, grade, and number of positive lymph nodes (257,258). This may be because occult micrometastatic disease that is resistant to chemotherapy is removed (257). However, identifying enlarged lymph nodes preoperatively will guide the surgeon in planning the retroperitoneal dissection.

Stage IV disease is defined by distant metastasis beyond the peritoneal cavity, and it occurs via hematogenous spread. It is the least common mode of tumor spread in ovarian carcinoma but typically occurs in the solid abdominal organs such as the liver, spleen, kidneys, adrenals, brain, and bone. Hematogenous metastases are uncommon at the time of diagnosis. The sensitivity of CT for the detection of extrapelvic disease is approximately 95% to 100% for liver involvement and 50% to 60% for nodal involvement (243,247). Overall staging accuracy for CT has been reported to be 77% (243). CT also has a high PPV for imaging bulky disease and is therefore useful for identifying patients with inoperable disease (243,247).

Magnetic Resonance Imaging

The overall staging accuracy of MRI in patients with ovarian malignancy is 75% to 78% (216,243), which is comparable to that of CT. However, MRI is recommended as a second-line technique for the staging of ovarian cancer, in the pelvis (232,233), where it has some advantages. The main reasons for MRI being used only in selected cases are the long examination time and the technical difficulties in covering a large field of view with adequate resolution. Expertise in interpreting

abdominal MRI, especially in distinguishing peritoneal/serosal deposits from bowel, is limited to specialist centers. Thus MRI is best reserved for problem solving and for staging ovarian cancer in patients for whom CT is contraindicated. The latter include pregnant patients, patients with renal insufficiency, and those with contraindications to contrast media.

Dynamic multiphase contrast-enhanced MRI has high per-lesion sensitivity (95%) and specificity (80%) for detecting peritoneal dissemination (259). Peritoneal/serosal implants and omental cake are best seen on delayed (5 min) images. However, longer delays beyond 5 min should be avoided as ascites may also enhance, impairing visualization of subtle peritoneal implants. Hepatic surface implants are usually well defined, biconvex, and peripheral, and they indent the liver. True intraparenchymal hepatic metastases are often ill-defined, circular, and partially or completely surrounded by liver tissue.

Recently, there has been a growing awareness of the potential of DW-MRI in improving the mapping of the extent of ovarian cancer and quantifying its early treatment response (260–265). The omental cake and peritoneal deposits retain high signal intensity with increasing b values against a background of suppressed signal from surrounding ascites, bowel contents, and fat, increasing conspicuity (260,266) (Fig. 11.25). Fujii et al. showed that DW-MRI is highly sensitive (90%) and specific (96%) in delineating the extent of peritoneal dissemination, with satisfactory interobserver agreement ($\kappa = 0.77$) (260). The combination of DW-MRI and gadolinium-enhanced MRI has been reported to improve the accuracy of tumor detection (accuracy of 84% to 88% compared to 52% to 72% for gadolinium-enhanced MRI alone and 71% to 81% for DW-MRI alone (267). Preliminary

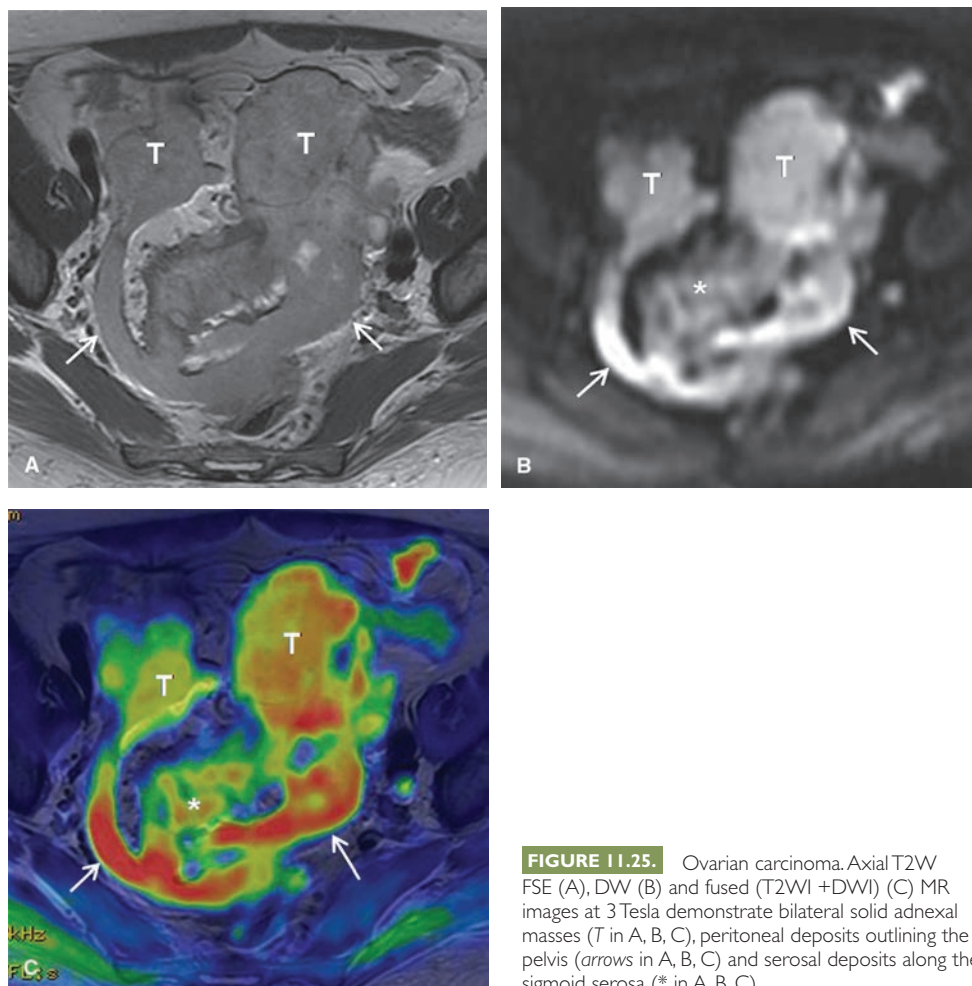


FIGURE 11.25. Ovarian carcinoma. Axial T2W FSE (A), DW (B) and fused (T2WI + DWI) (C) MR images at 3 Tesla demonstrate bilateral solid adnexal masses (T in A, B, C), peritoneal deposits outlining the pelvis (arrows in A, B, C) and serosal deposits along the sigmoid serosa (* in A, B, C).

results also show significantly lower ADC in peritoneal deposits than in primary ovarian tumors and omental cake, suggesting that site-specific diffusion patterns may reflect disease heterogeneity in ovarian cancer (268).

Positron Emission Tomography/Computed Tomography

There is growing evidence that FDG-PET/CT may play a role in preoperative staging of patients with advanced ovarian cancer. FDG-PET/CT can lead to stage migration (269). This is an important finding, as accurate pretreatment staging is one of the determinants of the amount of residual tumor after primary surgery, which is the strongest predictor of patient outcome.

FDG PET/CT has sensitivity ranging from 62% to 100% and improves overall diagnostic accuracy by 5% to 22% compared to CT alone (270–272). Fused PET/CT makes a greater incremental contribution to per-lesion accuracy in extra-pelvic sites, particularly because of its ability to characterize metastatic lymph nodes and to correctly differentiate diffuse serosal infiltration along small bowel loops from normal physiological intestinal activity, which often causes false-negative results in standalone PET (270,272). Nevertheless, diagnostic performance in detecting peritoneal carcinomatosis drops dramatically at an implant size threshold of 4–6 mm because of the limited spatial resolution of the gamma camera and the minimum level of FDG uptake that must be present for detection to occur (273,274). Another potential source of false-negative findings is mucinous tumors, which are associated with less FDG uptake.

Detecting Persistent or Recurrent Ovarian Cancer

The combination of clinical assessment and CA-125 measurement is routinely used to monitor patients treated for ovarian cancer in many institutions (275). However, CA-125 is limited as a tumor marker, since normal values do not exclude the presence of disease, and elevated values do not differentiate between localized and diffuse tumor recurrence (276–278). Furthermore, in the 10% subgroup of biochemically “silent” patients, imaging studies are the only means of assessing treatment response and presence of disease recurrence. Therefore, CT is widely used to

evaluate treatment response and to assess suspected relapse with rising CA-125 levels or clinically suspicious symptoms. Rising CA-125 levels may, however, precede clinical recurrence with a median lead time of 3 to 5 months (275). CT is reproducible, widely available, and well understood. Ultrasound is often used as the initial examination to investigate new symptoms. MRI is reserved as a problem-solving technique to clarify the nature of indeterminate masses on CT. MRI is also particularly useful if there is suspicion of pelvic sidewall invasion or if surgical resection of a pelvic recurrence is planned (279). Emerging data suggest that PET/CT may help in the assessment of patients with elevated CA-125 levels but negative imaging findings.

Ultrasound

US plays a limited role in the detection of recurrent ovarian cancer. US has the greatest sensitivity in detecting recurrent tumor in the pelvis or around the liver and right hemidiaphragm in the setting of ascites (280). However, US has poor sensitivity for detection of miliary peritoneal seeding and peritoneal implants <2 cm (280,281). Additionally, small, plaque-like lesions on the pelvic peritoneum are often missed on US (281). Despite these limitations, US can reliably confirm a clinical suspicion of gross macroscopic recurrent disease and is more accurate than clinical examination (280,281). US can also be used to guide biopsy of areas of suspected recurrence (1).

Computed Tomography

CT is the most commonly used cross-sectional imaging modality for the detection of persistent and recurrent ovarian cancer (Fig. 11.26). It has been demonstrated that there is a survival benefit when patients with advanced ovarian cancer undergo “optimal” versus “suboptimal” primary surgical cytoreduction or IDS (231,240,282). Patients who have no residual or minimal residual disease (<1 cm), at the end of primary surgery for advanced ovarian cancer, survive longer (231,282,283). Intraoperative surgical assessment through direct visualization and palpation is the current reference standard for evaluation of residual disease in patients with ovarian cancer who undergo primary or interval debulking surgery. This is inherently subjective and can be influenced by a number of factors such as surgeon experience, adequate exposure and evaluation of tumor sites, and surgeon and patient expectations (284,285).

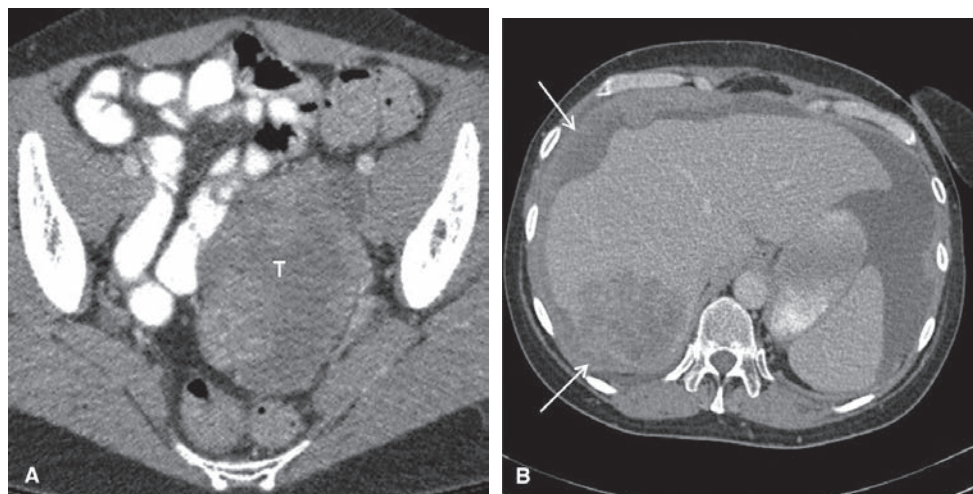


FIGURE 11.26. Recurrent ovarian carcinoma. Contrast-enhanced CT images in a patient with a previous history of ovarian cancer. A large solid mass is seen in the right adnexa (T in A). Multiple peritoneal deposits are seen in the undersurface of the right hemidiaphragm as well as a large subserosal liver deposit with deep invasion into the liver parenchyma (arrows in B).

CT has been used to more objectively assess residual disease following surgery. Two studies have compared the surgeons' operative assessments of residual disease to those identified on postoperative CT in patients with advanced ovarian carcinoma reported to have undergone optimal primary cytoreductive surgery. They found that there was only a 52% to 58% correlation between surgeons' assessments and postoperative CT evaluations of residual disease in patients for whom surgeons had reported optimal cytoreduction (286,287). Whereas the reliability of the direct visualization and palpation at completion of surgery is unquestionable, the estimation of the size or the volume of residual disease is far from accurate. Therefore, the additional value of postoperative CT may lie in those cases where there is surgical small-volume residual disease (visible but reported as <1 cm) (287).

Second-look surgery is no longer routinely performed; therefore, imaging diagnosis of recurrence is important, as secondary cytoreduction is only considered if complete resection is possible with no residual tumor. CT is widely used to assess suspected relapse with rising CA-125 levels or clinically suspicious symptoms. The sensitivity of CT ranges from 51% to 84% and its specificity ranges from 81% to 93% (288–290). False-positive results are usually caused by misdiagnosis of adherent bowel loops as a tumor mass. The sensitivity of CT for disease detection is proportional to lesion size. Many studies report limitations in the detection of small tumor nodules in the mesentery and along peritoneal surfaces (288,290). However, the use of sagittal and coronal reformatted images improves the detection of peritoneal implants (248).

If recurrent ovarian cancer is detected by CT, determination of resectability is an important next step. Currently, there is no consensus on CT criteria for determining nonresectability. However, Funt et al. (288) determined that hydronephrosis and invasion of the pelvic sidewall were most indicative of tumor nonresectability. CT-guided biopsy can be used to confirm suspected recurrence (1).

Magnetic Resonance Imaging

MRI plays an important role in evaluation of resectability of recurrent tumor in the pelvis. Recurrent tumor invading the pelvic sidewall represents nonresectable disease (Fig. 11.27). Pelvic muscle or bone invasion confirms sidewall involvement but this should also be suspected when tumor lies within 3 mm of the pelvic sidewall or when the iliac vessels are surrounded or distorted by tumor (Fig. 11.27). A few studies that compared MRI to second-look laparotomy found that dynamic multiphase contrast-enhanced MRI is comparable (sensitivity 90% and specificity 88%) to laparotomy (sensitivity 88% and specificity 100%) and superior to serum CA-125 (sensitivity 65% and specificity 88%) for detecting recurrent peritoneal and serosal deposits (259,291).

Positron Emission Tomography

FDG-PET/CT has been shown to be an extremely useful adjunct in the evaluation of recurrent ovarian cancer (Fig. 11.28). It has sensitivity, specificity, and accuracy of 72% to 100%, 40% to 90%, and 77% to 91%, respectively, for localization of clinical and biochemical recurrence (292–296); in comparison, the

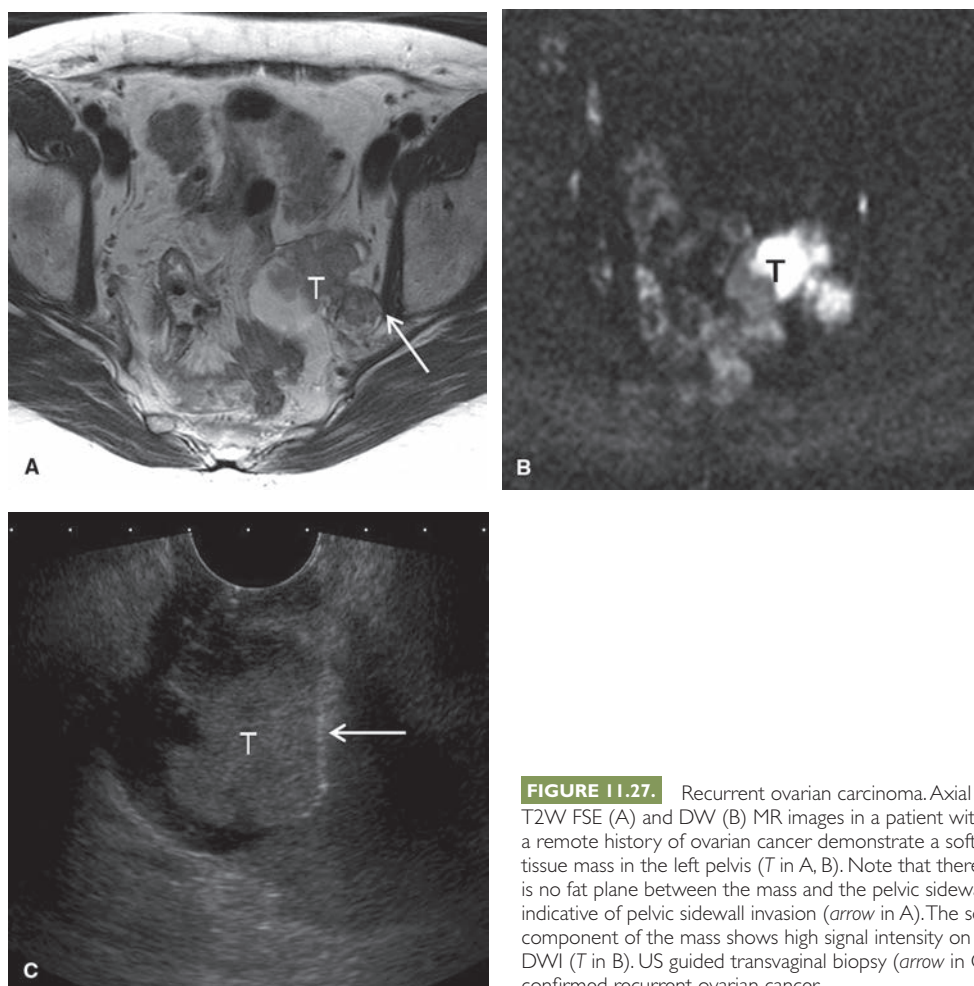


FIGURE 11.27. Recurrent ovarian carcinoma. Axial T2W FSE (A) and DW (B) MR images in a patient with a remote history of ovarian cancer demonstrate a soft tissue mass in the left pelvis (T in A, B). Note that there is no fat plane between the mass and the pelvic sidewall, indicative of pelvic sidewall invasion (arrow in A). The solid component of the mass shows high signal intensity on DWI (T in B). US guided transvaginal biopsy (arrow in C) confirmed recurrent ovarian cancer.

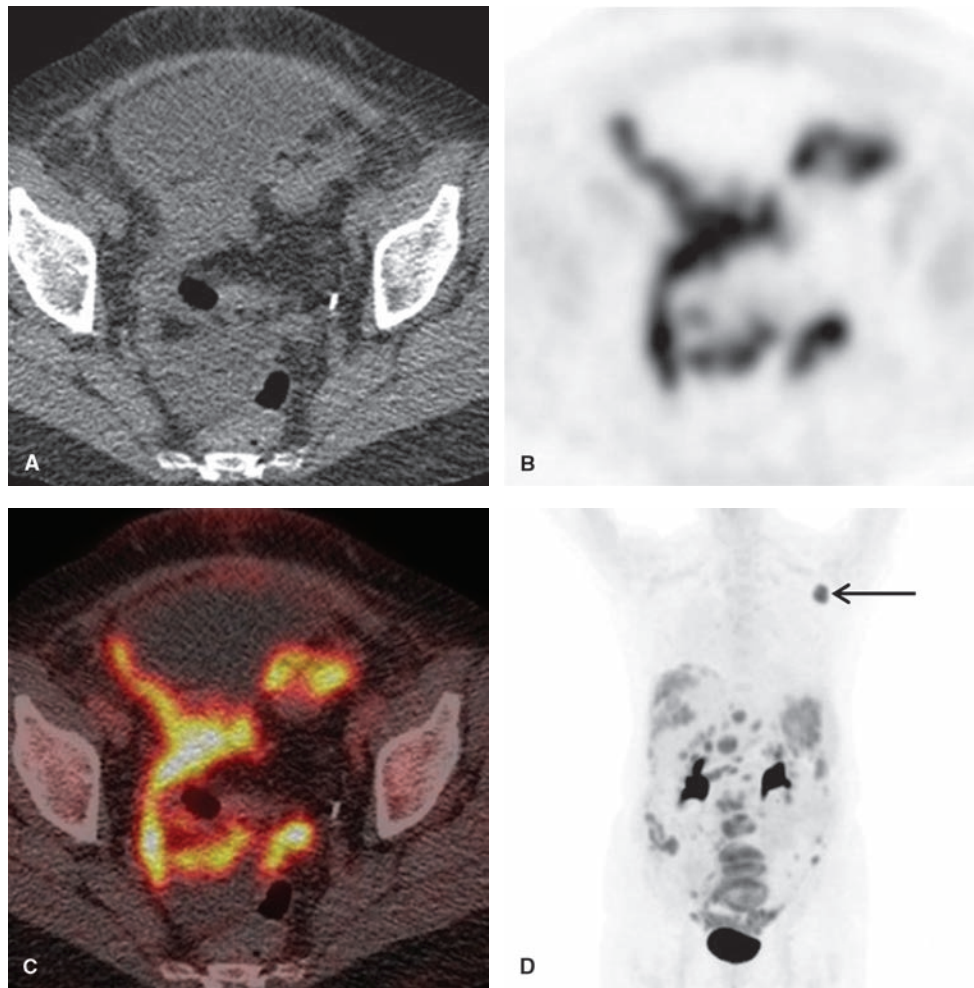


FIGURE 11.28. Recurrent ovarian carcinoma. Unenhanced CT image (A), FDG-PET image (B), and fused PET/CT image (C) demonstrate increased tracer uptake along the serosa of the sigmoid colon. Coronal MIP PET image (D) demonstrates widespread increased tracer uptake along the peritoneal and serosal surfaces in the abdomen and pelvis and avid tracer uptake in a left axillary lymph node (arrow in C).

performance of contrast-enhanced CT in assessing recurrence is inferior (accuracy 43% to 89%), primarily because of low tumor burden at relapse and distortion of pelvic anatomy after cytoreductive surgery (297,298). In two meta-analyses, PET/CT had the highest pooled sensitivity and specificity (91% and 86%, respectively) compared to PET and CT alone, MRI, and CA-125 (299,300). In prospective studies, PET/CT upstaged disease compared to purely anatomical imaging in 55% to 64% of patients by depicting additional sites and altered decisions on clinical management in 34% to 59% of cases, with 44% to 57% of changes rated as high impact (301–304). Fagotti et al. (294) assessed the role of a multimodal approach in the preoperative work-up of patients with recurrent ovarian cancer by prospectively comparing laparoscopy and PET/CT. They reported that combined PET/CT and laparoscopic evaluation had a NPV of 88.9%, a specificity of 59.3%, a PPV of 78.8%, a sensitivity of 95.3%, and an accuracy rate of 81.4%. The number of recurrent nodules identified by PET/CT corresponded to the number found at laparotomy in only 23 patients (40.3%), whereas 15 of 30 patients were correctly diagnosed (50.0%) by staging laparoscopy, suggesting that these techniques are complementary due to the potential of each one to identify a different site of disease recurrence. A recent study found that in patients with recurrent ovarian cancer, size, number, and SUV(max) of peritoneal deposits were significantly associated with poor survival, as were the long- and short-axis diameters, number, and SUV(max)

of distant lymph nodes (290). These preliminary data suggest that tumor size, number, and SUV(max) may have potential as prognostic biomarkers for patients with recurrent ovarian cancer.

In response assessment, a metabolic response defined as a minimum decrease in SUV of 20% after the first cycle and 55% after the third cycle of neoadjuvant chemotherapy was shown to predict macroscopically tumor-free surgery and median overall survival more accurately than clinical, biochemical and histopathological criteria (305). In another study, a cut-off value of 65% SUV reduction had 90% sensitivity, 82% specificity, and 86% accuracy in predicting histological response (306).

VAGINAL CANCER

Vaginal cancer is most often diagnosed and staged clinically. Diagnostic imaging is often performed only for the detection of pelvic lymphadenopathy or metastatic disease, with imaging playing no role in the detection and characterization of vaginal cancer. On MRI, vaginal tumors appear isointense on T1W sequences and may only be apparent if they alter the vaginal contour. On T2W sequences, a vaginal tumor appears as an intermediate to high signal intensity soft-tissue mass (Fig. 11.29) (307–309).

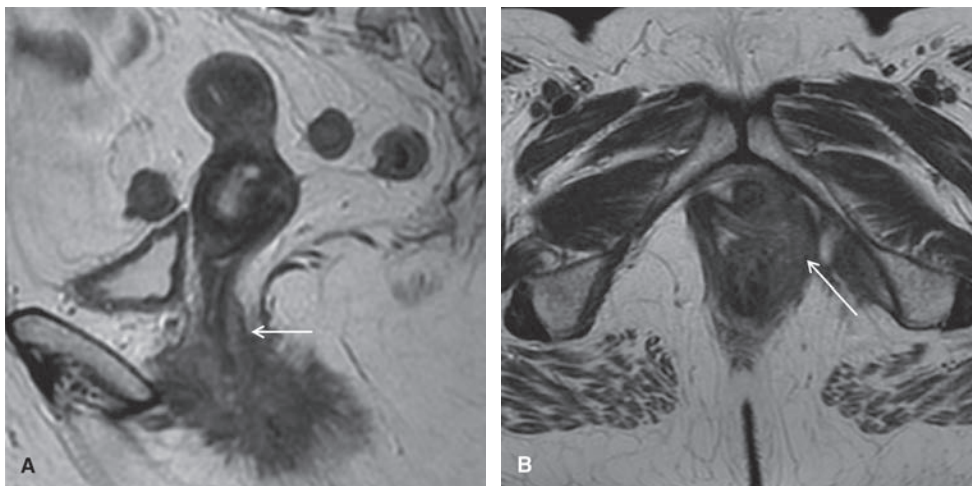


FIGURE 11.29. Vaginal carcinoma. Sagittal (A) and axial T2W FSE MR images demonstrate soft tissue thickening of the posterior vaginal wall (arrow in A, B).

Staging of vaginal cancer is most often clinical (63); however, MRI has a limited role in the staging of vaginal cancer. MRI criteria that correlate to the FIGO staging system have been developed. Stage I disease is defined as tumor that has invaded the epithelium but is confined to the vaginal mucosa. These lesions may be occult on MRI, or there may be abnormal high T2W signal penetrating the vaginal wall. The surrounding perivaginal fat is preserved.

Vaginal tumor that has invaded the paravaginal tissues but does not involve the pelvic sidewall is considered stage II disease. With stage II disease, the normally high-T2W-signal perivaginal fat is invaded by intermediate signal tumor.

Tumor that extends to involve the pelvic sidewall and/or pelvic adenopathy defines stage III disease. Tumor contiguous with the levator ani, obturator internus, or the piriformis muscle is diagnostic of pelvic sidewall invasion. Pelvic adenopathy is diagnosed in the usual manner on MRI.

Stage IV is defined as tumor invading the bladder and/or rectum and/or extrapelvic spread of disease. MRI is particularly well suited for imaging stage IV disease because of its multiplanar capabilities. Invasion of the bladder and/or rectum is diagnosed by identifying disruption of the normal high-T2W-signal mucosa of the bladder and/or rectum. Extrapelvic metastases are diagnosed in the usual manner.

Although these staging criteria have been developed, care must be taken when using MRI for the evaluation of vaginal cancer. It has been shown that inflammatory changes and/or congestion of the vagina may appear similar to carcinoma (307–309). CT and US have little role in the staging of vaginal cancer, although CT can be used for the detection of pelvic lymphadenopathy. Very little data is available on the utility of FDG-PET in vaginal cancer. Lamoreaux et al. demonstrated that FDG-PET was superior to CT in the detection of the primary tumor and pelvic adenopathy in patients with vaginal cancer (310).

Complications from vaginal cancer and/or vaginal cancer treatment can be imaged with US, CT, and/or MRI depending on the clinical concern. Known complications include fistulae, fluid collections, and postradiation therapy colitis. Fistulae are best diagnosed with contrast-enhanced CT or MRI.

VULVAR CANCER

Vulvar cancer is diagnosed and staged clinically. Local tumor extension and lymph node status play an important role in

treatment selection, treatment planning, and prognosis of patients with vulvar cancer, and relapse in the lymph node basin is associated with extremely poor survival. There is no role for diagnostic imaging in the primary detection and characterization of vulvar cancer. However, imaging (MRI) may play a role in evaluation of the local extent of disease in advanced cases, especially if urethral invasion is suspected, as well as in the evaluation of lymphadenopathy (US, CT, MRI) and distant metastatic disease (CT and PET/CT).

Vulvar cancer appears on US as a soft-tissue mass with internal vascularity. On CT, vulvar cancer appears as a nonspecific soft-tissue mass. On MRI, it demonstrates intermediate signal intensity on T1W sequences and high signal intensity on T2W sequences (Fig. 11.30). MRI may be used to evaluate tumor extension into adjacent structures (i.e., urethra) (311,312). MRI may also be used to differentiate recurrence from posttherapy changes, with the former demonstrating high signal intensity on T2W images, and the latter demonstrating intermediate signal intensity on T2W sequences.

The surgical management of early-stage vulvar cancer is now more conservative, and an individualized approach is increasingly used to improve the outcome and reduce the complication rate related to lymphadenectomy (313). Lymphadenopathy in vulvar cancer is usually treated by surgical lymph node dissection. However, sentinel lymph node excision is now being recommended in selected patients with early-stage squamous cell carcinoma (tumor <4 cm in diameter and clinically nonsuspicious groin nodes) as a means to avoid the operative morbidity associated with inguinofemoral lymphadenectomy (314–316). Patients with tumor larger than 4 cm in diameter and with suspected groin nodes will undergo radical excision and lymphadenectomy.

The combination of lymphoscintigraphy with technetium-99 m-labeled nanocolloid and blue dye is the most accurate technique for sentinel node detection (315). Patients with a positive sentinel node should undergo a full inguinofemoral lymphadenectomy followed by a postoperative radiation therapy to the involved groin and pelvis. However, if sentinel lymph nodes are negative, no further treatment is indicated. All vulvar cancers located within 1 cm of midline structures (clitoris, vagina, or anus) have the potential to spread to both groins, and should be treated by radical wide local excision and bilateral inguinofemoral lymphadenectomy.

US combined with fine-needle aspiration biopsy (FNA) of suspicious-looking nodes has been shown to influence surgical management with sensitivity, specificity, NPV, and PPV of 80%,

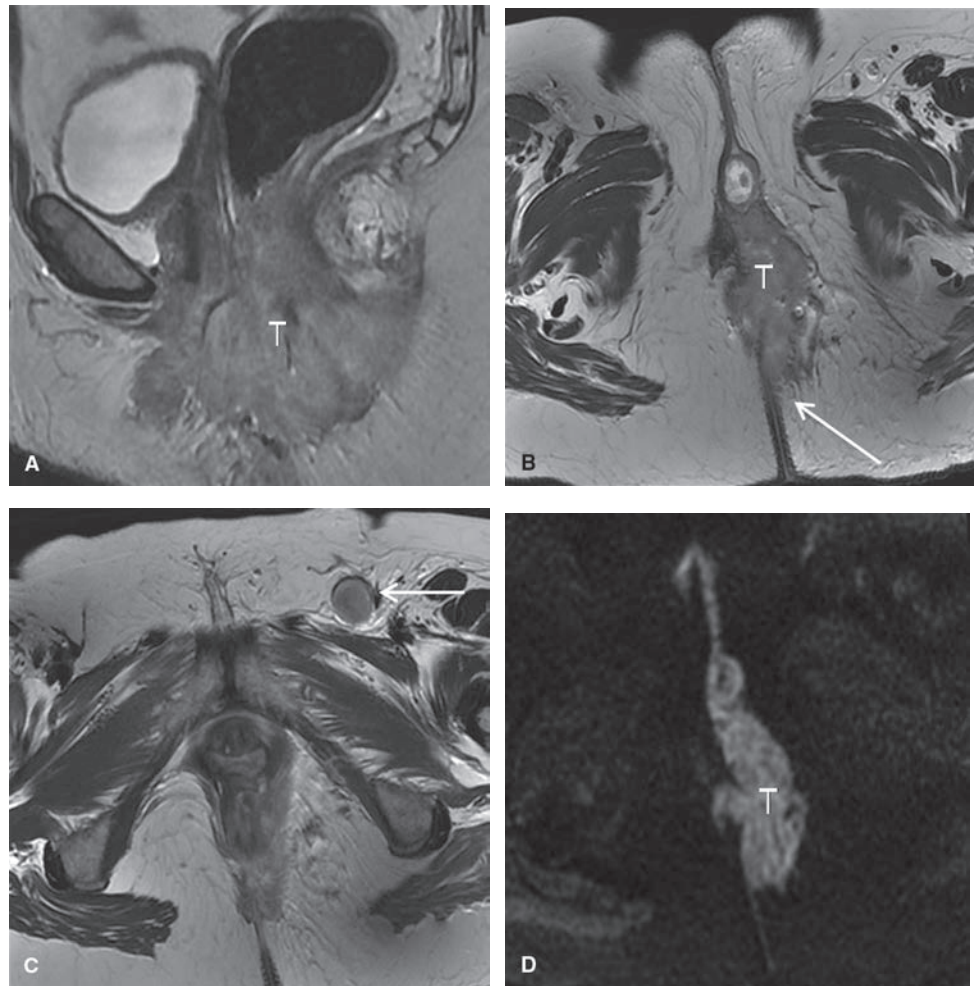


FIGURE 11.30. Vulvar carcinoma. Sagittal T2W FSE image (A), axial T2W FSE images (B, C), and DW MR image (D) demonstrate a large vulvar mass (T in A, B, D) invading the anus (arrow in B). The mass is of high signal intensity on DWI in keeping with restricted diffusion. Note presence of enlarged left inguinal lymph node (arrow in C) which proved to be metastatic at histopathology.

100%, 93%, and 100%, respectively (317–319). More recently, in a multi-center setting, high-resolution MRI sequences have been shown to achieve an accuracy of 87% in detection and characterization of inguinal (Fig. 11.30) and pelvic lymph nodes (312), indicating that MRI may be useful to triage patient for US-guided biopsy versus sentinel lymph node detection.

Very little has been published on the use of FDG-PET for vulvar cancer. In one study, FDG-PET had sensitivity of 80%, specificity of 90%, PPV of 80%, and NPV of 90% in the detection of pelvic adenopathy (320). Although these results are promising, more research in this area is needed.

CONCLUSION

Increased use of CT, MRI and PET/CT for staging gynecologic pelvic malignancies has led to a significant decline in the use of conventional and invasive radiologic studies such as intravenous urography and barium enema, which are now considered obsolete at most institutions. In addition, although US is the primary imaging modality for characterizing ovarian masses and evaluating the endometrium, US is no longer used for primary gynecologic cancer staging.

CT has a central role in pelvic imaging, mainly because of its relatively low cost, high spatial resolution, fast examination

times, and wide availability. CT is the modality of choice for staging ovarian cancer, detecting distant metastases and lymphadenopathy in endometrial and cervical cancer, and evaluating recurrent pelvic malignancies. Both US and CT are used to guide percutaneous drainage and biopsy.

MRI plays important roles in the management of gynecologic malignancies, ranging from initial evaluation of disease extent, to aiding treatment selection, to follow-up. In patients with endometrial cancer, MRI improves pretreatment risk stratification. It enables accurate surgical planning and selection of patients for pelvic or paraaortic lymph node dissection in high-risk disease, whilst obviating the need for extended surgery in patients with low-risk disease. In patients with cervical cancer, MRI improves FIGO clinical staging accuracy, leading to better treatment selection and planning. In those patients who wish to preserve fertility, MRI plays a paramount role in assessing eligibility for fertility-sparing surgical procedures. In patients with ovarian cancer, MRI is a problem-solving modality. There is growing evidence that DW-MRI may enable more accurate mapping of the extent of peritoneal disease than does CT. MRI certainly plays an important role in patients with recurrent ovarian cancer by assessing resectability in cases of solitary pelvic recurrences.

FDG-PET/CT is increasingly being used to evaluate gynecologic malignancies. It is useful in the primary staging of cervical cancer as well as the detection of recurrent ovarian, cervical, and endometrial cancers.

REFERENCES

- Griffin N, Grant LA, Freeman SJ, et al. Image-guided biopsy in patients with suspected ovarian carcinoma: a safe and effective technique? *Eur Radiol*. 2009;19(1):230–235.
- Andreotti RF, Fleischer AC, Mason LE Jr. Three-dimensional sonography of the endometrium and adjacent myometrium: preliminary observations. *J Ultrasound Med*. 2006;25(10):1313–1319.
- Hagel J, Bicknell SG. Impact of 3D sonography on workroom time efficiency. *AJR Am J Roentgenol*. 2007;188(4):966–969.
- Lev-Toaff AS. Sonohysterography: evaluation of endometrial and myometrial abnormalities. *Semin Roentgenol*. 1996;31(4):288–298.
- Sohacy R, Woodward P. Sonohysterography: technique, endometrial findings, and clinical applications. *Semin Ultrasound CT MR*. 1999;20(4):250–258.
- Lev-Toaff AS, Pinheiro LW, Bega G, et al. Three-dimensional multiplanar sonohysterography: comparison with conventional two-dimensional sonohysterography and X-ray hysterosalpingography. *J Ultrasound Med*. 2001;20(4):295–306.
- Lyons EA, Gratton D, Harrington C. Transvaginal sonography of normal pelvic anatomy. *Radiol Clin North Am*. 1992;30(4):663–675.
- Arger PH. Transvaginal ultrasonography in postmenopausal patients. *Radiol Clin North Am*. 1992;30(4):759–767.
- Levine D, Gosink BB, Johnson LA. Change in endometrial thickness in postmenopausal women undergoing hormone replacement therapy. *Radiology*. 1995;197(3):603–608.
- Hewitt MJ, Anderson K, Hall GD, et al. Women with peritoneal carcinomatosis of unknown origin: efficacy of image-guided biopsy to determine site-specific diagnosis. *Br J Obstet Gynecol*. 2007;114(1):46–50.
- Pombo F, Rodriguez E, Martin R, et al. CT-guided core-needle biopsy in omental pathology. *Acta Radiol*. 1997;38(6):978–981.
- Spencer JA, Swift SE, Wilkinson N, et al. Peritoneal carcinomatosis: image-guided peritoneal core biopsy for tumor type and patient care. *Radiology*. 2001;221(1):173–177.
- Kim SH, Choi BI, Han JK, et al. Preoperative staging of uterine cervical carcinoma: comparison of CT and MRI in 99 patients. *J Comput Assist Tomogr*. 1993;17(4):633–640.
- Kim SH, Kim HD, Song YS, et al. Detection of deep myometrial invasion in endometrial carcinoma: comparison of transvaginal ultrasound, CT, and MRI. *J Comput Assist Tomogr*. 1995;19(5):766–772.
- Kinkel K, Ariche M, Tardivon AA, et al. Differentiation between recurrent tumor and benign conditions after treatment of gynecologic pelvic carcinoma: value of dynamic contrast-enhanced subtraction MR imaging. *Radiology*. 1997;204(1):55–63.
- Dooms GC, Hricak H, Crooks LE, et al. Magnetic resonance imaging of the lymph nodes: comparison with CT. *Radiology*. 1984;153(3):719–728.
- Hricak H, Powell CB, Yu KK, et al. Invasive cervical carcinoma: role of MR imaging in pretreatment work-up-cost minimization and diagnostic efficacy analysis. *Radiology*. 1996;198(2):403–409.
- Yu KK, Hricak H. Can MRI of the pelvis be cost effective? *Abdom Imaging*. 1997;22(6):597–601.
- Hardesty LA, Sumkin JH, Nath ME, et al. Use of preoperative MR imaging in the management of endometrial carcinoma: cost analysis. *Radiology*. 2000;215(1):45–49.
- Kinkel K, Forstner R, Danza FM, et al. Staging of endometrial cancer with MRI: guidelines of the European Society of Urogenital Imaging. *Eur Radiol*. 2009;19(7):1565–1574.
- Spencer JA, Messiou C, Swift SE. MR staging of endometrial cancer: needed or wanted? *Cancer Imaging*. 2008;8:1–5.
- Hricak H, Chen M, Coakley FV, et al. Complex adnexal masses: detection and characterization with MR imaging—multivariate analysis. *Radiology*. 2000;214(1):39–46.
- Sala E. Magnetic resonance imaging of the female pelvis. *Semin Roentgenol*. 2008;43(4):290–302.
- Johnson W, Taylor MB, Carrington BM, et al. The value of hyoscine butylbromide in pelvic MRI. *Clin Radiol*. 2007;62(11):1087–1093.
- Sala E, Wakely S, Senior E, et al. MRI of malignant neoplasms of the uterine corpus and cervix. *AJR Am J Roentgenol*. 2007;188(6):1577–1587.
- deSouza NM, Dina R, McIndoe GA, et al. Cervical cancer: value of an endovaginal coil magnetic resonance imaging technique in detecting small volume disease and assessing parametrial extension. *Gynecol Oncol*. 2006;102(1):80–85.
- deSouza NM, Whittle M, Williams AD, et al. Magnetic resonance imaging of the primary site in stage I cervical carcinoma: a comparison of endovaginal coil with external phased array coil techniques at 0.5T. *J Magn Reson Imaging*. 2000;12(6):1020–1026.
- Amendola MA, Hricak H, Mitchell DG, et al. Utilization of diagnostic studies in the pretreatment evaluation of invasive cervical cancer in the United States: results of intergroup protocol ACRIN 6651/ GOG 183. *J Clin Oncol*. 2005;23(30):7454–7459.
- Balleuquier C, Sala E, Da Cunha T, et al. Staging of uterine cervical cancer with MRI: guidelines of the European Society of Urogenital Radiology. *Eur Radiol*. 2011;21(5):1102–1110.
- Shibutani O, Joia I, Shiraiwa M, et al. Endometrial carcinoma: efficacy of thin-section oblique axial MR images for evaluating cervical invasion. *Abdom Imaging*. 1999;24(5):520–526.
- Shiraiwa M, Joia I, Asakawa T, et al. Cervical carcinoma: efficacy of thin-section oblique axial T2-weighted images for evaluating parametrial invasion. *Abdom Imaging*. 1999;24(5):514–519.
- Sohaib SA, Sahdev A, Van Trappen P, et al. Characterization of adnexal mass lesions on MR imaging. *AJR Am J Roentgenol*. 2003;180(5):1297–1304.
- Thomassin-Naggara I, Bazot M, Darai E, et al. Epithelial ovarian tumors: value of dynamic contrast-enhanced MR imaging and correlation with tumor angiogenesis. *Radiology*. 2008;248(1):148–159.
- Akita A, Shinmoto H, Hayashi S, et al. Comparison of T2-weighted and contrast-enhanced T1-weighted MR imaging at 1.5 T for assessing the local extent of cervical carcinoma. *Eur Radiol*. 2011;21(9):1850–1857.
- Rechichi G, Galimberti S, Signorelli M, et al. Myometrial invasion in endometrial cancer: diagnostic performance of diffusion-weighted MR imaging at 1.5-T. *Eur Radiol*. 2009;20:754–762.
- Beddy P, Moyle P, Kataoka M, et al. Evaluation of depth of myometrial invasion and overall staging in endometrial cancer: comparison of diffusion-weighted and dynamic contrast-enhanced MR imaging. *Radiology*. 2012;262(2):530–537.
- Shen SH, Chiou YY, Wang JH, et al. Diffusion-weighted single-shot echo-planar imaging with parallel technique in assessment of endometrial cancer. *AJR Am J Roentgenol*. 2008;190(2):481–488.
- McCarthy S, Scott G, Majumdar S, et al. Uterine junctional zone: MR study of water content and relaxation properties. *Radiology*. 1989;171(1):241–243.
- Scoutt LM, Flynn SD, Luthringer DJ, et al. Junctional zone of the uterus: correlation of MR imaging and histologic examination of hysterectomy specimens. *Radiology*. 1991;179(2):403–407.
- Mitchell DG, Schonholz L, Hilpert PL, et al. Zones of the uterus: discrepancy between US and MR images. *Radiology*. 1990;174(3 Pt 1):827–831.
- Demas BE, Hricak H, Jaffe RB. Uterine MR imaging: effects of hormonal stimulation. *Radiology*. 1986;159(1):123–126.
- deSouza NM, Hall AS, Puni R, et al. High resolution magnetic resonance imaging of the anal sphincter using a dedicated endoanal coil. Comparison of magnetic resonance imaging with surgical findings. *Dis Colon Rectum*. 1996;39(8):926–934.
- Scoutt LM, McCauley TR, Flynn SD, et al. Zonal anatomy of the cervix: correlation of MR imaging and histologic examination of hysterectomy specimens. *Radiology*. 1993;186(1):159–162.
- Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009;50(suppl 1):122S–150S.
- Nishizawa S, Inubushi M, Okada H. Physiological 18F-FDG uptake in the ovaries and uterus of healthy female volunteers. *Eur J Nucl Med Mol Imaging*. 2005;32(5):549–556.
- Hricak H, Hamm B, Semelka RC, et al. Carcinoma of the uterus: use of gadopentetate dimeglumine in MR imaging. *Radiology*. 1991;181(1):95–106.
- Hricak H, Rubinstein LV, Gherman GM, et al. MR imaging evaluation of endometrial carcinoma: results of an NCI cooperative study. *Radiology*. 1991;179(3):829–832.
- Hricak H, Stern JL, Fisher MR, et al. Endometrial carcinoma staging by MR imaging. *Radiology*. 1987;162(2):297–305.
- Manfredi R, Mirk P, Maresca G, et al. Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning. *Radiology*. 2004;231(2):372–378.
- Rockall AG, Meroni R, Sohaib SA, et al. Evaluation of endometrial carcinoma on magnetic resonance imaging. *Int J Gynecol Cancer*. 2007;17(1):188–196.
- Sala E, Crawford R, Senior E, et al. Added value of dynamic contrast-enhanced magnetic resonance imaging in predicting advanced stage disease in patients with endometrial carcinoma. *Int J Gynecol Cancer*. 2009;19(1):141–146.
- Goldstein RB, Bree RL, Benson CB, et al. Evaluation of the woman with postmenopausal bleeding: Society of radiologists in ultrasound-sponsored consensus conference statement. *J Ultrasound Med*. 2001;20(10):1025–1036.
- Medverd JR, Dubinsky TJ. Cost analysis model: US versus endometrial biopsy in evaluation of peri- and postmenopausal abnormal vaginal bleeding. *Radiology*. 2002;222(3):619–627.
- Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *Jama*. 1998;280(17):1510–1517.
- Sladkevicius P, Valentin L, Marsal K. Endometrial thickness and Doppler velocimetry of the uterine arteries as discriminators of endometrial status in women with postmenopausal bleeding: a comparative study. *Am J Obstet Gynecol*. 1994;171(3):722–728.
- Dubinsky TJ, Stroehlein K, Abu-Ghazze Y, et al. Prediction of benign and malignant endometrial disease: hysterosonographic-pathologic correlation. *Radiology*. 1999;210(2):393–397.

57. Williams PL, Laifer-Narin SL, Ragavendra N. US of abnormal uterine bleeding. *Radiographics*. 2003;23(3):703–718.
58. Langer RD, Pierce JJ, O'Hanlan KA, et al. Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease. Postmenopausal Estrogen/Progestin Interventions Trial. *N Engl J Med*. 1997;337(25):1792–1798.
59. Hann LE, Giess CS, Bach AM, et al. Endometrial thickness in tamoxifen-treated patients: correlation with clinical and pathologic findings. *AJR Am J Roentgenol*. 1997;168(3):657–661.
60. Sheth S, Hamper UM, Kurman RJ. Thickened endometrium in the postmenopausal woman: sonographic-pathologic correlation. *Radiology*. 1993;187(1):135–139.
61. Sheth S, Hamper UM, McCollum ME, et al. Endometrial blood flow analysis in postmenopausal women: can it help differentiate benign from malignant causes of endometrial thickening? *Radiology*. 1995;195(3):661–665.
62. Affinito P, Palomba S, Pellicano M, et al. Ultrasonographic measurement of endometrial thickness during hormonal replacement therapy in postmenopausal women. *Ultrasound Obstet Gynecol*. 1998;11(5):343–346.
63. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009;105(2):103–104.
64. Sala E, Rockall A, Kubik-Huch RA. Advances in magnetic resonance imaging of endometrial cancer. *Eur Radiol*. 2011;21(3):468–473.
65. Kinkel K, Kaji Y, Yu KK, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. *Radiology*. 1999;212(3):711–718.
66. DelMaschio A, Vanzulli A, Sironi S, et al. Estimating the depth of myometrial involvement by endometrial carcinoma: efficacy of transvaginal sonography vs. MR imaging. *AJR Am J Roentgenol*. 1993;160(3):533–538.
67. Gruboeck K, Jurkovic D, Lawton F, et al. The diagnostic value of endometrial thickness and volume measurements by three-dimensional ultrasound in patients with postmenopausal bleeding. *Ultrasound Obstet Gynecol*. 1996;8(4):272–276.
68. Ascher SM, Reinhold C. Imaging of cancer of the endometrium. *Radiol Clin North Am*. 2002;40(3):563–576.
69. Hardesty LA, Sumkin JH, Hakim C, et al. The ability of helical CT to preoperatively stage endometrial carcinoma. *AJR Am J Roentgenol*. 2001;176(3):603–606.
70. Connor JP, Andrews JL, Anderson B, et al. Computed tomography in endometrial carcinoma. *Obstet Gynecol*. 2000;95(5):692–696.
71. Chan JK, Cheung MK, Huh WK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer*. 2006;107(8):1823–1830.
72. Dowdy SC, Mariani A. Lymphadenectomy in endometrial cancer: when, not if. *Lancet*. 2010;375(9721):1138–1140.
73. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst*. 2008;100(23):1707–1716.
74. Kitchener H, Swart AM, Qian Q, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*. 2009;373(9658):125–136.
75. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet*. 2010;375(9721):1165–1172.
76. Frei KA, Kinkel K, Bonel HM, et al. Prediction of deep myometrial invasion in patients with endometrial cancer: clinical utility of contrast-enhanced MR imaging—a meta-analysis and Bayesian analysis. *Radiology*. 2000;216(2):444–449.
77. Larson DM, Connor GP, Broste SK, et al. Prognostic significance of gross myometrial invasion with endometrial cancer. *Obstet Gynecol*. 1996;88(3):394–398.
78. Querleu D, Planchamp F, Narducci F, et al. Clinical practice guidelines for the management of patients with endometrial cancer in France: recommendations of the Institut National du Cancer and the Societe Francaise d'Oncologie Gynecologique. *Int J Gynecol Cancer*. 2011;21(5):945–950.
79. Vargas HA, Akin O, Zheng J, et al. The value of MR imaging when the site of uterine cancer origin is uncertain. *Radiology*. 2011;258(3):785–792.
80. Ito K, Matsumoto T, Nakada T, et al. Assessing myometrial invasion by endometrial carcinoma with dynamic MRI. *J Comput Assist Tomogr*. 1994;18(1):77–86.
81. Nakao Y, Yokoyama M, Hara K, et al. MR imaging in endometrial carcinoma as a diagnostic tool for the absence of myometrial invasion. *Gynecol Oncol*. 2006;102(2):343–347.
82. Seki H, Kimura M, Sakai K. Myometrial invasion of endometrial carcinoma: assessment with dynamic MR and contrast-enhanced T1-weighted images. *Clin Radiol*. 1997;52(1):18–23.
83. Sironi S, Colombo E, Villa G, et al. Myometrial invasion by endometrial carcinoma: assessment with plain and gadolinium-enhanced MR imaging. *Radiology*. 1992;185(1):207–212.
84. Yamashita Y, Harada M, Sawada T, et al. Normal uterus and FIGO stage I endometrial carcinoma: dynamic gadolinium-enhanced MR imaging. *Radiology*. 1993;186(2):495–501.
85. Lien HH, Blomlie V, Trope C, et al. Cancer of the endometrium: value of MR imaging in determining depth of invasion into the myometrium. *AJR Am J Roentgenol*. 1991;157(6):1221–1223.
86. Barwick TD, Rockall AG, Barton DP, et al. Imaging of endometrial adenocarcinoma. *Clin Radiol*. 2006;61(7):545–555.
87. Rockall AG, Sohaib SA, Harisinghani MG, et al. Diagnostic performance of nanoparticle-enhanced magnetic resonance imaging in the diagnosis of lymph node metastases in patients with endometrial and cervical cancer. *J Clin Oncol*. 2005;23(12):2813–2821.
88. Kitajima K, Murakami K, Kaji Y, et al. Established, emerging and future applications of FDG-PET/CT in the uterine cancer. *Clin Radiol*. 2011;66(4):297–307.
89. Park JY, Kim EN, Kim DY, et al. Comparison of the validity of magnetic resonance imaging and positron emission tomography/computed tomography in the preoperative evaluation of patients with uterine corpus cancer. *Gynecol Oncol*. 2008;108(3):486–492.
90. Kitajima K, Murakami K, Yamasaki E, et al. Accuracy of 18F-FDG PET/CT in detecting pelvic and paraaortic lymph node metastasis in patients with endometrial cancer. *AJR Am J Roentgenol*. 2008;190(6):1652–1658.
91. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet*. 2000;355(9213):1404–1411.
92. Sohaib SA, Houghton SL, Meroni R, et al. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. *Clin Radiol*. 2007;62(1):28–34; discussion 35–26.
93. Franchi M, La Fianza A, Babilonti L, et al. Clinical value of computerized tomography (CT) in assessment of recurrent uterine cancers. *Gynecol Oncol*. 1989;35(1):31–37.
94. Belhocine T, De Barse C, Hustinx R, et al. Usefulness of (18)F-FDG PET in the post-therapy surveillance of endometrial carcinoma. *Eur J Nucl Med Mol Imaging*. 2002;29(9):1132–1139.
95. Kitajima K, Suzuki K, Nakamoto Y, et al. Low-dose non-enhanced CT versus full-dose contrast-enhanced CT in integrated PET/CT studies for the diagnosis of uterine cancer recurrence. *Eur J Nucl Med Mol Imaging*. 2010;37(8):1490–1498.
96. Kitajima K, Murakami K, Yamasaki E, et al. Performance of FDG-PET/CT in the diagnosis of recurrent endometrial cancer. *Ann Nucl Med*. 2008;22(2):103–109.
97. Park JY, Kim EN, Kim DY, et al. Clinical impact of positron emission tomography or positron emission tomography/computed tomography in the posttherapy surveillance of endometrial carcinoma: evaluation of 88 patients. *Int J Gynecol Cancer*. 2008;18(6):1332–1338.
98. Harlow BL, Weiss NS, Lofton S. The epidemiology of sarcomas of the uterus. *J Natl Cancer Inst*. 1986;76(3):399–402.
99. Curtis RE, Freedman DM, Sherman ME, et al. Risk of malignant mixed müllerian tumors after tamoxifen therapy for breast cancer. *J Natl Cancer Inst*. 2004;96(1):70–74.
100. Huang YT, Huang KG, Ueng SH, et al. Irradiation-induced uterine malignant mixed müllerian tumor. *Taiwan J Obstet Gynecol*. 2006;45(4):353–355.
101. Bharwani N, Newland A, Tunari N, et al. MRI appearances of uterine malignant mixed müllerian tumors. *AJR Am J Roentgenol*. 2010;195(5):1268–1275.
102. Sahdev A, Sohaib SA, Jacobs I, et al. MR imaging of uterine sarcomas. *AJR Am J Roentgenol*. 2001;177(6):1307–1311.
103. Shapeero LG, Hricak H. Mixed müllerian sarcoma of the uterus: MR imaging findings. *AJR Am J Roentgenol*. 1989;153(2):317–319.
104. Teo SY, Babagbemi KT, Peters HE, et al. Primary malignant mixed müllerian tumor of the uterus: findings on sonography, CT, and gadolinium-enhanced MRI. *AJR Am J Roentgenol*. 2008;191(1):278–283.
105. Amant F, Cadron I, Fuso L, et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. *Gynecol Oncol*. 2005;98(2):274–280.
106. Callister M, Ramondetta LM, Jhingran A, et al. Malignant mixed Müllerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. *Int J Radiat Oncol Biol Phys*. 2004;58(3):786–796.
107. Vaidya AP, Horowitz NS, Oliva E, et al. Uterine malignant mixed müllerian tumors should not be included in studies of endometrial carcinoma. *Gynecol Oncol*. 2006;103(2):684–687.
108. Koyama T, Togashi K, Konishi I, et al. MR imaging of endometrial stromal sarcoma: correlation with pathologic findings. *AJR Am J Roentgenol*. 1999;173(3):767–772.
109. Ueda M, Otsuka M, Hatakenaka M, et al. MR imaging findings of uterine endometrial stromal sarcoma: differentiation from endometrial carcinoma. *Eur Radiol*. 2001;11(1):28–33.
110. Green CL, Angtuaco TL, Shah HR, et al. Gestational trophoblastic disease: a spectrum of radiologic diagnosis. *Radiographics*. 1996;16(6):1371–1384.
111. Preidler KW, Luschn G, Tamussino K, et al. Magnetic resonance imaging in patients with gestational trophoblastic disease. *Invest Radiol*. 1996;31(8):492–496.

112. Wagner BJ, Woodward PJ, Dickey GE. From the archives of the AFIP. Gestational trophoblastic disease: radiologic-pathologic correlation. *Radiographics*. 1996;16(1):131-148.
113. Benson CB, Genest DR, Bernstein MR, et al. Sonographic appearance of first trimester complete hydatidiform moles. *Ultrasound Obstet Gynecol*. 2000;16(2):188-191.
114. Lazarus E, Hulka C, Siewert B, et al. Sonographic appearance of early complete molar pregnancies. *J Ultrasound Med*. 1999;18(9):589-594; quiz 595-586.
115. Dobkin GR, Berkowitz RS, Goldstein DP, et al. Duplex ultrasonography for persistent gestational trophoblastic tumor. *J Reprod Med*. 1991;36(1):14-16.
116. Miyasaka Y, Hachiya J, Furuya Y, et al. CT evaluation of invasive trophoblastic disease. *J Comput Assist Tomogr*. 1985;9(3):459-462.
117. Su WH, Wang PH, Chang SP. Successful treatment of a persistent mole with myometrial invasion by direct injection of methotrexate. *Eur J Gynaecol Oncol*. 2001;22(4):283-286.
118. Lim AK, Agarwal R, Seckl MJ, et al. Embolization of bleeding residual uterine vascular malformations in patients with treated gestational trophoblastic tumors. *Radiology*. 2002;222(3):640-644.
119. Hricak H, Demas BE, Braga CA, et al. Gestational trophoblastic neoplasm of the uterus: MR assessment. *Radiology*. 1986;161(1):11-16.
120. Sironi S, Picchio M, Mangili G, et al. [18F] fluorodeoxyglucose positron emission tomography as a useful indicator of metastatic gestational trophoblastic tumor: preliminary results in three patients. *Gynecol Oncol*. 2003;91(1):226-230.
121. Chang TC, Yen TC, Li YT, et al. The role of 18F-fluorodeoxyglucose positron emission tomography in gestational trophoblastic tumours: a pilot study. *Eur J Nucl Med Mol Imaging*. 2006;33(2):156-163.
122. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet*. 2009;105(2):107-108.
123. Lagasse LD, Creasman WT, Shingleton HM, et al. Results and complications of operative staging in cervical cancer: experience of the Gynecologic Oncology Group. *Gynecol Oncol*. 1980;9(1):90-98.
124. Van Nagell J Jr, Roddick JW Jr, Lowin DM. The staging of cervical cancer: inevitable discrepancies between clinical and pathologic findings. *Am J Obstet Gynecol*. 1971;110(7):973-978.
125. Innocenti P, Pulli F, Savino L, et al. Staging of cervical cancer: reliability of transrectal US. *Radiology*. 1992;185(1):201-205.
126. Hricak H, Gatsonis C, Chi DS, et al. Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. *J Clin Oncol*. 2005;23(36):9329-9337.
127. Mitchell DG, Snyder B, Coakley F, et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. *J Clin Oncol*. 2006;24(36):5687-5694.
128. Hricak H, Gatsonis C, Coakley FV, et al. Early invasive cervical cancer: CT and MR imaging in preoperative evaluation—ACRIN/GOG comparative study of diagnostic performance and interobserver variability. *Radiology*. 2007;245(2):491-498.
129. Pannu HK, Fishman EK. Evaluation of cervical cancer by computed tomography: current status. *Cancer*. 2003;98(suppl 9):2039-2043.
130. Kilcheski TS, Arger PH, Mulhern CB Jr, et al. Role of computed tomography in the presurgical evaluation of carcinoma of the cervix. *J Comput Assist Tomogr*. 1981;5(3):378-383.
131. Nicolet V, Carignan L, Bourdon F, et al. MR imaging of cervical carcinoma: a practical staging approach. *Radiographics*. 2000;20(6):1539-1549.
132. Okamoto Y, Tanaka YO, Nishida M, et al. MR imaging of the uterine cervix: imaging-pathologic correlation. *Radiographics*. 2003;23(2):425-445; quiz 534-425.
133. Hricak H, Lacey CG, Sandles LG, et al. Invasive cervical carcinoma: comparison of MR imaging and surgical findings. *Radiology*. 1988;166(3):623-631.
134. Subak LL, Hricak H, Powell CB, et al. Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging. *Obstet Gynecol*. 1995;86(1):43-50.
135. Peppercorn PD, Jeyarajah AR, Woolas R, et al. Role of MR imaging in the selection of patients with early cervical carcinoma for fertility-preserving surgery: initial experience. *Radiology*. 1999;212(2):395-399.
136. Sahdev A, Jones J, Shepherd JH, et al. MR imaging appearances of the female pelvis after trachelectomy. *Radiographics*. 2005;25(1):41-52.
137. Sahdev A, Sohaib SA, Wenaden AE, et al. The performance of magnetic resonance imaging in early cervical carcinoma: a long-term experience. *Int J Gynecol Cancer*. 2007;17(3):629-636.
138. Zand KR, Reinhold C, Abe H, et al. Magnetic resonance imaging of the cervix. *Cancer Imaging*. 2007;7:69-76.
139. Scheidler J, Heuck AF. Imaging of cancer of the cervix. *Radiol Clin North Am*. 2002;40(3):577-590.
140. Sheu MH, Chang CY, Wang JH, et al. Preoperative staging of cervical carcinoma with MR imaging: a reappraisal of diagnostic accuracy and pitfalls. *Eur Radiol*. 2001;11(9):1828-1833.
141. Kaur H, Silverman PM, Iyer RB, et al. Diagnosis, staging, and surveillance of cervical carcinoma. *AJR Am J Roentgenol*. 2003;180(6):1621-1631.
142. Rockall AG, Ghosh S, Alexander-Sefre F, et al. Can MRI rule out bladder and rectal invasion in cervical cancer to help select patients for limited EUA? *Gynecol Oncol*. 2006;101(2):244-249.
143. Aoki Y, Sasaki M, Watanabe M, et al. High-risk group in node-positive patients with stage IB, IIA, and IIB cervical carcinoma after radical hysterectomy and postoperative pelvic irradiation. *Gynecol Oncol*. 2000;77(2):305-309.
144. Cheng X, Cai S, Li Z, et al. The prognosis of women with stage IB-IIB node-positive cervical carcinoma after radical surgery. *World J Surg Oncol*. 2004;2:47.
145. Larciprete G, Casalino B, Segatore MF, et al. Pelvic lymphadenectomy for cervical cancer: extraperitoneal versus laparoscopic approach. *Eur J Obstet Gynecol Reprod Biol*. 2006;126(2):259-263.
146. Addley HC, Vargas HA, Moyle PL, et al. Pelvic imaging following chemotherapy and radiation therapy for gynecologic malignancies. *Radiographics*. 2010;30(7):1843-1856.
147. Beddy P, Rangarajan RD, Sala E. Role of MRI in intracavitary brachytherapy for cervical cancer: what the radiologist needs to know. *AJR Am J Roentgenol*. 2011;196(3):W341-W347.
148. Taylor A, Rockall AG, Reznick RH, et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1604-1612.
149. Ascher SM, Takahama J, Jha RC. Staging of gynecologic malignancies. *Top Magn Reson Imaging*. 2001;12(2):105-129.
150. Rose PG, Adler LP, Rodriguez M, et al. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol*. 1999;17(1):41-45.
151. Sugawara Y, Eisbruch A, Kosuda S, et al. Evaluation of FDG PET in patients with cervical cancer. *J Nucl Med*. 1999;40(7):1125-1131.
152. Lin WC, Hung YC, Yeh LS, et al. Usefulness of (18)F-fluorodeoxyglucose positron emission tomography to detect para-aortic lymph nodal metastasis in advanced cervical cancer with negative computed tomography findings. *Gynecol Oncol*. 2003;89(1):73-76.
153. Loft A, Berthelsen AK, Roed H, et al. The diagnostic value of PET/CT scanning in patients with cervical cancer: a prospective study. *Gynecol Oncol*. 2007;106(1):29-34.
154. Reinhardt MJ, Ehrhrt-Braun C, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology*. 2001;218(3):776-782.
155. Narayan K, Hicks RJ, Jobling T, et al. A comparison of MRI and PET scanning in surgically staged loco-regionally advanced cervical cancer: potential impact on treatment. *Int J Gynecol Cancer*. 2001;11(4):263-271.
156. Magne N, Chargari C, Vicenzi L, et al. New trends in the evaluation and treatment of cervix cancer: the role of FDG-PET. *Cancer Treat Rev*. 2008;34(8):671-681.
157. Chao A, Ho KC, Wang CC, et al. Positron emission tomography in evaluating the feasibility of curative intent in cervical cancer patients with limited distant lymph node metastases. *Gynecol Oncol*. 2008;110(2):172-178.
158. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. *J Clin Oncol*. 2010;28(12):2108-2113.
159. Kidd EA, Siegel BA, Dehdashti F, et al. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. *Cancer*. 2007;110(8):1738-1744.
160. Kidd EA, Siegel BA, Dehdashti F, et al. Pelvic lymph node F-18 fluorodeoxyglucose uptake as a prognostic biomarker in newly diagnosed patients with locally advanced cervical cancer. *Cancer*. 2010;116(6):1469-1475.
161. Kidd EA, Siegel BA, Dehdashti F, et al. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010;77(4):1085-1091.
162. Ma DJ, Zhu JM, Grigsby PW. Tumor volume discrepancies between FDG-PET and MRI for cervical cancer. *Radiother Oncol*. 2011;98(1):139-142.
163. Babar S, Rockall A, Goode A, et al. Magnetic resonance imaging appearances of recurrent cervical carcinoma. *Int J Gynecol Cancer*. 2007;17(3):637-645.
164. Estape R, Angioli R. Surgical management of advanced and recurrent cervical cancer. *Semin Surg Oncol*. 1999;16(3):236-241.
165. Fulcher AS, O'Sullivan SG, Segreti EM, et al. Recurrent cervical carcinoma: typical and atypical manifestations. *Radiographics*. 1999;19 Spec No:S103-S116; quiz S264-S265.
166. Flueckiger F, Ebner F, Poschauko H, et al. Cervical cancer: serial MR imaging before and after primary radiation therapy—a 2-year follow-up study. *Radiology*. 1992;184(1):89-93.
167. Hricak H, Quivey JM, Campos Z, et al. Carcinoma of the cervix: predictive value of clinical and magnetic resonance (MR) imaging assessment of prognostic factors. *Int J Radiat Oncol Biol Phys*. 1993;27(4):791-801.

168. Hricak H, Swift PS, Campos Z, et al. Irradiation of the cervix uteri: value of unenhanced and contrast-enhanced MR imaging. *Radiology*. 1993; 189(2):381–388.
169. Zahra MA, Tan LT, Priest AN, et al. Semiquantitative and quantitative dynamic contrast-enhanced magnetic resonance imaging measurements predict radiation response in cervix cancer. *Int J Radiat Oncol Biol Phys*. 2009;74(3):766–773.
170. Mayr NA, Wang JZ, Lo SS, et al. Translating response during therapy into ultimate treatment outcome: a personalized 4-dimensional MRI tumor volumetric regression approach in cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010;76(3):719–727.
171. Mayr NA, Wang JZ, Zhang D, et al. Longitudinal changes in tumor perfusion pattern during the radiation therapy course and its clinical impact in cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010;77(2):502–508.
172. Mayr NA, Yuh WT, Jajoura D, et al. Ultra-early predictive assay for treatment failure using functional magnetic resonance imaging and clinical prognostic parameters in cervical cancer. *Cancer*. 2010;116(4):903–912.
173. Chen J, Zhang Y, Liang B, et al. The utility of diffusion-weighted MR imaging in cervical cancer. *Eur J Radiol*. 2010;74(3):e101–e106.
174. Harry VN, Semple SI, Gilbert FJ, et al. Diffusion-weighted magnetic resonance imaging in the early detection of response to chemoradiation in cervical cancer. *Gynecol Oncol*. 2008;111(2):213–220.
175. Naganawa S, Sato C, Kumada H, et al. Apparent diffusion coefficient in cervical cancer of the uterus: comparison with the normal uterine cervix. *Eur Radiol*. 2005;15(1):71–78.
176. Harry VN, Semple SI, Parkin DE, et al. Use of new imaging techniques to predict tumour response to therapy. *Lancet Oncol*. 2010;11(1):92–102.
177. Vincens E, Balleyguier C, Rey A, et al. Accuracy of magnetic resonance imaging in predicting residual disease in patients treated for stage IB2/II cervical carcinoma with chemoradiation therapy: correlation of radiologic findings with surgical pathologic results. *Cancer*. 2008;113(8):2158–2165.
178. Weber TM, Sostman HD, Spritzer CE, et al. Cervical carcinoma: determination of recurrent tumor extent versus radiation changes with MR imaging. *Radiology*. 1995;194(1):135–139.
179. Yamashita Y, Harada M, Torashima M, et al. Dynamic MR imaging of recurrent postoperative cervical cancer. *J Magn Reson Imaging*. 1996; 6(1):167–171.
180. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia*. 2009;11(2):102–125.
181. Schwarz JK, Grigsby PW, Dehdashti F, et al. The role of 18F-FDG PET in assessing therapy response in cancer of the cervix and ovaries. *J Nucl Med*. 2009;50(suppl 1):64S–73S.
182. Jover R, Lourido D, Gonzalez C, et al. Role of PET/CT in the evaluation of cervical cancer. *Gynecol Oncol*. 2008;110(3 suppl 2):S55–S59.
183. Kitajima K, Murakami K, Yamasaki E, et al. Performance of FDG-PET/CT for diagnosis of recurrent uterine cervical cancer. *Eur Radiol*. 2008;18(10):2040–2047.
184. Mittra E, El-Maghraby T, Rodriguez CA, et al. Efficacy of 18F-FDG PET/CT in the evaluation of patients with recurrent cervical carcinoma. *Eur J Nucl Med Mol Imaging*. 2009;36(12):1952–1959.
185. Pallardy A, Bodet-Milin C, Oudoux A, et al. Clinical and survival impact of FDG PET in patients with suspicion of recurrent cervical carcinoma. *Eur J Nucl Med Mol Imaging*. 2010; 37(7):1270–1278.
186. Brooks RA, Rader JS, Dehdashti F, et al. Surveillance FDG-PET detection of asymptomatic recurrences in patients with cervical cancer. *Gynecol Oncol*. 2009;112(1):104–109.
187. Cannistra SA. Cancer of the ovary. *N Engl J Med*. 2004;351(24):2519–2529.
188. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
189. Schwartz PE. Nongenetic screening of ovarian malignancies. *Obstet Gynecol Clin North Am*. 2001;28(4):637–651.
190. Taylor KJ, Schwartz PE. Screening for early ovarian cancer. *Radiology*. 1994;192(1):1–10.
191. National Institutes of Health Consensus Development Conference Statement. Ovarian cancer: screening, treatment, and follow-up. *Gynecol Oncol*. 1994;55(3 Pt 2):S4–S14.
192. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. *Jama*. 1997;277(12):997–1003.
193. Burke W, Petersen G, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. *Jama*. 1997;277(11):915–919.
194. Troiano RN, Quedens-Cas C, Taylor KJ. Correlation of findings on transvaginal sonography with serum CA 125 levels. *AJR Am J Roentgenol*. 1997;168(6):1587–1590.
195. Olivier RI, Lubsen-Brandtsma MA, Verhoef S, et al. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. *Gynecol Oncol*. 2006;100(1):20–26.
196. Buys SS, Partridge E, Greene MH, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. *Am J Obstet Gynecol*. 2005;193(5): 1630–1639.
197. van Nagell JR Jr, DePriest PD, Ueland FR, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. *Cancer*. 2007;109(9):1887–1896.
198. Buy JN, Ghossain MA, Hugol D, et al. Characterization of adnexal masses: combination of color Doppler and conventional sonography compared with spectral Doppler analysis alone and conventional sonography alone. *AJR Am J Roentgenol*. 1996;166(2):385–393.
199. Jain KA. Prospective evaluation of adnexal masses with endovaginal gray-scale and duplex and color Doppler US: correlation with pathologic findings. *Radiology*. 1994;191(1):63–67.
200. Stein SM, Laifer-Narin S, Johnson MB, et al. Differentiation of benign and malignant adnexal masses: relative value of gray-scale, color Doppler, and spectral Doppler sonography. *AJR Am J Roentgenol*. 1995;164(2):381–386.
201. Fleischer AC, Brader KR. Sonographic depiction of ovarian vascularity and flow: current improvements and future applications. *J Ultrasound Med*. 2001;20(3):241–250.
202. Hamper UM, Sheth S, Abbas FM, et al. Transvaginal color Doppler sonography of adnexal masses: differences in blood flow impedance in benign and malignant lesions. *AJR Am J Roentgenol*. 1993;160(6):1225–1228.
203. Levine D, Feldstein VA, Babcock CJ, et al. Sonography of ovarian masses: poor sensitivity of resistive index for identifying malignant lesions. *AJR Am J Roentgenol*. 1994;162(6):1355–1359.
204. Brown DL, Doubilet PM, Miller FH, et al. Benign and malignant ovarian masses: selection of the most discriminating gray-scale and Doppler sonographic features. *Radiology*. 1998;208(1):103–110.
205. DePriest PD, Varner E, Powell J, et al. The efficacy of a sonographic morphology index in identifying ovarian cancer: a multi-institutional investigation. *Gynecol Oncol*. 1994;55(2):174–178.
206. Timmerman D, Schwarzler P, Collins WP, et al. Subjective assessment of adnexal masses with the use of ultrasonography: an analysis of interobserver variability and experience. *Ultrasound Obstet Gynecol*. 1999;13(1):11–16.
207. Kinkel K, Hricak H, Lu Y, et al. US characterization of ovarian masses: a meta-analysis. *Radiology*. 2000;217(3):803–811.
208. Cohen LS, Escobar PF, Scharm C, et al. Three-dimensional power Doppler ultrasound improves the diagnostic accuracy for ovarian cancer prediction. *Gynecol Oncol*. 2001;82(1):40–48.
209. Fleischer AC, Lyschick A, Jones HW 3rd, et al. Diagnostic parameters to differentiate benign from malignant ovarian masses with contrast-enhanced transvaginal sonography. *J Ultrasound Med*. 2009;28(10):1273–1280.
210. Marret H, Sauguet S, Giraudeau B, et al. Contrast-enhanced sonography helps in discrimination of benign from malignant adnexal masses. *J Ultrasound Med*. 2004;23(12):1629–1639; quiz 1641–1642.
211. Orden MR, Jurvelin JS, Kirkinen PP. Kinetics of a US contrast agent in benign and malignant adnexal tumors. *Radiology*. 2003;226(2):405–410.
212. Buy JN, Ghossain MA, Sciort C, et al. Epithelial tumors of the ovary: CT findings and correlation with US. *Radiology*. 1991;178(3):811–818.
213. Ghossain MA, Buy JN, Ligneres C, et al. Epithelial tumors of the ovary: comparison of MR and CT findings. *Radiology*. 1991;181(3):863–870.
214. Zhang J, Mironov S, Hricak H, et al. Characterization of adnexal masses using feature analysis at contrast-enhanced helical computed tomography. *J Comput Assist Tomogr*. 2008;32(4):533–540.
215. Kim SH, Kim WH, Park KJ, et al. CT and MR findings of Krukenberg tumors: comparison with primary ovarian tumors. *J Comput Assist Tomogr*. 1996;20(3):393–398.
216. Stevens SK, Hricak H, Stern JL. Ovarian lesions: detection and characterization with gadolinium-enhanced MR imaging at 1.5 T. *Radiology*. 1991;181(2):481–488.
217. Van Vierzen PB, Massuger LF, Ruys SH, et al. Borderline ovarian malignancy: ultrasound and fast dynamic MR findings. *Eur J Radiol*. 1998;28(2):136–142.
218. Dilks P, Narayanan P, Reznick R, et al. Can quantitative dynamic contrast-enhanced MRI independently characterize an ovarian mass? *Eur Radiol*. 2010;20(9):2176–2183.
219. Nakayama T, Yoshimitsu K, Irie H, et al. Diffusion-weighted echo-planar MR imaging and ADC mapping in the differential diagnosis of ovarian cystic masses: usefulness of detecting keratinoid substances in mature cystic teratomas. *J Magn Reson Imaging*. 2005;22(2):271–278.
220. Thomassin-Naggara I, Darai E, Cuenod CA, et al. Contribution of diffusion-weighted MR imaging for predicting benignity of complex adnexal masses. *Eur Radiol*. 2009;19(6):1544–1552.
221. Katayama M, Masui T, Kobayashi S, et al. Diffusion-weighted echo planar imaging of ovarian tumors: is it useful to measure apparent diffusion coefficients? *J Comput Assist Tomogr*. 2002;26(2):250–256.
222. Thomassin-Naggara I, Toussaint I, Perrot N, et al. Characterization of complex adnexal masses: value of adding perfusion- and diffusion-weighted MR imaging to conventional MR imaging. *Radiology*. 2010;258(3):793–803.

223. Hubner KF, McDonald TW, Niethammer JG, et al. Assessment of primary and metastatic ovarian cancer by positron emission tomography (PET) using 2-[18F]deoxyglucose (2-[18F]FDG). *Gynecol Oncol*. 1993;51(2):197–204.
224. Risum S, Hogdall C, Loft A, et al. The diagnostic value of PET/CT for primary ovarian cancer—a prospective study. *Gynecol Oncol*. 2007;105(1):145–149.
225. Castellucci P, Perrone AM, Picchio M, et al. Diagnostic accuracy of 18F-FDG PET/CT in characterizing ovarian lesions and staging ovarian cancer: correlation with transvaginal ultrasonography, computed tomography, and histology. *Nucl Med Commun*. 2007;28(8):589–595.
226. Hornung R, Urs E, Serenella E, et al. Analysis of potential prognostic factors in 111 patients with ovarian cancer. *Cancer Lett*. 2004;206(1):97–106.
227. Munstedt K, Franke FE. Role of primary surgery in advanced ovarian cancer. *World J Surg Oncol*. 2004;2(1):32.
228. Huober J, Meyer A, Wagner U, et al. The role of neoadjuvant chemotherapy and interval laparotomy in advanced ovarian cancer. *J Cancer Res Clin Oncol*. 2002;128(3):153–160.
229. Schwartz PE, Chambers JT, Makuch R. Neoadjuvant chemotherapy for advanced ovarian cancer. *Gynecol Oncol*. 1994;53(1):33–37.
230. van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med*. 1995;332(10):629–634.
231. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med*. 2010;363(10):943–953.
232. Kurtz AB, Tsimikas JV, Tempany CM, et al. Diagnosis and staging of ovarian cancer: comparative values of Doppler and conventional US, CT, and MR imaging correlated with surgery and histopathologic analysis—report of the Radiology Diagnostic Oncology Group. *Radiology*. 1999;212(1):19–27.
233. Tempany CM, Zou KH, Silverman SG, et al. Staging of advanced ovarian cancer: comparison of imaging modalities—report from the Radiological Diagnostic Oncology Group. *Radiology*. 2000;215(3):761–767.
234. Coakley FV. Staging ovarian cancer: role of imaging. *Radiol Clin North Am*. 2002;40(3):609–636.
235. Coakley FV, Choi PH, Gougoutas CA, et al. Peritoneal metastases: detection with spiral CT in patients with ovarian cancer. *Radiology*. 2002;223(2):495–499.
236. Chi DS, Abu-Rustum NR, Sonoda Y, et al. The benefit of video-assisted thoracoscopic surgery before planned abdominal exploration in patients with suspected advanced ovarian cancer and moderate to large pleural effusions. *Gynecol Oncol*. 2004;94(2):307–311.
237. Eitan R, Levine DA, Abu-Rustum N, et al. The clinical significance of malignant pleural effusions in patients with optimally debulked ovarian carcinoma. *Cancer*. 2005;103(7):1397–1401.
238. Juretzka MM, Abu-Rustum NR, Sonoda Y, et al. The impact of video-assisted thoracic surgery (VATS) in patients with suspected advanced ovarian malignancies and pleural effusions. *Gynecol Oncol*. 2007;104(3):670–674.
239. Mironov O, Ishill NM, Mironov S, et al. Pleural effusion detected at CT prior to primary cytoreduction for stage III or IV ovarian carcinoma: effect on survival. *Radiology*. 2011;258(3):776–784.
240. Chi DS, McCaughy K, Diaz JP, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. *Cancer*. 2006;106(9):1933–1939.
241. Morgan RJ Jr, Alvarez RD, Armstrong DK, et al. NCCN Clinical Practice Guidelines in Oncology: epithelial ovarian cancer. *J Natl Compr Canc Netw*. 2011;9(1):82–113.
242. Qayyum A, Coakley FV, Westphalen AC, et al. Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer. *Gynecol Oncol*. 2005;96(2):301–306.
243. Forstner R, Hricak H, Occhipinti KA, et al. Ovarian cancer: staging with CT and MR imaging. *Radiology*. 1995;197(3):619–626.
244. Buy JN, Moss AA, Ghossain MA, et al. Peritoneal implants from ovarian tumors: CT findings. *Radiology*. 1988;169(3):691–694.
245. Coakley FV, Hricak H. Imaging of peritoneal and mesenteric disease: key concepts for the clinical radiologist. *Clin Radiol*. 1999;54(9):563–574.
246. Forstner R, Hricak H, Powell CB, et al. Ovarian cancer recurrence: value of MR imaging. *Radiology*. 1995;196(3):715–720.
247. Meyer JJ, Kennedy AW, Friedman R, et al. Ovarian carcinoma: value of CT in predicting success of debulking surgery. *AJR Am J Roentgenol*. 1995;165(4):875–878.
248. Pannu HK, Bristow RE, Montz FJ, et al. Multidetector CT of peritoneal carcinomatosis from ovarian cancer. *Radiographics*. 2003;23(3):687–701.
249. Cooper C, Jeffrey RB, Silverman PM, et al. Computed tomography of omental pathology. *J Comput Assist Tomogr*. 1986;10(1):62–66.
250. Akin O, Sala E, Moskowitz CS, et al. Peritoneal metastases from ovarian cancer: sensitivity and specificity of CT for the detection of metastases with and those without liver parenchymal invasion. *Radiology*. 2008;248(2):511–517.
251. Levy AD, Shaw JC, Sobin LH. Secondary tumors and tumorlike lesions of the peritoneal cavity: imaging features with pathologic correlation. *Radiographics*. 2009;29(2):347–373.
252. Moran BJ, Cecil TD. The etiology, clinical presentation, and management of pseudomyxoma peritonei. *Surg Oncol Clin N Am*. 2003;12(3):585–603.
253. Mitchell DG, Hill MC, Hill S, et al. Serous carcinoma of the ovary: CT identification of metastatic calcified implants. *Radiology*. 1986;158(3):649–652.
254. Burkill GJ, Allen SD, A'Hern RP, et al. Significance of tumour calcification in ovarian carcinoma. *Br J Radiol*. 2009;82(980):640–644.
255. Okada S, Ohaki Y, Inoue K, et al. Calcifications in mucinous and serous cystic ovarian tumors. *J Nihon Med Sch*. 2005;72(1):29–33.
256. Tangjitgamol S, Manusirivithaya S, Sheanakul C, et al. Can we rely on the size of the lymph node in determining nodal metastasis in ovarian carcinoma? *Int J Gynecol Cancer*. 2003;13(3):297–302.
257. Chan JK, Urban R, Hu JM, et al. The potential therapeutic role of lymph node resection in epithelial ovarian cancer: a study of 13918 patients. *Br J Cancer*. 2007;96(12):1817–1822.
258. Panici PB, Maggioni A, Hacker N, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. *J Natl Cancer Inst*. 2005;97(8):560–566.
259. Ricke J, Sehoul J, Hach C, et al. Prospective evaluation of contrast-enhanced MRI in the depiction of peritoneal spread in primary or recurrent ovarian cancer. *Eur Radiol*. 2003;13(5):943–949.
260. Fujii S, Matsusue E, Kanasaki Y, et al. Detection of peritoneal dissemination in gynecological malignancy: evaluation by diffusion-weighted MR imaging. *Eur Radiol*. 2008;18(1):18–23.
261. Sala E, Priest AN, Kataoka M, et al. Apparent diffusion coefficient and vascular signal fraction measurements with magnetic resonance imaging: feasibility in metastatic ovarian cancer at 3 Tesla: technical development. *Eur Radiol*. 2010;20(2):491–496.
262. Kyriazi S, Collins DJ, Messiou C, et al. Metastatic ovarian and primary peritoneal cancer: assessing chemotherapy response with diffusion-weighted MR imaging—value of histogram analysis of apparent diffusion coefficients. *Radiology*. 2011;261(1):182–192.
263. Kyriazi S, Collins DJ, Morgan VA, et al. Diffusion-weighted imaging of peritoneal disease for noninvasive staging of advanced ovarian cancer. *Radiographics*. 2011;30(5):1269–1285.
264. Kyriazi S, Kaye SB, deSouza NM. Imaging ovarian cancer and peritoneal metastases—current and emerging techniques. *Nat Rev Clin Oncol*. 2010;7(7):381–393.
265. Kyriazi S, Nye E, Stamp G, et al. Value of diffusion-weighted imaging for assessing site-specific response of advanced ovarian cancer to neoadjuvant chemotherapy: correlation of apparent diffusion coefficients with epithelial and stromal densities on histology. *Cancer Biomark*. 2010;7(4):201–210.
266. Low RN, Gurney J. Diffusion-weighted MRI (DWI) in the oncology patient: value of breath-hold DWI compared to unenhanced and gadolinium-enhanced MRI. *J Magn Reson Imaging*. 2007;25(4):848–858.
267. Low RN, Sebrechts CP, Barone RM, et al. Diffusion-weighted MRI of peritoneal tumors: comparison with conventional MRI and surgical and histopathologic findings—a feasibility study. *AJR Am J Roentgenol*. 2009;193(2):461–470.
268. Sala E, Priest AN, Kataoka M, et al. Apparent diffusion coefficient and vascular signal fraction measurements with magnetic resonance imaging: feasibility in metastatic ovarian cancer at 3 Tesla: technical development. *Eur Radiol*. 2010;20(2):491–496.
269. Risum S, Hogdall C, Loft A, et al. Does the use of diagnostic PET/CT cause stage migration in patients with primary advanced ovarian cancer? *Gynecol Oncol*. 2010;116(3):395–398.
270. Dirisamer A, Schima W, Heinisch M, et al. Detection of histologically proven peritoneal carcinomatosis with fused 18F-FDG-PET/MDCT. *Eur J Radiol*. 2009;69(3):536–541.
271. Kitajima K, Murakami K, Yamasaki E, et al. Diagnostic accuracy of integrated FDG-PET/contrast-enhanced CT in staging ovarian cancer: comparison with enhanced CT. *Eur J Nucl Med Mol Imaging*. 2008;35(10):1912–1920.
272. Yoshida Y, Kurokawa T, Kawahara K, et al. Incremental benefits of FDG positron emission tomography over CT alone for the preoperative staging of ovarian cancer. *AJR Am J Roentgenol*. 2004;182(1):227–233.
273. Nakamoto Y, Saga T, Ishimori T, et al. Clinical value of positron emission tomography with FDG for recurrent ovarian cancer. *AJR Am J Roentgenol*. 2001;176(6):1449–1454.
274. Rose PG, Faulhaber P, Miraldi F, et al. Positive emission tomography for evaluating a complete clinical response in patients with ovarian or peritoneal carcinoma: correlation with second-look laparotomy. *Gynecol Oncol*. 2001;82(1):17–21.

275. Gadducci A, Cosio S. Surveillance of patients after initial treatment of ovarian cancer. *Crit Rev Oncol Hematol*. 2009;71(1):43–52.
276. Folk JJ, Botsford M, Musa AG. Monitoring cancer antigen 125 levels in induction chemotherapy for epithelial ovarian carcinoma and predicting outcome of second-look procedure. *Gynecol Oncol*. 1995;57(2):178–182.
277. Patsner B, Orr JW Jr, Mann WJ, et al. Does serum CA-125 level prior to second-look laparotomy for invasive ovarian adenocarcinoma predict size of residual disease? *Gynecol Oncol*. 1990;38(3):373–376.
278. Rubin SC, Hoskins WJ, Hakes TB, et al. Serum CA 125 levels and surgical findings in patients undergoing secondary operations for epithelial ovarian cancer. *Am J Obstet Gynecol*. 1989;160(3):667–671.
279. Funt SA, Hricak H. Ovarian malignancies. *Top Magn Reson Imaging*. 2003;14(4):329–337.
280. Murolo C, Costantini S, Foglia G, et al. Ultrasound examination in ovarian cancer patients. A comparison with second look laparotomy. *J Ultrasound Med*. 1989;8(8):441–443.
281. Khan O, Cosgrove DO, Fried AM, et al. Ovarian carcinoma follow-up: US versus laparotomy. *Radiology*. 1986;159(1):111–113.
282. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol*. 2002;20(5):1248–1259.
283. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21(17):3194–3200.
284. Prefontaine M, Gelfand AT, Donovan JT, et al. Reproducibility of tumor measurements in ovarian cancer: a study of interobserver variability. *Gynecol Oncol*. 1994;55(1):87–90.
285. Aletti GD, Gostout BS, Podratz KC, et al. Ovarian cancer surgical resectability: relative impact of disease, patient status, and surgeon. *Gynecol Oncol*. 2006;100(1):33–37.
286. Chi DS, Ramirez PT, Teitcher JB, et al. Prospective study of the correlation between postoperative computed tomography scan and primary surgeon assessment in patients with advanced ovarian, tubal, and peritoneal carcinoma reported to have undergone primary surgical cytoreduction to residual disease 1 cm or less. *J Clin Oncol*. 2007;25(31):4946–4951.
287. Sala E, Mannelli L, Yamamoto K, et al. The value of postoperative/preadjuvant chemotherapy computed tomography in the management of patients with ovarian cancer. *Int J Gynecol Cancer*. 2011;21:296–301.
288. Funt SA, Hricak H, Abu-Rustum N, et al. Role of CT in the management of recurrent ovarian cancer. *AJR Am J Roentgenol*. 2004;182(2):393–398.
289. Prayer L, Kainz C, Kramer J, et al. CT and MR accuracy in the detection of tumor recurrence in patients treated for ovarian cancer. *J Comput Assist Tomogr*. 1993;17(4):626–632.
290. Sala E, Kataoka M, Pandit-Taskar N, et al. Recurrent ovarian cancer: use of contrast-enhanced CT and PET/CT to accurately localize tumor recurrence and to predict patients' survival. *Radiology*. 2010;257(1):125–134.
291. Low RN, Duggan B, Barone RM, et al. Treated ovarian cancer: MR imaging, laparotomy reassessment, and serum CA-125 values compared with clinical outcome at 1 year. *Radiology*. 2005;235(3):918–926.
292. Sironi S, Messa C, Mangili G, et al. Integrated FDG PET/CT in patients with persistent ovarian cancer: correlation with histologic findings. *Radiology*. 2004;233(2):433–440.
293. Thrall MM, DeLoia JA, Gallion H, et al. Clinical use of combined positron emission tomography and computed tomography (FDG-PET/CT) in recurrent ovarian cancer. *Gynecol Oncol*. 2007;105(1):17–22.
294. Fagotti A, Fanfani F, Rossitto C, et al. A treatment selection protocol for recurrent ovarian cancer patients: the role of FDG-PET/CT and staging laparoscopy. *Oncology*. 2008;75(3–4):152–158.
295. Pannu HK, Cohade C, Bristow RE, et al. PET-CT detection of abdominal recurrence of ovarian cancer: radiologic-surgical correlation. *Abdom Imaging*. 2004;29(3):398–403.
296. Risum S, Hogdall C, Markova E, et al. Influence of 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography on recurrent ovarian cancer diagnosis and on selection of patients for secondary cytoreductive surgery. *Int J Gynecol Cancer*. 2009;19(4):600–604.
297. Kubik-Huch RA, Dorffler W, von Schulthess GK, et al. Value of (18F)-FDG positron emission tomography, computed tomography, and magnetic resonance imaging in diagnosing primary and recurrent ovarian carcinoma. *Eur Radiol*. 2000;10(5):761–767.
298. Sebastian S, Lee SI, Horowitz NS, et al. PET-CT vs. CT alone in ovarian cancer recurrence. *Abdom Imaging*. 2008;33(1):112–118.
299. Gu P, Pan LL, Wu SQ, et al. CA 125, PET, CT, and MRI in diagnosing recurrent ovarian carcinoma: a systematic review and meta-analysis. *Eur J Radiol*. 2009;71(1):164–174.
300. Havrilesky LJ, Kulasingam SL, Matchar DB, et al. FDG-PET for management of cervical and ovarian cancer. *Gynecol Oncol*. 2005;97(1):183–191.
301. Fulham MJ, Carter J, Baldey A, et al. The impact of PET-CT in suspected recurrent ovarian cancer: a prospective multi-centre study as part of the Australian PET Data Collection Project. *Gynecol Oncol*. 2009;112(3):462–468.
302. Mangili G, Picchio M, Sironi S, et al. Integrated PET/CT as a first-line re-staging modality in patients with suspected recurrence of ovarian cancer. *Eur J Nucl Med Mol Imaging*. 2007;34(5):658–666.
303. Simcock B, Neesham D, Quinn M, et al. The impact of PET/CT in the management of recurrent ovarian cancer. *Gynecol Oncol*. 2006;103(1):271–276.
304. Soussan M, Wartski M, Cherel P, et al. Impact of FDG PET-CT imaging on the decision making in the biologic suspicion of ovarian carcinoma recurrence. *Gynecol Oncol*. 2008;108(1):160–165.
305. Avril N, Sassen S, Schmalfeldt B, et al. Prediction of response to neoadjuvant chemotherapy by sequential F-18-fluorodeoxyglucose positron emission tomography in patients with advanced-stage ovarian cancer. *J Clin Oncol*. 2005;23(30):7445–7453.
306. Nishiyama Y, Yamamoto Y, Kanenishi K, et al. Monitoring the neoadjuvant therapy response in gynecological cancer patients using FDG PET. *Eur J Nucl Med Mol Imaging*. 2008;35(2):287–295.
307. Chang SD. Imaging of the vagina and vulva. *Radiol Clin North Am*. 2002;40(3):637–658.
308. Chang YC, Hricak H, Thurnher S, et al. Vagina: evaluation with MR imaging. Part II. Neoplasms. *Radiology*. 1988;169(1):175–179.
309. Griffin N, Grant LA, Sala E. Magnetic resonance imaging of vaginal and vulval pathology. *Eur Radiol*. 2008;18(6):1269–1280.
310. Lamoaux WT, Grigsby PW, Dehdashti F, et al. FDG-PET evaluation of vaginal carcinoma. *Int J Radiat Oncol Biol Phys*. 2005;62(3):733–737.
311. Sohaib SA, Richards PS, Ind T, et al. MR imaging of carcinoma of the vulva. *AJR Am J Roentgenol*. 2002;178(2):373–377.
312. Kataoka MY, Sala E, Baldwin P, et al. The accuracy of magnetic resonance imaging in staging of vulvar cancer: a retrospective multi-centre study. *Gynecol Oncol*. 2010;117(1):82–87.
313. de Hullu JA, van der Zee AG. Groin surgery and the sentinel lymph node. *Best Pract Res Clin Obstet Gynaecol*. 2003;17(4):571–589.
314. Decesare SL, Fiorica JV, Roberts WS, et al. A pilot study utilizing intraoperative lymphoscintigraphy for identification of the sentinel lymph nodes in vulvar cancer. *Gynecol Oncol*. 1997;66(3):425–428.
315. Fons G, ter Rahe B, Sloof G, et al. Failure in the detection of the sentinel lymph node with a combined technique of radioactive tracer and blue dye in a patient with cancer of the vulva and a single positive lymph node. *Gynecol Oncol*. 2004;92(3):981–984.
316. Levenback C, Coleman RL, Burke TW, et al. Intraoperative lymphatic mapping and sentinel node identification with blue dye in patients with vulvar cancer. *Gynecol Oncol*. 2001;83(2):276–281.
317. Land R, Herod J, Moskovic E, et al. Routine computerized tomography scanning, groin ultrasound with or without fine needle aspiration cytology in the surgical management of primary squamous cell carcinoma of the vulva. *Int J Gynecol Cancer*. 2006;16(1):312–317.
318. Hall TB, Barton DP, Trott PA, et al. The role of ultrasound-guided cytology of groin lymph nodes in the management of squamous cell carcinoma of the vulva: 5-year experience in 44 patients. *Clin Radiol*. 2003;58(5):367–371.
319. Moskovic EC, Shepherd JH, Barton DP, et al. The role of high resolution ultrasound with guided cytology of groin lymph nodes in the management of squamous cell carcinoma of the vulva: a pilot study. *Br J Obstet Gynaecol*. 1999;106(8):863–867.
320. Cohn DE, Dehdashti F, Gibb RK, et al. Prospective evaluation of positron emission tomography for the detection of groin node metastases from vulvar cancer. *Gynecol Oncol*. 2002;85(1):179–184.

Biologic and Physical Principles of Radiation Oncology

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RADIATION ONCOLOGY AS A SPECIALTY

Radiation oncology is a specialty focused primarily on the treatment of malignancies, although there are a number of benign diseases for which radiation can be used. Training in radiation oncology begins with internship, followed by 4 years of residency. Board certification follows, requiring successful completion of both written and oral exams. Residency training includes an in-depth understanding of the natural history and treatment of all malignancies including the roles of surgery and systemic therapy in this era of multimodality therapies. An in-depth understanding of surgical procedures, pathology, and radiologic anatomy, as well as the efficacies and toxicities of systemic therapy, is required. Formal instruction in physics and radiobiology is also part of the residency training. Subspecialization can follow with a specific practice focus on gynecologic or other cancers. Only a few centers sponsor fellowships, which are usually focused on brachytherapy or other special procedures. Brachytherapy skills are especially important in the curative treatment of patients with gynecologic cancer. In addition, contemporary treatment of gynecologic malignancies requires mastery of rapidly evolving technology for delivering external beam irradiation with techniques such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). Radiation oncologists are important contributors in the management of individual patients and in multidisciplinary tumor boards. Having a knowledgeable and subspecialized radiation oncologist and gynecologic oncologist paired is a great benefit to all. In addition to radiation oncologists, other allied health professionals are integral to the radiation oncology department and treatment delivery. Radiation therapists are the individuals who actually operate the radiation equipment and deliver the radiation treatments. Some of them will obtain a Bachelor of Science degree followed by a 13-month training program in radiation therapy. Alternatively, a 2-year associate degree in diagnostic radiology can be obtained followed by 1 to 2 years in radiation therapy training. Dosimetrists are primarily responsible for planning the radiation therapy or dosimetry prior to treatment delivery. Most of these individuals are former radiation therapists. An additional 1 to 2 years of training under a physicist and board-certified dosimetrist and additional years of practice are required to be eligible for board certification. Radiation physicists supervise and review the work of dosimetrists. Physicists are also integral to the introduction and maintenance of the rapidly evolving technology in radiation oncology departments. They are very involved with quality assurance and radiation safety. They can be Master's-level or PhD-level physicists and should be board certified.

INTRODUCTION TO RADIOBIOLOGY

Radiobiology is the study of the action of ionizing radiations on living things (1). It is important for radiation oncologists to know the most appropriate dose to potentially eradicate the tumor and the normal tissue tolerance doses for those organs in the radiation field. The published literature includes clinical and laboratory data to support various dose/fractionation schemes as well as acceptable dose ranges to the normal tissues. The size and histology of the tumor as well as the relationship of the tumor to the normal organs within the radiation field will help to determine the total dose and the dose per fraction. Almost every radiation oncologist approaches treatment planning by considering whether the therapy is curative versus palliative. If curative, then the focus becomes identifying the location of the disease and how best to eradicate it. Typically, radiation and chemotherapy treatments take place over many months, and upon completion of treatment, if there is still a clonogenically viable cell that remains, then the tumor will ultimately recur. Clinical radiobiology focuses on steps that maximize the chance for cure and decrease the chance for side effects.

As in pharmacology, radiation effects exhibit a sigmoidal dose-response curve. In the case of radiation, the interpretation of the curve becomes far more complex because multiple independent processes govern responses to radiation. Pharmacology, on the other hand, tends to be simpler because classic examples can be described by a ligand binding to a group of receptors initiating subsequent events. Keeping this in mind, consider the following theoretical dose-response curve for tumor control probability and normal tissue complications in the presence and absence of chemotherapy (Fig. 12.1). Ideally, there is a great deal of separation between the curve on the left, representing chances of tumor control, and the curve on the right, representing the chance for toxicity. An intolerable situation is where the curves are close together since, as they approach one another, the chances of control and toxicity become equal and the therapeutic range (TR) narrows. Therefore, the most important goal of radiobiology is to understand the basic science behind the interaction of radiation and cells with the hope of maximizing the risk-benefit ratio for patients.

Models for Cell Kill

Tumor Control Probability

The simplest model one can envision for the sterilization of cancer cells by radiation in a given volume is the log cell kill model. A typical course of radiation therapy is given in 10 to 40 fractions

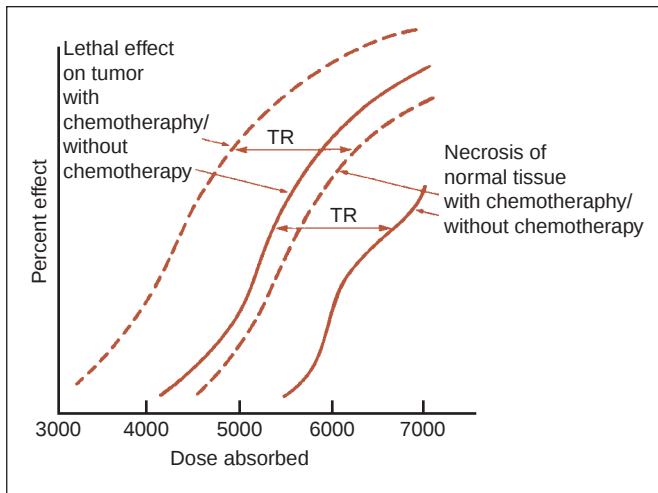


FIGURE 12.1. Theoretic curves for tumor control and complications as a function of radiation dose both with and without chemotherapy. TR, therapeutic range, or the difference between tumor control and complication frequency.

Source: Reprinted from Perez CA, Thomas PRM. Radiation therapy: basic concepts and clinical implications. In: Sutow VVV, Fernbach DJ, Vietti TJ, eds. *Clinical Pediatric Oncology*. 3rd ed. St. Louis: Mosby; 1984:167, with permission from Elsevier.

administered over 2 to 8 weeks. Each fraction kills a fixed percentage of cells. We are trained at a young age to mathematically think in base 10, and therefore a convenient number to consider is the D_{10} or the dose that kills 90% of the cells. If there are 100 cells and a D_{10} dose is administered, 10 viable cells remain. D_{01} , a commonly used term, is the dose of radiation that kills 63% of cells. D_{01} is related to the more convenient parameter D_{10} by the following formula: $D_{10} = 2.3 \times D_{01}$. Consider a tumor 1 g in size, which has 10^9 cells. If the D_{10} for this tumor is 3 Gy, how many fractions are required for a 90% chance of sterilization? The log cell kill model gets slightly more complicated when dealing in fractions, as 1/10 of a viable cell does not exist. Instead, 0.1 cells represent a 10% chance that a viable cell will exist at the end of therapy. Therefore, a tumor with 10^9 cells requires 10 decades of cell kill for a 90% chance of tumor control. Three Gy $\times$ 10 fractions = 30 Gy total dose. This model makes a number of invalid assumptions such as D_{10} remaining constant throughout the course of radiation. As discussed later, there are data that support D_{10} both increasing and decreasing throughout treatment.

When it comes to actually treating patients, physicians do not actively engage in the above mental exercise. However, the basic concepts of the log kill model are reflected in the administered treatments. Consider, for example, curative therapy for cervical cancer. Radiation oncologists begin treatment planning by first identifying the targets GTV (gross target volume) and CTV (clinical target volume) (Fig. 12.2). The CTV is any region that has a high likelihood of harboring malignancy, but otherwise appears normal. For cervical cancer, this could be normal-sized pelvic and possibly paraaortic lymph nodes or an area of positive margin. The CTV typically requires a lower dose of radiation for control, ranging from 45 to 54 Gy. The GTV is defined as any disease that is identified either radiographically or by physical exam, and requires a higher dose of radiation, such as 80 to 90 Gy, in cervical cancer patients. Attaining these doses of radiation while respecting normal tissue tolerance is not feasible with external beam radiation therapy alone and brachytherapy is required. If a patient undergoes a hysterectomy where bulk tumor is removed, then there is not a GTV and brachytherapy is often not needed. So, while the cell kill model is of little practical importance, it is used nonquantitatively for almost every patient receiving radiation treatments.

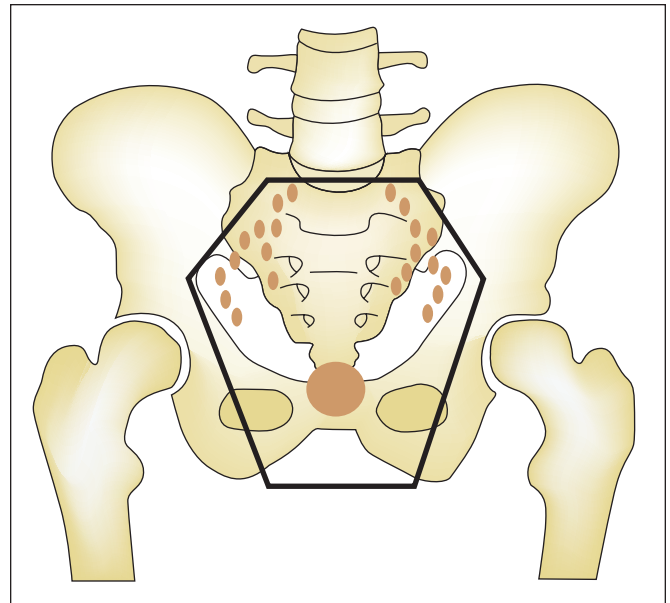


FIGURE 12.2. Target definition in radiation treatment planning for cervical cancer. The solid circle represents the gross target volume (GTV), which is the cervical primary defined both clinically and radiographically. The clinical target volume (CTV) is the pelvic lymph nodes, which have a high probability of at least microscopic involvement. The planning target volume (PTV) is shown as the outer solid line and represents the margin added to the CTV to account for organ motion and daily setup error.

Cell Survival Curves

The log cell kill model describes cell kill in very simplistic terms such that a given radiation dose will kill a certain percentage of cells and that a tumor receiving a fractionated course of radiation gets progressively smaller with time. This approach looks at behavior in a population of cells, which is practical, but gains very little insight into events at the molecular level. The reason is that measuring the diameter of the tumor is not a very accurate way of estimating cell kill. Additionally, tumor cells may have undergone clonogenic cell death, wherein they are still present but unable to reproduce. Therefore, one does not necessarily have to kill all cancer cells in order to achieve cure if the remaining ones are unable to reproduce.

In order to understand events at the molecular level, one needs to accurately measure cell kill. The technique used most commonly first involves creating a suspension containing the target population of cells at a known concentration (Fig. 12.3). An aliquot with a known number of cells is plated on agarose growth media and allowed to incubate. As one would expect, not all the cells successfully form a colony, and so plating efficiency must be calculated by dividing the number of formed colonies by the starting number of cells. The experiment is repeated, but after plating and before incubation, the petri dish is irradiated. The number of colonies formed is divided by the starting number of cells, which is then divided by plating efficiency to yield the ratio of surviving cells. This experiment is repeated over a range of doses of radiation and under various conditions to yield a cell survival curve. The first feature to notice about a cell survival curve is that it uses a logarithmic scale on the y-axis such that as survival approaches 0, the curve goes to negative infinity. The benefit of plotting the data on a logarithmic scale is that, visually speaking, we are able to interpret whether the events driving cell kill are simple or complex. Consider the analogy of a completely different process, such as the decay of a pure radioisotope over time. Plotting this on a linear scale over time would yield an exponential curve, which is difficult to interpret.

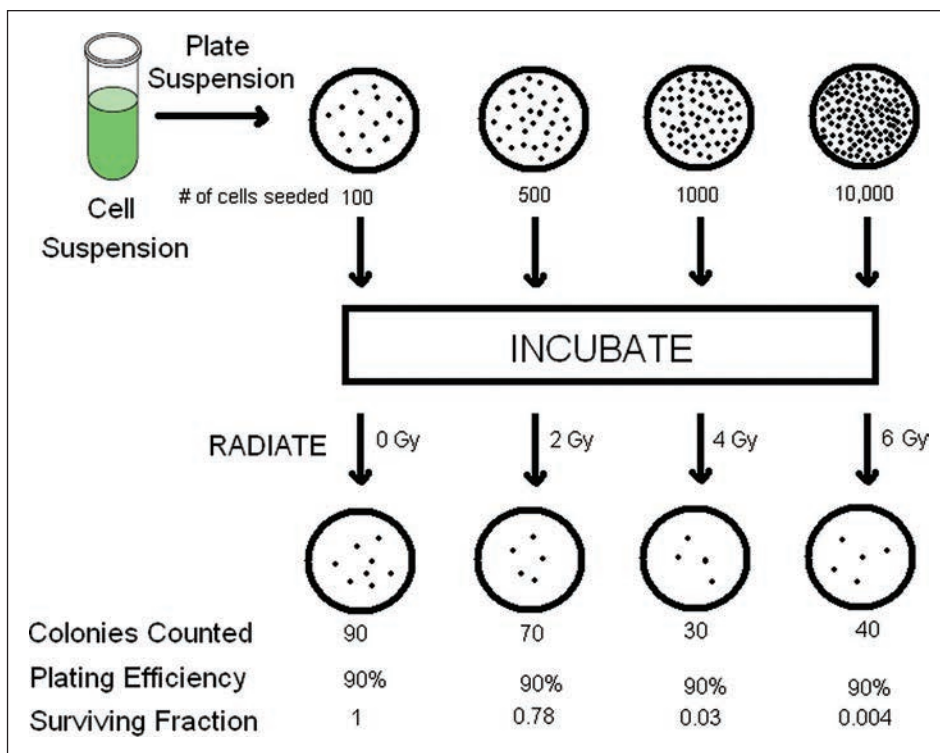


FIGURE 12.3. Cell culture technique used to generate a cell survival curve. A cell suspension is used to plate Petri dishes with a known number of cells, which are subsequently irradiated. Viable cells will form colonies after incubation. The number of viable cells divided by the plating efficiency is used to calculate the surviving fraction. The experiment is repeated over a wide range of doses to produce the cell survival curve.

However, plotting this on a logarithmic scale would yield a perfect straight line, indicating that a single isotope is involved. Consider a slightly more complex situation where the decay is represented by 2 radioactive isotopes with similar half-lives. Plotting this on a linear scale would also reveal an exponential curve, which is unrevealing by inspection. However, creating a plot on a logarithmic scale would yield 2 lines superimposed on one another, clearly indicating that 2 radioisotopes are involved.

Two theoretical experimental cell survival curves are shown in Figure 12.4 under LDR (low-dose-rate) and HDR (high-dose-rate) radiation conditions. The curve for LDR is best fit by a straight line, while the HDR curve is shown to have 2 components, an earlier linear component mirroring the LDR curve followed by a quadratic component. At higher doses of radiation, the HDR curve always has a higher proportion of cell kill than the LDR curve for any given dose.

The rate at which radiation is delivered causes dramatic differences in the shape of the cell survival curve. This is best described by considering the linear-quadratic model with DNA as the lethal target. The evidence for DNA as one of the targets for radiation is substantial: (a) incorporation of radioactive tritium into DNA causes cell death at greater rates than cytoplasmic tritium (2); (b) halogenated pyrimidines, when present in DNA, increase the cell's inherent radiosensitivity in an amount proportionate to the degree of incorporation; (c) a correlation between radiation, DNA double-stranded break repair, and clonogenic survival has also been observed; (d) the concentration of DNA in the nucleus correlates positively with radiosensitivity (3); (e) microirradiation techniques have shown the nucleus to be the most radiosensitive organelle (4).

In most instances, radiation must cause DNA damage that results in a net loss of genetic material, thereby causing a lethal outcome. Radiation exerts most of its deleterious effects by causing breaks in the DNA backbone. Figure 12.5 shows possible

outcomes of photon interaction with the DNA backbone. Because DNA is composed of a double helix with multiple local base pairs acting cooperatively, a single-strand nick is thought to be inconsequential and is repaired by the cellular machinery (Fig. 12.5B). In fact, multiple single-strand nicks can occur, and if they are remote from one another, a normal cell can repair the damage with little chance of a deleterious outcome (Fig. 12.5C). However, 2 opposing single-strand breaks locally disrupt cooperativity, and a double-stranded break (DSB) develops.

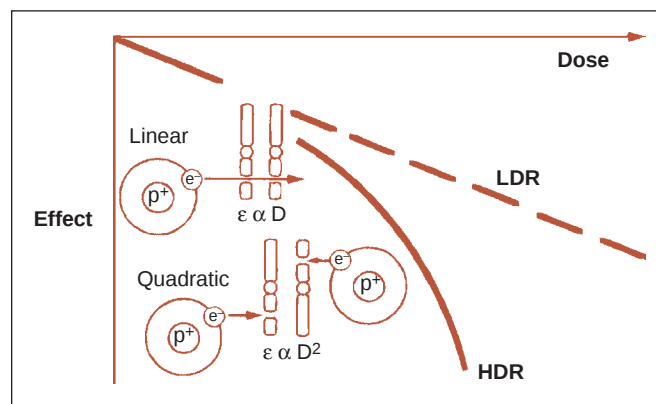


FIGURE 12.4. Cell killing by radiation is largely due to aberrations caused by breaks in 2 chromosomes. The dose-response curve for high-dose-rate irradiation is linear-quadratic: the 2 breaks may be caused by the same electron (dominant at low doses) or by 2 different electrons (dominant at higher doses). For low-dose-rate irradiation, where radiation is delivered over a protracted period, the principal mechanism of cell killing is by the single electron. Consequently, the LDR survival curve is an extension of the low-dose region of the HDR survival curve.

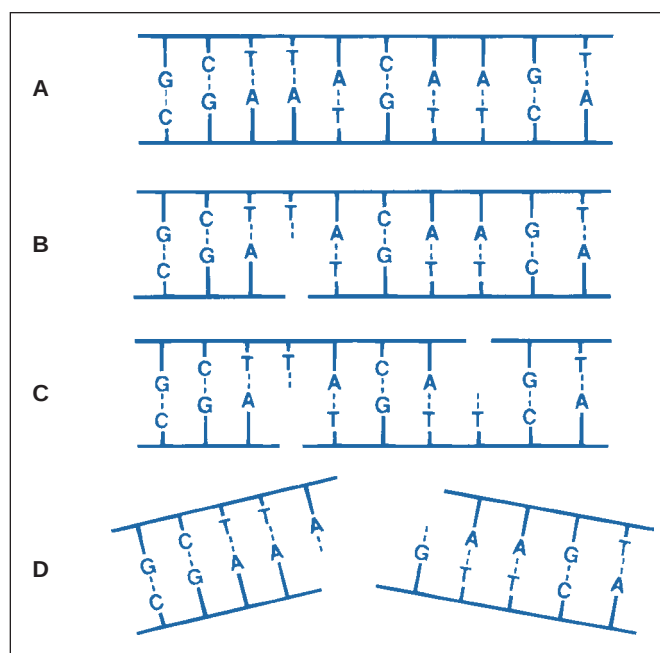


FIGURE 12.5. Diagrams of single- and double-strand DNA breaks caused by radiation. **A:** Two-dimensional representation of the normal DNA double helix. The base pairs carrying the genetic code are complementary (i.e., adenine pairs with thymine, guanine pairs with cytosine). **B:** A break in one strand is of little significance because it is readily repaired, using the opposite strand as a template. **C:** Breaks in both strands, if well separated, are repaired as independent breaks. **D:** If breaks occur in both strands and are directly opposite or separated by only a few base pairs, this may lead to a double-strand break, where the chromatin snaps into 2 pieces.

Source: Courtesy of Dr. John Ward. From Hall EJ. *Radiobiology for the Radiologist*. 4th ed. Philadelphia, PA: JB Lippincott Co.; 1994, with permission.

Once a DSB develops, the cell attempts repair by rejoining the cut ends, as shown in Figure 12.6. There are 2 possible outcomes with repair of the DSBs: the lethal outcomes are shown at the top of Figure 12.6, wherein the chromosomes rearrange such that a portion lacks a centromere, an acentric fragment. When the cell undergoes mitosis, these acentric fragments are eventually lost and may be identified in micronuclei, a smaller “subnucleus” found in the cytoplasm in a separate compartment from the chromosomes (5,6,7). The nonlethal outcomes are shown at the bottom of Figure 12.6, where repair results in a reciprocal translocation and preservation of the genetic information. In some instances, the reciprocal translocation results in activation of an oncogene, which may manifest as a malignancy. It is worth noting that a “bystander effect” has been described using microbeam irradiation techniques (8). In this approach, a nanoscale α -particle beam is directed at the nucleus of a single cell. DSBs can be seen to develop in immediately adjacent unirradiated cells. This is just one notable example where classic radiation DNA damage models fail to explain an observation.

With the above information, the differences in the shape of the cell survival curve under HDR versus LDR conditions can be more easily understood. Referring back to Figure 12.4, in the inset is shown the linear-quadratic model depicting 2 DSBs that develop as result of a photon ejecting an electron, which interacts with DNA. Recall from Figure 12.6 that 2 separate chromosomal breaks are necessary for a potentially lethal outcome. Above the quadratic model is the linear model represented as a single ejected electron causing both DSBs and described mathematically by $\epsilon\alpha D$, where ϵ and α are both constants and D is dose. The important point is that the degree of the linear component of cell kill, also known as α kill, is proportional to D since only one photon/electron is involved. The quadratic model also shows 2 chromosomal breaks. This is caused by 2 separate ejected electrons and is described by $\epsilon\beta D^2$, where ϵ and β are constants and D is dose. Cell kill accounted for by the quadratic model, or β kill, is proportional to D^2 because 2 photons/electrons are involved. Looking at the HDR curve at low doses

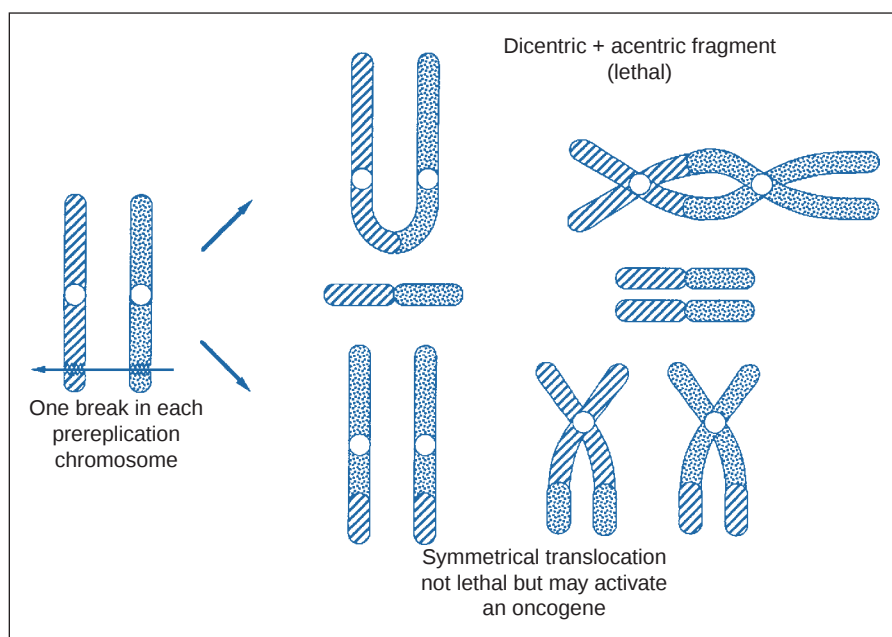


FIGURE 12.6. Most biologic effects of radiation are due to the incorrect joining of breaks in 2 chromosomes. For example, the 2 broken chromosomes may recombine to form a dicentric (a chromosome with 2 centromeres) and an acentric fragment (a fragment with no centromere). This is a lethal lesion resulting in cell death. Alternatively, the 2 broken chromosomes may exchange broken ends, called symmetrical translocation, which does not lead to death of the cell, but in a few special cases activates an oncogene by moving it from a quiescent to an active site.

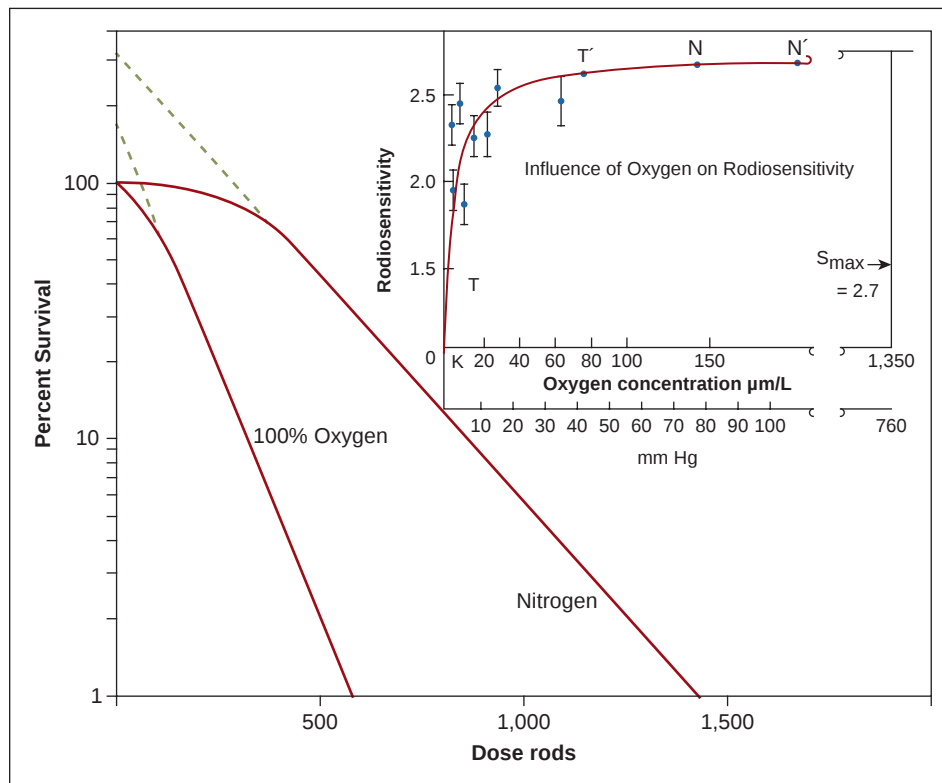


FIGURE 12.7. Influence of oxygen tension on radiosensitivity. Survival curve for human embryo liver cells in tissue culture irradiated with and without oxygen.

Source: From Johns HE, Cunningham JR. *The Physics of Radiology*. 3rd ed. Springfield, IL: Charles C. Thomas; 1972, with permission.

of radiation, there is very little β kill; however, at higher doses, the β component increases exponentially because of D^2 . Under LDR conditions, the β component is absent, leaving only α kill. This is best explained by the idea that β kill involves damage to one chromosome and so is more easily repaired provided that the radiation dose rate and rate of DSB formation is not significantly greater than the cell's repair capacity.

DNA Damage Repair and the Shape of Cell Survival Curves

The concept that DNA damage repair drives the shapes of cell survival curves is well illustrated by experiments showing the effectiveness of oxygen as a sensitizer. Oxygen is known to chemically modify radiation-induced DNA damage making it irreparable (8). This is known as the oxygen fixation hypothesis. Therefore, under anoxic conditions, DNA damage repair would be expected to increase considerably. Figure 12.7 shows an experiment on cultured human embryo liver cells irradiated under 100% oxygen and nitrogen conditions. Hypoxia causes the cell survival curve to shift to the right and change shape.

Up to this point, the linear-quadratic model has been used to describe cell survival curve experiments. Another way to describe the observations is using the multitarget single hit model, which simply states that multiple targets within a cell must be damaged for a lethal outcome. Therefore, at very low doses of radiation, there will be nearly 100% survival. The model is described mathematically by $\text{Survival} = 1 - (1 - e^{-D/D_0})^n$, where D is dose delivered, D_0 is the amount of radiation to achieve approximately 63% cell kill. The parameter n is the extrapolation coefficient or the number of targets in each cell, and is identified by where an imaginary straight line drawn back from the linear portion of the cell survival curve crosses the y -intercept. It is important

to note that this model makes no statement about what the targets actually are. Since we already know that the primary target is DNA, which can trigger multiple complicated events such as repair and apoptosis, the multitarget single hit model falls short of perfection. Nevertheless, it is a good model for understanding the general shapes of survival curves. Contrast this model to the single-target single hit model, which states that a cell needs only to sustain a single hit for lethality, and is described mathematically by $\text{Survival} = e^{-D/D_0}$. Therefore, even at very low doses of radiation, there will be cell kill. Note that this model does not have an extrapolation coefficient.

Referring back to Figure 12.7, the cell survival curve under anoxic conditions can be interpreted as having a higher extrapolation coefficient when compared to 100% oxygen. The extrapolation coefficient is shown diagrammatically by following the dotted lines of the survival curves back to the y -intercept. The dotted line crosses the y -intercept at n .

The inset shows a dose-response relationship between oxygen and radiosensitivity. The typical sigmoidal relationship is lost because oxygen is extremely effective at fixing DNA damage even at low pressures. In fact, only approximately 20 mm Hg or 2% to 3% oxygen is required to achieve the maximum oxygen effect. The half-maximum sensitization is typically observed at 3 mm Hg or 0.5% of oxygen.

The linear-quadratic model is stated more explicitly by the following equation:

$$-\ln S = \alpha D + \beta D^2$$

where S is the surviving fraction and the remaining parameters α , β , and D are the same definitions as above. The formula was used to generate Figure 12.8. The dashed line represents the α component and is generated by extrapolating the initial slope of the curve to higher doses of radiation. The point at which the α and β kill are equal is shown, and the dose at which this occurs is called

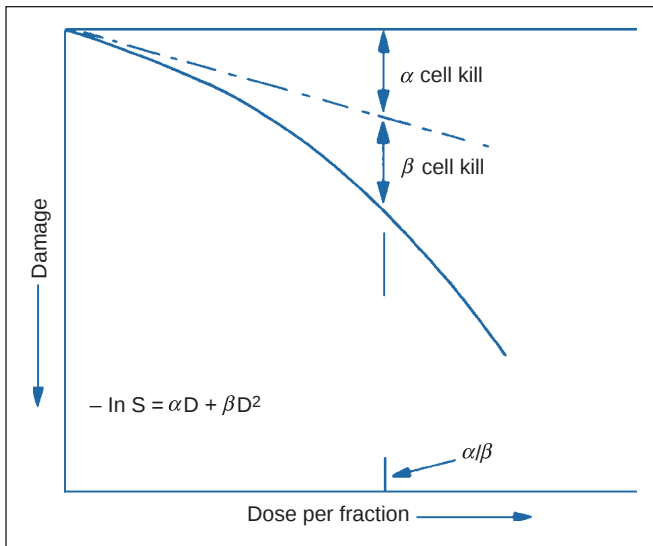


FIGURE 12.8. At a dose equal to the α/β ratio, the log cell kill due to the α process (nonreparable) is equal to that due to the β process (reparable injury): α/β is thus a measure of how soon the survival curve begins to bend over significantly.

Source: Reprinted from Fowler JR. Fractionation and therapeutic gain. In: Steel GG, Adams GE, Peckham MJ, eds. *Biologic Basis of Radiotherapy*. Amsterdam: Elsevier Science; 1983:181–194, with permission from Elsevier.

the α/β ratio. It is worth noting that the α/β ratio is a bit of a misnomer, as ratios typically are unitless values. However, α/β has the units of Gy^{-1} . The α/β ratio for early side effects is thought to be higher, around 10 Gy^{-1} , than for tumor control and late side effects, which is around 3 Gy^{-1} .

Biologically Equivalent Dose

It is clear from Figure 12.4 that both the total dose of radiation and how fast it is delivered can produce very different outcomes. The same holds true for fractionated courses of radiation. For example, 16 Gy delivered in a single treatment, as is the case for radiosurgery, can sterilize a small tumor of cancer cells. However, the same treatment delivered over 8 days would be clinically insignificant. Figure 12.9 shows theoretical cell survival curves for early and late reactions under two separate experimental conditions, single fraction and multifraction regimens. Note that by breaking up the radiotherapy in fractions, the shoulder of the

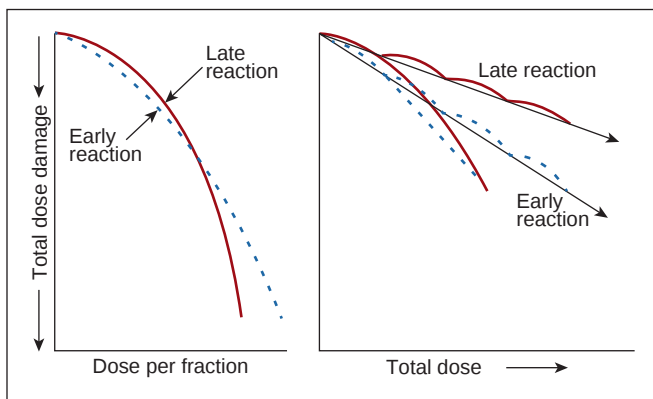


FIGURE 12.9. Difference in cell survival curves for acute and late radiation effects with single or multifractionated doses of irradiation.

Source: Reprinted from Fowler JF. Fractionation and therapeutic gain. In: Steel GG, Adams GE, Peckham MT, eds. *Biologic Basis of Radiotherapy*. Amsterdam: Elsevier Science; 1983:181, with permission from Elsevier.

cell survival curve is repeated. A formula that would normalize a biologic endpoint under various dose fractionation schemes is necessary. The linear-quadratic equation can be used to derive an equation to be used as a guide to predict various biologic endpoints and is given by the following equation:

$$\text{BED} = D[1 + d/(\alpha/\beta)]$$

Where:

BED = biologically equivalent dose

D = total dose

d = dose per fraction

α/β = dose where the α component of cell kill equals the β component

A good example where the formula aided the design of a randomized trial, RTOG 8305, is shown below (9). This trial investigated two different fractionation schemes in the treatment of metastatic melanoma.

Early Side Effects (assumes an α/β of 10)

Arm 1 (32 Gy at 8 Gy/fxn):

$$\begin{aligned}\text{BED} &= D[1 + d/(\alpha/\beta)] \\ &= 32 \text{ Gy} (1 + 8 \text{ Gy}/10 \text{ Gy}) \\ &= 57.6 \text{ Gy}\end{aligned}$$

Arm 2 (50 Gy at 2.5 Gy/fxn):

$$\begin{aligned}\text{BED} &= D[1 + d/(\alpha/\beta)] \\ &= 50 \text{ Gy} (1 + 2.5 \text{ Gy}/10 \text{ Gy}) \\ &= 62.5 \text{ Gy}\end{aligned}$$

Late Side Effects/Tumor Control (assumes an α/β of 3)

Arm 1 (32 Gy at 8 Gy/fxn):

$$\begin{aligned}\text{BED} &= D[1 + d/(\alpha/\beta)] \\ &= 32 \text{ Gy} (1 + 8 \text{ Gy}/3 \text{ Gy}) \\ &= 117 \text{ Gy}\end{aligned}$$

Arm 2 (50 Gy at 2.5 Gy/fxn):

$$\begin{aligned}\text{BED} &= D[1 + d/(\alpha/\beta)] \\ &= 50 \text{ Gy} (1 + 2.5 \text{ Gy}/3 \text{ Gy}) \\ &= 92 \text{ Gy}\end{aligned}$$

In this instance, the BED calculations predict that arm 1 will have slightly more early and late side effects but better tumor control. BED calculations are used as a guide for determining doses. Oftentimes the calculations do not translate directly into the clinical setting outcomes. For example, RTOG 8305 was not able to detect a difference between the two dose fractionation schemes.

The Cell Cycle

The cell cycle is an ordered set of events, resulting in cell growth and division into two daughter cells. The steps pictured in the middle of Figure 12.10 are G_1 -S- G_2 -M. The G_1 stands for “gap 1,” and S phase stands for “synthesis” and is the point at which DNA replication occurs. Late S phase is the most radioresistant phase of the cell cycle since the DNA repair machinery for replication can also repair radiation damage. The G_2 stage stands for “gap 2,” and M phase stands for “mitosis” and is when nuclear division occurs. M phase is also the most radiosensitive phase of the cell cycle since this is an all or nothing event. In other words, once the cell enters into M phase, it will attempt to complete this phase of the cycle without arresting. Therefore, any DNA damage caused generally will be passed along to the daughter cells and may be fatal. This is one important reason why rapidly dividing cells such as cancers are radiosensitive. Not shown in

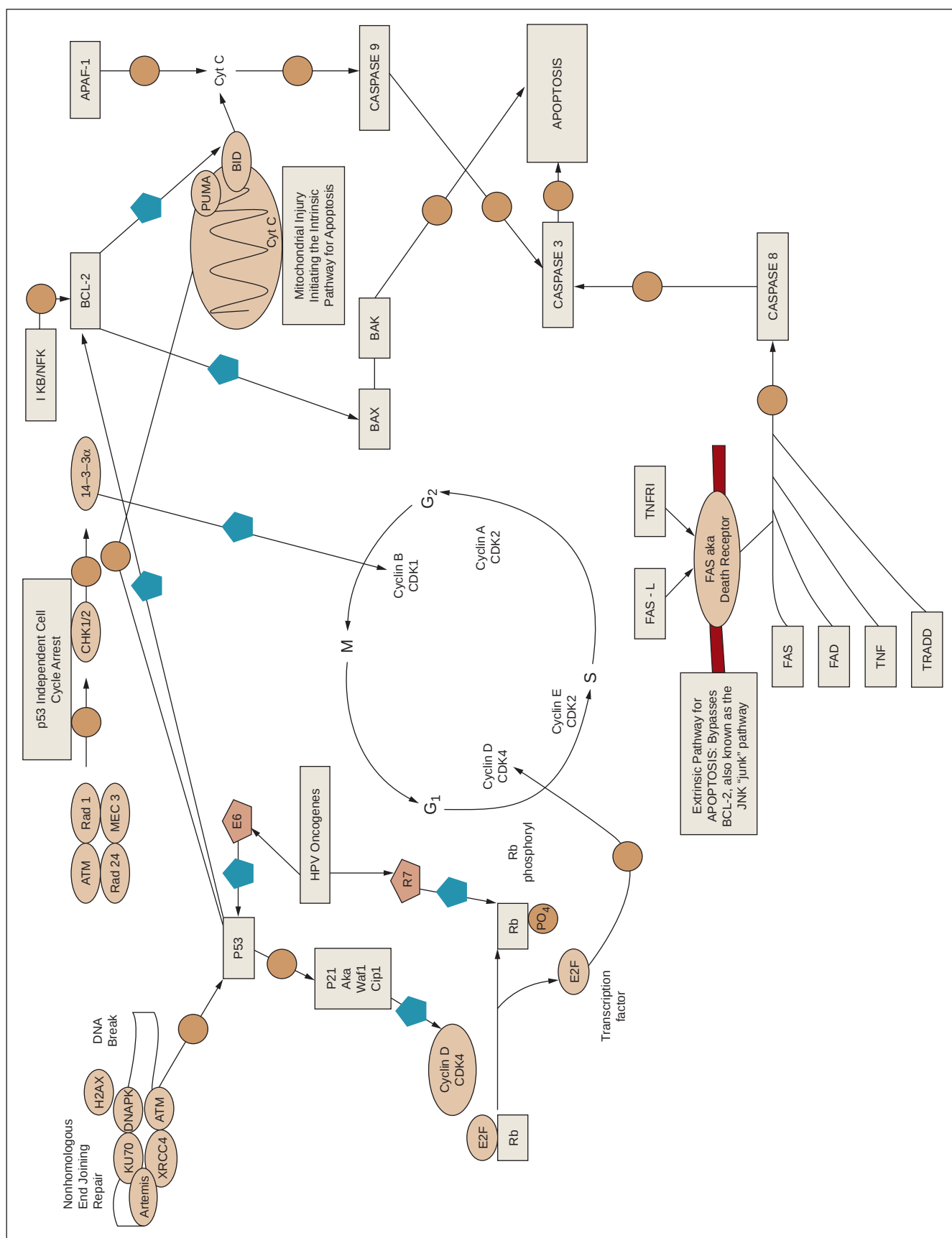


FIGURE 12.10. The cell cycle and important molecular biologic pathways driving cell cycle arrest, apoptosis, and survival are shown. The solid pentagon denotes a net inhibitory step and the open circle indicates a downstream step.

Figure 12.10 is G_0 , which is a stable state of the cell and is typically observed with well-differentiated cells that have reached end stage of development and are no longer dividing (i.e., neuron).

There are three major classes of proteins that orchestrate the cell cycle in mammalian cells: (a) cyclins, (b) cyclin-dependent kinases (cdk in mammals, cdc in yeast), (c) proteins that regulate (a) and (b). Cyclins are generally synthesized and degraded for each phase of the cell cycle. Alone they have no intrinsic enzymatic activity; rather, they bind to and activate cdks. Monomeric cdks are protein kinases that are inactive and require association with a specific cyclin and phosphorylation of a series of conserved threonine residues to become active. Cyclin D/cdk4 is involved with G_1 phase of the cell cycle, cyclin E/cdk2 with G_1 to S phase, cyclin A/cdk2 with S to G_2 , and cyclin B/cdk1 with M.

Cellular Response to Radiation

When a cell is irradiated, there are, in general, four possible outcomes. The cell can survive, undergo apoptosis, undergo a mitotic death, or senesce. Survival requires cell cycle arrest and repair of damaged DNA. Apoptosis requires intact molecular biologic pathways that favor an ordered process of programmed cell death within hours of exposure to radiation. Unfortunately, most tumors have mutations in these pathways, but in malignancies such as lymphoma where these pathways are intact, the tumors can respond after only a couple of radiation treatments. Cells that die a mitotic death undergo a catastrophic event when trying to replicate and so responses may take days. Tumors that die via this mechanism are more radioresistant and result in necrotic masses on imaging after completing a course of radiation. Senescence is a state in which proliferation is irreversibly arrested and the cell may eventually die. Note that senescence is a metabolically active state, which is different from G_0 , which is typically metabolically inactive.

Inherent to the cell is a type of thermostat, which influences the radiation responses to favor any of the above processes. Protooncogenes are regulator proteins that, due to either overexpression or mutation, have a higher activity level, thereby promoting unregulated division. Because this mechanism is a net gain of function, only one allele needs to be affected in order to see phenotypic expression. Tumor suppressor genes keep the cell cycle in check, and so loss of function of both alleles is typically required for dysregulation to be observed.

Cell Cycle Arrest

As previously mentioned, when a cell is irradiated, repair of the DNA backbone is attempted, and in order for this process to occur the cell cycle must typically arrest. There are two prototypical points in the cell cycle during which arrest occurs: G_1 and G_2 (10,11). A major regulator of the cell cycle is the transcription factor p53, which is a tumor-suppressor gene that has many pathways both upstream and downstream and is important for G_1 arrest (Fig. 12.10) (12). For example, breaks in the DNA backbone are rejoined via the nonhomologous end-joining (NHEJ) repair mechanisms (top left of Fig. 12.10) (13). One critical gene, the ataxia telangiectasia gene (ATM) has a net positive regulatory effect on p53, which, via p21 (CCDN1A), has a net inhibitory effect on cyclin D/cdk4, thereby favoring arrest. This is the p53-dependent pathway of cell-cycle arrest. An alternative pathway, independent of p53, operates via chk1/2 and 14-3-3 α gene products and has a net inhibitory effect on cyclin B/cdk1, which promotes arrest during G_2 (14).

Retinoblastoma Gene, E2F, and Human Papillomavirus

Retinoblastoma protein (Rb) is another critical regulator of the G_1 phase of the cell cycle (15). This gene is located on chromosome

13 and mutations can cause a number of tumors, the earliest of which to manifest is retinoblastoma. Knudson et al. developed the two-hit hypothesis for the inheritance pattern of this disease (16). He recognized that there were 2 forms: (a) sporadic, which comprises 60% of the cases of retinoblastoma, whereby mutations occur as random events in both alleles. Patients typically have unilateral disease and a marginal risk for developing second malignancies in response to radiation; and (b) Inherited, where a germ-line mutation results when an abnormal allele is inherited from a parent. Patients with this form of retinoblastoma are more likely to develop bilateral disease and have a profound sensitivity toward developing radiation-induced second malignancies. Rb acts by binding and inhibiting E2F, a transcription factor essential for G_1 . Phosphorylation of Rb results in release of inhibition of E2F and subsequent cell cycle progression. Human papillomavirus gene product produces an oncogene, E7, which binds to Rb and releases inhibition of E2F, thereby promoting cell division (17).

Apoptosis

Apoptosis can begin in 2 distinct manners: (a) extrinsic pathway, where the apoptotic stimulus occurs extracellularly, or (b) intrinsic pathway, where the cascade of events is contained intracellularly. Figure 12.10 shows both pathways converging on caspase 8 (cysteine aspartic acid-specific proteases). Caspases are expressed as inactive precursors (procaspases), which are proteolytically cleaved to an active state following an apoptotic stimulus. Upstream from caspase 8, the pathways diverge. The extrinsic pathway begins by binding of a specific ligand such as Fas-L or tumor necrosis factor (TNF) to a membrane-bound death receptor. The intrinsic pathway, on the other hand, requires disruption of the mitochondrial membrane and release of mitochondrial cytochrome c to the cytoplasm. Cyt c then combines with 2 other cytosolic protein factors, Apaf-1 (apoptotic protease activating factor-1) and procaspase-9, to promote the assembly of a caspase-activating complex termed the apoptosome, thereby promoting the apoptotic caspase cascade. Bcl-2 and its family member proteins are important regulators of apoptosis. Bcl-2 is antiapoptotic by inhibiting proapoptotic factor bax and inhibiting the release of cyt c into the cytoplasm. p53 is an important inhibitor of bcl-2. All of these pathways interact to determine whether a cell will survive or apoptose in response to an insulting stimulus such as radiation.

Radiation Effects on Embryo and Fetus

In Utero Exposure to Ionizing Radiation

There are 2 models that describe the negative clinical sequelae of exposure to radiation to a developing fetus or embryo. (a) Deterministic effects describe how radiation affects a large population of cells resulting in end organ damage. A large number of cells must die in order to induce organ failure. As such, deterministic effects tend to have a sigmoidal dose-response relationship with a threshold dose. As long as the threshold dose is respected, there is very little chance of a given toxicity. (b) Stochastic effects describe events at the cellular level and how radiation induces malignancies. Stochastic effects have more of a constant, steep dose-response relationship. As such, there is no threshold dose; that is, exposure to even miniscule amounts of additional radiation theoretically increases the chance of inducing a malignancy.

Deterministic Effects—End Organ Damage and Failure

The most sensitive phase of the cell cycle to ionizing radiation is M phase because little repair to the DNA backbone occurs

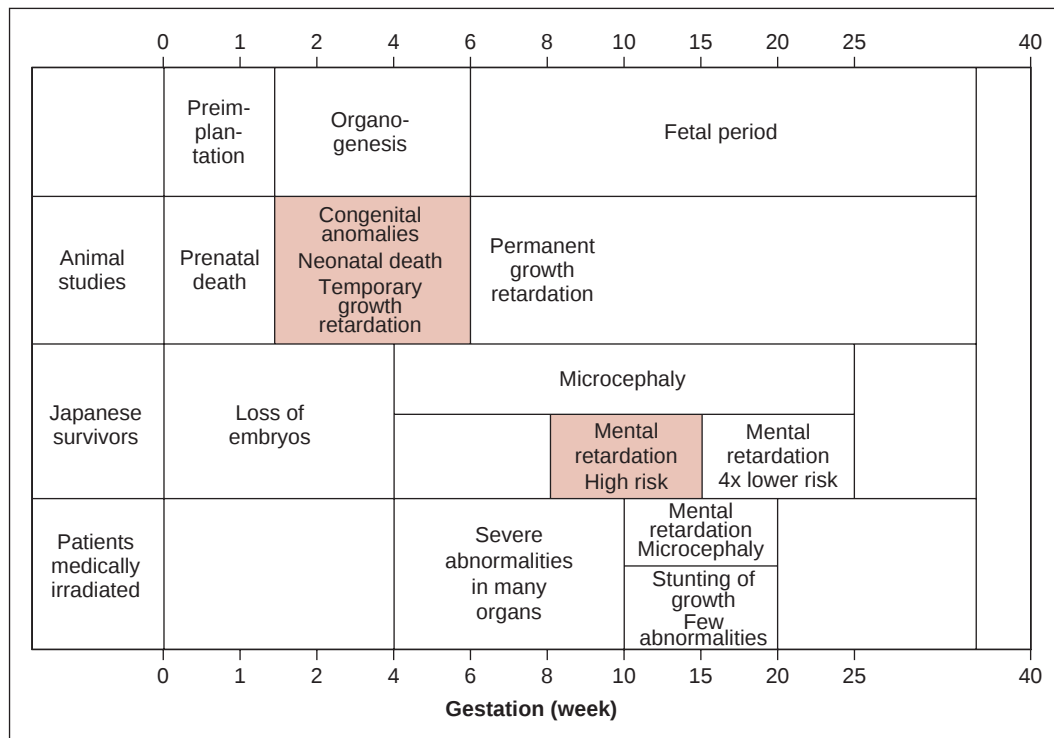


FIGURE 12.11. Summary of the effects of radiation on the developing embryo and fetus from 3 principal sources: medical radiation, laboratory animal studies, and survivors of the atomic bomb attacks on Nagasaki and Hiroshima. The animal studies indicate a wide range of structural abnormalities during organogenesis, whereas the principal effect observed in humans is reduced head diameter with or without severe mental retardation.

Source: Modified from Hall EJ. *Radiobiology for the Radiologist*. 4th ed. Philadelphia: JB Lippincott Co.; 1994, with permission.

during this period. Most of the cell molecular machinery is geared toward completing mitosis and any DNA double-stranded breaks are passed along to the daughter cells and are typically fatal. Since embryos and fetuses are composed of rapidly dividing cells, they are exquisitely sensitive to radiation and exhibit an extremely low threshold dose. Gestational age is also a key determinant when predicting outcomes of radiation exposure. As Figure 12.11 shows, exposure of several gray during the first 1 to 2 weeks of gestation (peri-implantation stage) results in loss of the embryo. However, if the embryo survives the insult, it will go on to develop without obvious abnormalities. This phenomenon is termed the “all or nothing effect.” During weeks 2 to 6, the period of organogenesis is occurring and exposure at this point results in congenital anomalies, neonatal death, and temporary growth retardation. Doses as low as 2 Gy have a 70% mortality. The fetal period occurs beyond 6 weeks and exposure results in permanent growth retardation. Irradiation during weeks 4 through 16 may produce severe eye, skeletal, and genital organ abnormalities as well as microcephaly and mental retardation. According to the Japanese survival data, the risk is approximately 40% per gray. Exposure during weeks 16 through 20 may cause a less severe form of stunting of growth, microcephaly, and mental retardation. After 30 weeks, low doses of radiation do not typically result in gross abnormalities.

Stochastic Effects—Cancer Induction

The Oxford Survey by Kneale and Stewart suggested that there was an association between leukemia risk and *in utero* exposure to diagnostic X-rays (18). Doll and Wakeford summarized the data with the following general conclusions: Low-dose irradiation increases the risk of childhood malignancies, particularly in the third trimester (19). An X-ray exam increases the risk

by approximately 40% above the spontaneous rate. Doses as low as approximately 10 mGy increase the risk, and the excess absolute risk is around 6% per gray. Solid tumors have a longer latency period of approximately 20 to 40 years, whereas leukemias have an average latency of around 7 years. When counseling the pregnant patient or worker, it is important to let them know the magnitude of and potential for side effects. According to the International Council of Radiation Protection (ICRP) Publication 84, doses less than 1 mGy may be considered negligible, which is the approximate dose of normal background radiation (20). Exposures above 1 mGy require a more in-depth discussion with the patient. ICRP Publication 84 provides detailed risk assessments and counseling guidelines for *in utero* exposure.

Occupational Exposure

Once pregnancy has been declared, the employee is encouraged to formally inform her employer. Further, the radiation safety officer should interview her, her employment should be evaluated for exposure history, and steps should be taken to minimize exposure. The National Council on Radiological Protection recommends that the embryo/fetus have limited exposure to less than 0.5 Sv/month (21).

INTRODUCTION TO RADIATION PHYSICS

Radiation physics is the study of the interaction of radiation with matter. In the treatment of patients with radiation, this matter is either tumor tissue or normal tissues such as the skin, the internal organs, or the supporting tissues and structures.

Units Used in Radiation and Radiation Therapy

Radiation is an abbreviation for electromagnetic radiation. It can occur in numerous forms. The most common forms used in radiation therapy are X-rays, γ -rays, and electrons. X-rays and γ -rays are also known as photons or packets of energy and are used to treat most body sites where radiation is deemed efficacious. Other particles or forms of radiation, such as protons, neutrons, and heavier α particles, are less commonly used in radiation therapy except in select clinical situations. Protons, other heavy charged particles, and neutrons have a higher linear energy transfer coefficient when compared to high energy photons and therefore are more efficient at transferring or depositing their energy in tissue. Protons are used increasingly in the treatment of prostate cancers, choroidal melanomas, skull base and paraspinal tumors, and pediatric tumors. Neutrons have been used for salivary gland tumors, sarcomas, and prostate cancers. Protons are positively charged particles that can be accelerated in an electric field to high energies. The primary characteristic of a proton beam is its Bragg peak. The Bragg peak describes at what depth the majority of a proton's energy is deposited. Prior to the depth of the Bragg peak, only a very small amount of the proton energy is deposited. The Bragg peak depth is determined by the energy of the incident protons and covers only very small width of tissue at that depth. In order to cover more tissue, the energy of the incoming proton beam is varied. The net dose deposition results in a low entrance dose and a finely controlled width of treatment dose at depth. This makes proton treatments an excellent choice for the treatment of tumors adjacent to critical structures. Neutrons are relatively massive uncharged particles that can be generated by cyclotrons. Poor treatment geometry and dose distributions have limited the enthusiasm for neutron beam therapy (22).

X-rays and γ -rays are forms of electromagnetic radiation, similar to visible light, but with a much smaller wavelength, that is, greater energy. The difference between X-rays and γ -rays is only their respective origins. X-rays are derived from interactions in the atom that are outside the nucleus, typically by bombardment of the atom or target with high-speed electrons. This is the source of radiation produced by most modern radiotherapy treatment machines termed linear accelerators or linacs. Their name derives from acceleration of these electrons. γ -rays arise from a process within the nucleus of the atom called radioactive decay, which occurs in brachytherapy sources and cobalt (^{60}Co) teletherapy treatment machines. This type of electromagnetic radiation can penetrate several millimeters to centimeters of normal tissue in close proximity to tumors or tissues at risk. There is increased penetration as the energy of the gamma rays is increased. The X-rays produced by linear accelerators are much more penetrating than ^{60}Co gamma rays and are used to treat tumors or tissues at a distance from the linear accelerator such as deep within the pelvis or abdomen.

Electrons are small, negatively charged particles. Because of their inherent charge, these particles interact more strongly with the atoms found in tissue. Electrons will usually only penetrate a few millimeters to centimeters in tissue. Similar to photons, the higher the energy of the electron, the farther it will penetrate into the tissue. Electrons are used to treat tumors or tissues close to the skin surface such as superficial inguinal nodes and tumors of the skin, including vulvar cancers.

Regarding photon interactions with tissue, the dominant process at energies used in radiation therapy is termed the Compton effect (Fig. 12.12). The probability that a photon will interact with a target atom is inversely proportional to the energy of the incident photon and nearly independent of the atomic number of the target material. As a result, at the energies used in radiation therapy, termed megavoltage (MV), the absorbed dose in normal tissues is comparable to that in nearby bone. At much

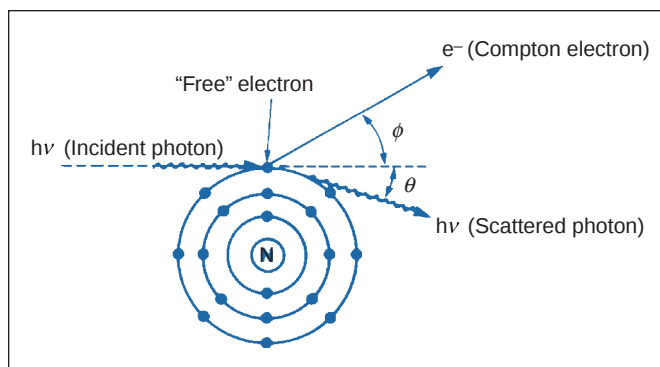


FIGURE 12.12. Schematic drawing illustrating the process of the Compton effect. The incident photon interacts with one of the atom's outer electrons, and the energy is shared between the ejected electron and a scattered photon.

Source: From Purdy JA. Principles of radiologic physics, dosimetry, and treatment planning. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 3rd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998, with permission.

lower energies, termed kilovoltage (kV), the absorbed dose would scale with the atomic number of the target with higher absorbed dose in bone compared to normal soft tissues.

At the second International Congress of Radiology in 1928, the basic unit of exposure, the roentgen (R), was defined (22). Although the original definition evolved over time, the fundamental idea remained the same. The roentgen is the amount of photon radiation that causes 0.001293 g of air to produce one electrostatic unit of positive or negative charge (esu). The value of 0.001293 g is the mass of 1 cc of air at a temperature of 0°C and a pressure of 760 mm Hg. The definition of the roentgen can also be expressed in other equivalent terms:

$$1 \text{ R} = 2.58 \times 10^{-4} \text{ C/kg air}$$

or, conversely, expressed in SI units, the unit of exposure is defined by:

$$1 \text{ C/kg} = 3,876 \text{ R}$$

Table 12.1 lists some basic units of radiation and radiation therapy, both in historic context and in terms of modern SI units. Kerma (kinetic energy release per unit mass) defines the transfer of energy from photons to directly ionized particles. These directly ionized particles, in turn, transfer some of their energy to the medium (usually tissue). This transfer of energy is defined as the absorbed dose to the medium from the radiation beam. The SI unit for kerma is joule per kilogram (J/kg) or gray (Gy). In a slightly confusing definition, the SI unit for absorbed dose is also joule per kilogram or gray. The term gray has replaced the previously used term "rad." Oftentimes the term centigray (cGy) is used. The cGy is equivalent to the rad and 1 gray equals 100 cGy.

Another rationale to think and communicate in SI units is that the roentgen was defined explicitly for photon interactions

Table 12.1 SI Units for Radiation Therapy

Quantity	SI Unit (Special Name)	Non-SI Unit	Conversion Factor
Exposure	C kg ⁻¹	roentgen (R)	1 C kg ⁻¹ ≈ 3876 R
Absorbed dose, kerma	J kg ⁻¹ (gray [Gy])	rad	1 Gy = 100 rad
Dose equivalent	J kg ⁻¹ (sievert [Sv])	rem	1 Sv = 100 rem
Activity	s ⁻¹ (becquerel [Bq])	curie	1 Bq = 2.7 × 10 ⁻¹¹ Ci

and not charged particles. Kerma and absorbed dose, although they have equivalence to the roentgen and exposure, can be defined equally for photons and charged particles.

RADIATION PRODUCTION

Radioactive Isotopes

As mentioned before, γ -rays are typically derived from radioactive isotopes, such as ^{60}Co . Electrons or beta particles also come from radioactive isotopes. In fact, most radioactive material produces a combination of photons (gamma rays) and electrons during the decay process. Radioactivity is the result of an atom changing its “energy” state, usually to a lower “energy” state, by the emission/absorption/internal conversion of photons or electrons in the atom. These processes result in disintegrations or radioactive decay, whereby the atom releases photons or electrons or both during the change in “energy” states. The release of these particles is a form of radiation (or energy) that can be used to irradiate tissues. The absorbed dose resulting from this radiation depends on the energy and particle type as mentioned above, as well as the tissue in which it interacts.

Radioactivity, or activity, is denoted by the symbol A and is defined as the number of disintegrations per unit of time. The following relationship defines activity, the decay constant, and ultimately the half-life for a radioactive material:

$$A = N/t = \gamma N$$

This equation is solved using an exponential solution:

$$A = A_0 e^{-\lambda t}$$

where A is the initial activity, λ is the decay constant, and t is some unit of time later. Other important units for radioactivity and radioactive decay are the half-life, $T_{1/2}$, and the average life, T_a . The half-life is the amount of time necessary to reduce the original amount of material by half. This is also equivalent to reducing the original activity by half. $T_{1/2}$ is related to the decay constant by $T_{1/2} = 0.693/\lambda$. The average life represents the period of time that a hypothetical source would need, if it retained its original activity for a fixed period of time (T_a) before suddenly decaying to zero activity, to produce the same number of disintegrations over an infinite amount time by the same source if it decayed exponentially. T_a is related to the decay constant and the half-life by $T_a = 1/\lambda = 1.44 T_{1/2}$.

Radioactive isotopes can occur naturally or be created artificially. Artificially created isotopes are usually created by neutron bombardment of otherwise stable isotopes. The resulting interactions produce atoms that are inherently unstable and will decay to a more stable form with a predictable half-life, releasing energy or radiation through this decay. Naturally occurring radioactive isotopes originally come from one of three standard series—the uranium series, the actinium series, and the thorium series—so named because of a dominant radioactive isotope in each series. In general, the higher the atomic number, the more likely an isotope will be radioactive. Table 12.2 lists many of the more common radioactive isotopes and their physical properties. For gynecologic cancers, use of radium 226 (^{226}Ra) sources is now historic. Though cost-effective because of its long half-life (1,622 years), radium releases a by-product, radon gas, if

Table 12.2 Physical Properties and Uses of Brachytherapy Radionuclides

Element	Isotope	Energy (MeV)	Half-Life	HVL-Lead (mm)	Source Form	Clinical Application
Obsolete Sealed Sources of Historic Significance						
Radium	^{226}Ra	0.83 (avg)	1,626 years	16	Radium salt encapsulated in tubes and needles	LDR intracavitary and interstitial
Radon	^{222}Rn	0.83 (avg)	3.83 days	16	Radon	Permanent interstitial; temporary molds
Currently Used Sealed Sources						
Cesium	^{137}Cs	0.662	30 years	6.5	Cesium salt encapsulated in tubes and needles	LDR intracavitary and interstitial
Iridium	^{192}Ir	0.397 (avg)	74 days	6	Seeds in nylon ribbon; encapsulated source on steel cable	LDR temporary interstitial; HDR interstitial and intracavitary
Cobalt	^{60}Co	1.25	5.26 years	11	Encapsulated spheres	HDR intracavitary
Iodine	^{125}I	0.028	59.6 days	0.025	Seeds	Permanent interstitial
Palladium	^{103}Pd	0.020	17 days	0.013	Seeds	Permanent interstitial
Gold	^{198}Au	0.412	2.7 days	6	Seeds	Permanent interstitial
Strontium	^{90}Sr - ^{90}Y	2.24 MeV β_{max}	28.9 years	—	Plaque	Superficial ocular lesions
Cesium-131	^{131}Cs	0.030 MeV	9.7 days	0.042	Seeds	Permanent interstitial
Developmental Sealed Sources						
Americium	^{241}Am	0.060	432 years	0.12	Tubes	LDR intracavitary
Ytterbium	^{169}Yb	0.093	32 days	0.48	Seeds	LDR temporary interstitial
Californium	^{252}Cf	2.4 (avg) neutrons	2.65 years	—	—	—
Samarium	^{145}Sm	0.043	340 days	0.060	Seeds	LDR temporary interstitial

(Continued)

Table 12.2 Physical Properties and Uses of Brachytherapy Radionuclides (Continued)

Element	Isotope	Energy (MeV)	Half-Life	HVL-Lead (mm)	Source Form	Clinical Application
Unsealed Radioisotopes Used for Radiopharmaceutical Therapy						
Strontium	^{89}Sr	1.4 MeV β_{max}	51 days	—	SrCl ₂ IV solution	Diffuse bone metastases
Iodine	^{131}I	0.61 MeV β_{max} 0.364 MeV γ	8.06 days	—	Capsule NaI oral solution	Thyroid cancer
Phosphorus	^{32}P	1.71 MeV β_{max}	14.3 days	—	Chromic phosphate colloid instillation; Na ² PO ₃ solution	Ovarian cancer seeding; peritoneal surface; poly- cythemia vera, chronic leukemia

LDR, low-dose rate; HDR, high-dose rate.

the integrity of the source capsule is compromised. This could require closure of hospital wards due to radon gas contamination. Cesium 137 (^{137}Cs) has replaced radium as a safer yet effective radioisotope. Less shielding is required for cesium than radium, and there is no risk of radon gas leakage. With a half-life of 30 years, it is also cost-effective due to the infrequent need for replacement. Cesium can be used clinically for years without replacement, but the treatment duration must be adjusted to allow for radioactive decay (23). It is typically used for low-dose-rate gynecologic brachytherapy in tandem and ovoid and cylinder applicators. Iridium 192 (^{192}Ir) comes in various activities and can be used for interstitial and intracavitary gynecologic implants. Its half-life of 74.2 days requires frequent replacement and, typically, this is custom ordered individually for each implant rather than stored in the radiation oncology department like ^{137}Cs sources. High activity ^{192}Ir (^{10}Ci) sources are used for high-dose-rate brachytherapy and are replaced every 3 months, and lower activity ^{192}Ir sources are used for LDR brachytherapy.

Linear Accelerators

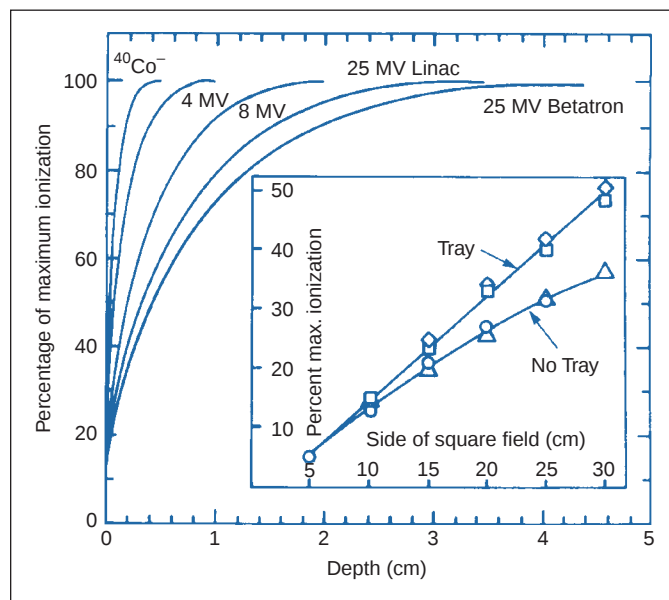
Linacs are another method of producing radiation for treatment of malignancies. Linacs can produce both photon and electron beams of different energies depending on their construction. The principles behind a linac involve accelerating an initial beam of electrons across a variable electric field. The greater the strength of the electric field, the more energetic the electron beam. This electron beam can be adjusted to control its shape and intensity before delivery to the patient. Alternatively, the electron beam can be directed to a tungsten target. The electron-target interaction creates a forward scattered photon beam or X-ray. The resulting photon beam can then be modified by the machine using filters and collimators to produce the desired radiation field shape.

Photon beams of different energies have a different absorbed dose pattern within tissues. This pattern is normally characterized as a percent depth dose or variation of dose as a function of depth within tissue, as shown in Figure 12.13 and Figure 12.14, and by dose profiles, or variation of dose as a function of lateral distance at a given depth (Fig. 12.15). The key feature in all of the figures is that higher-energy photons deposit dose at greater depths. Because of the way dose is deposited and absorbed in tissue, the higher the photon energy, the less dose is deposited at shallow depths toward the surface of the patient. This is called “skin sparing” and is a characteristic of high-energy photons. In fact, the higher the photon energy, the deeper the point at which the maximum absorbed dose is deposited. After this D_{max} , the absorbed dose decreases because the photon beam is attenuated by the tissues through which it passes.

Figure 12.16 shows a simplified drawing of a linac. The gantry (or part of the linac where radiation exits the machine) can rotate 360° around the patient on the treatment table. The table can also be rotated about the vertical axis of the radiation beam. This combination of angles allows the radiation to be directed to almost any part of a patient's body.

Modern linacs come equipped with multileaf collimators (MLCs) and asymmetric jaws to control the shape of the radiation beam directed before it reaches the patient (Fig. 12.17). Prior to asymmetric jaws and MLCs, photon beam shaping was achieved using poured blocks mounted below the lowest machine jaws. The composition and thickness of the poured block material are sufficient to block more than 97% of the radiation, allowing less than 3% of the radiation to penetrate the block and reach the patient. MLCs have mostly replaced poured blocks, but in some cases, poured blocks are still necessary for detailed field shaping.

MLCs are small (projected size at the patient ~1 cm), adjustable collimators built into the linac gantry that work together to create a shaped opening mimicking the effects of a poured block. Because each MLC is adjustable, a new field shape can be “programmed” into the gantry without the necessity of pouring a different block for every treatment field. With the advent of computer-controlled motion of the MLCs, the radiation field can be further controlled to produce an intensity-modulated

**FIGURE 12.13.** ^{60}Co to 25-MV X-rays.

Source: From Velkley DE, Manson DJ, Purdy JA, et al. Build-up region of megavoltage photon radiation sources. *Med Phys.* 1975;2:14–19, with permission.

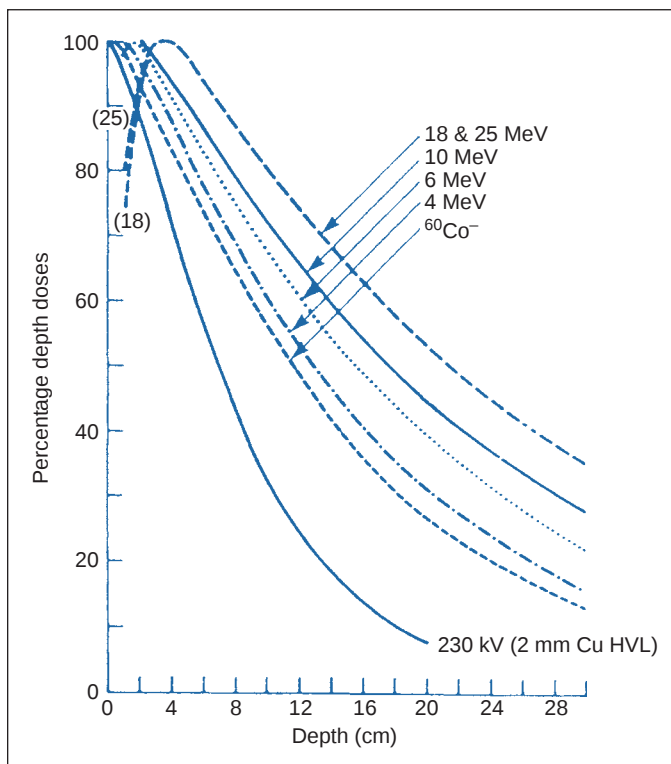


FIGURE 12.14. Typical X-ray or photon beam central-axis percentage depth-dose curves for a 10×10 cm beam for 230 kV (2 mm Cu HVL) at 50 cm SSD, ^{60}Co and 4 MV at 80 cm SSD, and 6 MV, 10 MV, 18 MV, and 25 MV at 100 cm SSD. The last 2 beams coincide at most depths but do not coincide in the first few millimeters of the build-up region. The 4-MV, 6-MV, 18-MV, and 25-MV data are for the Varian Clinic 4, 6, 20, and 35 units, respectively, at the Department of Radiation Oncology, Washington University in St. Louis. Source: From Cohen M, Jones DEA, Greene D. Central axis depth dose data for use in radiotherapy. *Br J Radiol.* 1972;11:21, with permission.

radiation therapy (IMRT) treatment. In IMRT treatments, the MLCs are used to create many small fields of radiation within a larger treatment field. By opening and closing these small fields, the intensity at any point within the large field can be modulated to give more or less dose to the tissues directly exposed to the radiation. At one gantry angle, the IMRT field may need to spare a critical normal structure but still treat the target to a lower dose, while in another gantry angle, that same critical structure may be out of the field and the target can get a higher intensity to compensate for the lowered intensity in the first field. This adaptability allows the radiation treatment planner to create and deliver very complex treatment fields that improve target coverage while attempting to spare normal tissues. In practical terms, IMRT treatment plans are an improvement of the more conventional three-dimensional (3-D) conformal treatment plans. 3-D conformal treatment plans use fewer fields to achieve nominal coverage of the treatment target. At each gantry angle, the radiation is either hitting the target/normal tissue or not with a simple shaped treatment field. Normal tissues may be impossible to spare relative to adjacent targets. IMRT treatment plans may use similar gantry angle setups, but with the additional intensity modulation, the IMRT fields can create a complicated dose distribution within the patient. In some cases, where the normal tissues are relatively far from the target tissues, there may be no benefit or rationale for the more complex IMRT treatment plan compared to 3-D conformal treatment plans. In cases where the proximity of normal tissues and target vary across a field and between gantry angles, IMRT may prove the more efficient treatment plan to protect normal tissues while focusing dose onto the target (Fig. 12.18).

IMRT is being used in the treatment of gynecologic cancers. The setting where it may be the most helpful and the most widely accepted is postoperatively for select endometrial and cervical cancer presentations (24,25). Results of the RTOG 0418 study showed a decrease in both acute and late toxicity in the postoperative setting in patients with either cervical or endometrial cancers (26). In this setting, there is often a significant amount of small bowel in the pelvis that can be avoided to a greater degree with IMRT than 3-D conformal radiation techniques (Fig. 12.19). Bone marrow sparing can also be improved over a 3-D conformal approach (27). Bladder and rectosigmoid doses can also be reduced. Margin sizes around the target and bladder and rectal filling are important considerations, as are immobilization techniques when using IMRT. Target delineation and normal organ delineation are extremely important when using IMRT. What is not defined is either not adequately treated or spared (28). RTOG 0418 defined parameters for contouring of targets and normal organs, margin size, and dose volume constraints in the postoperative setting in early cervical or endometrial cancers (29). An online atlas available on the RTOG website was developed to improve consistency between multiple contouring physicians and continues to be used to guide in target delineation even though the protocol has been completed (30). This same atlas has been used in GOG studies, which include IMRT techniques with minor modifications over time. A normal tissue-contouring atlas is also available on the RTOG website (31). Other atlases are available to guide radiation oncologists in defining these structures of interest (32,33). When using IMRT to treat the intact uterus, bladder filling can have even more influence on the position of the uterus, and the vagina and uterus can move several centimeters as a result (34,28). Stool in the rectosigmoid can also cause movement of the adjacent pelvic organs and alter the dose distribution in the rectosigmoid.

Where there is more controversy is in the use of IMRT for intact cervical cancer. Use of IMRT in the definitive management of cervical cancer has been piloted at the University of Chicago (35). In their series, IMRT has reduced both acute and late gastrointestinal (GI) toxicities and helped to spare bone marrow during treatment (35). Other series have shown a similar decrease in toxicity with use of IMRT (36). There is concern in this setting about organ motion relative to the dose distribution. This can be due to bladder or rectosigmoid filling, disease regression, or sporadic motion (37–40). Careful attention to organ filling, patient immobilization, and margin size can help to minimize such motion which could compromise target and normal organ doses (28). Daily CT imaging prior to treatment can also help to assess for this motion and adapt the treatment plan as needed (41,39). A consensus guideline has been published to begin to define the most appropriate clinical target volume for intact cervical cancer with recognition of the significant uncertainties caused by motion in this setting (42). Practice guidelines for IMRT have been published by ASTRO and ACR (43,44). Use of IMRT for extended field irradiation to treat the pelvic and paraaortic regions, is successfully implemented to decrease dose to the small bowel, kidneys, liver, spinal cord, and bone marrow (Fig. 12.20). Selective boosting of gross nodal disease may allow for safer dose escalation (37,39,45–47). IMRT techniques have also been used for whole abdominal irradiation to reduce doses to the gastrointestinal tract, liver, kidneys, and bone marrow and to increase dose to the peritoneal surfaces and lymph nodes (48,49) as well as for vulvar cancers to help spare the upper femur as well as the small bowel and bone marrow (50).

A pivotal treatment technique for the success of IMRT is image-guided radiation therapy (IGRT) (41,39,51). Historically, treatment setups were verified by orthogonal radiographs and treatment fields by port films or X-rays of the treatment fields superimposed on the patient. Modern linacs have added on-board imaging (OBI) that allows the treatment fields to be recorded electronically at every treatment setup using an

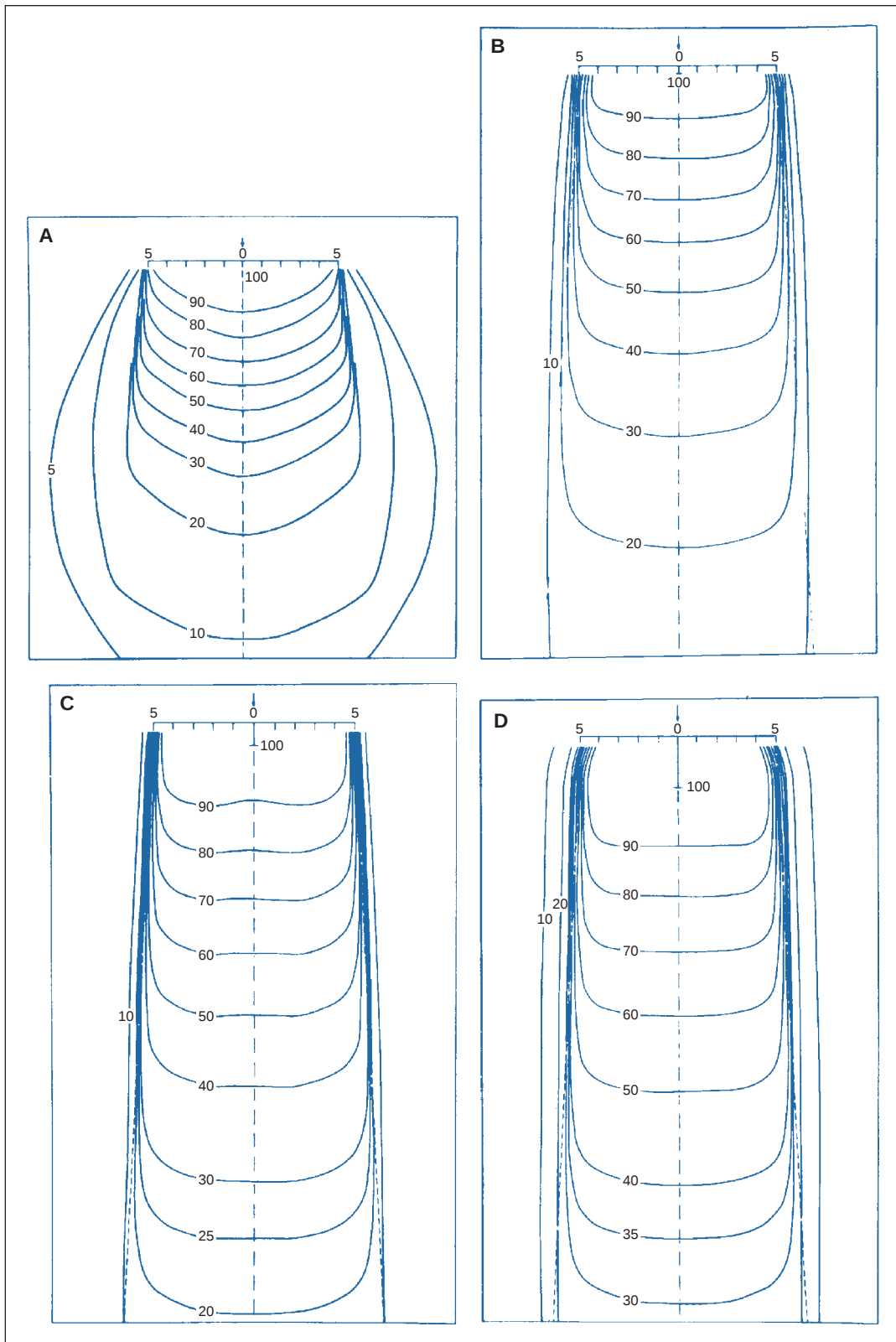


FIGURE 12.15. Isodose distributions for different quality radiation. **A:** 200 kVp, SSD = 50 cm, HVL = 1 mm Cu, field size = 10 × 10 cm. **B:** ^{60}Co , SSD = 80 cm, field size = 10 × 10 cm. **C:** 4-MV X-rays, SSD = 100 cm, field size = 10 × 10 cm. **D:** 10-MV X-rays, SSD = 100 cm, field size = 10 × 10 cm.
Source: From Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Baltimore: Williams & Wilkins; 1994, with permission.

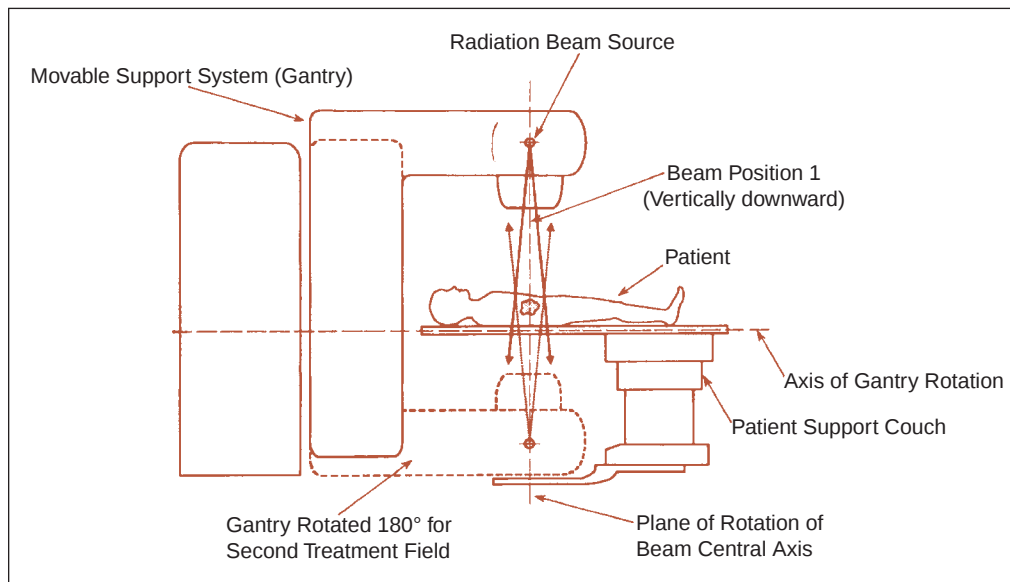


FIGURE 12.16. Example of multifield radiation therapy using parallel opposite beams with an isocentrically mounted radiation source.

electronic portal-imaging device (EPID). By comparing computer generated radiographs (DRRs or digitally reconstructed radiographs) with the actual patient images, discrepancies in field shape and patient setup can be corrected before the delivered treatment. This type of corrective behavior before treatment is the foundation of IGRT. The latest variation on IGRT is the addition of computed tomography (CT) scanners within the linear accelerator to verify more completely the correct alignment of the patient on the treatment table prior to treatment. CT scans are obtained prior to each treatment. In some cases, the CT scans are constructed based on the photon beams (MV) that will be used for treatment. In other cases, a different photon source (kV) is used to reconstruct the CT scan. Because cone beam CT (CBCT) or megavoltage CT (MVCT) uses a high-energy photon beam to gather the information for reconstruction, the image quality suffers because of poor soft-tissue contrast. KVCT or normal CT images, because they use a lower energy photon beam to reconstruct the patient image, have better soft-tissue contrast, but are prone to distorting artifacts from

high-density objects within the patient, that is, hip prostheses. In either case, the CT image at the time of treatment and its corresponding isocenter location are compared to the treatment planning CT and isocenter for agreement. Adjustments for rotation, lateral, vertical, and longitudinal discrepancies are made prior to treatment. The intent of these IGRT treatments is to improve the accuracy of the treatment setup on a daily basis relative to the original treatment plan. This enables decreasing the size of the radiation fields, as there is not as much need for a large margin on the target, which can decrease normal tissue irradiation and even allow for dose escalation to the target. Guidelines for use of IGRT have been published by ASTRO and ACR (52). On-line MR imaging has recently been added to radiation treatment machines and will allow for better soft-tissue resolution of intact cancers such as cervical or vaginal cancers to guide treatment accuracy.

Intensity-modulated arc therapy has been used to deliver IMRT. Tomotherapy is one form of arc therapy. Tomotherapy (Fig. 12.21) is a special type of linac/CT combination (51).

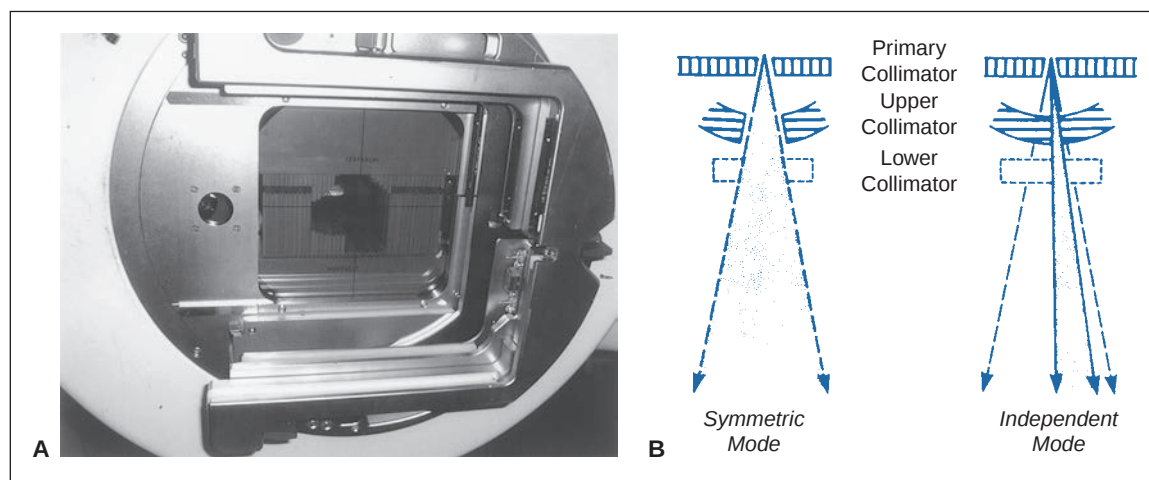


FIGURE 12.17. **A:** Multileaf collimator. **B:** Treatment technique for breast cancer using independent collimators.

Source: From Purday JA, Klein EE. External photon beam dosimetry and treatment planning. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 3rd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998:281, with permission. Source: Courtesy of Varian Associates, Palo Alto, California, USA.

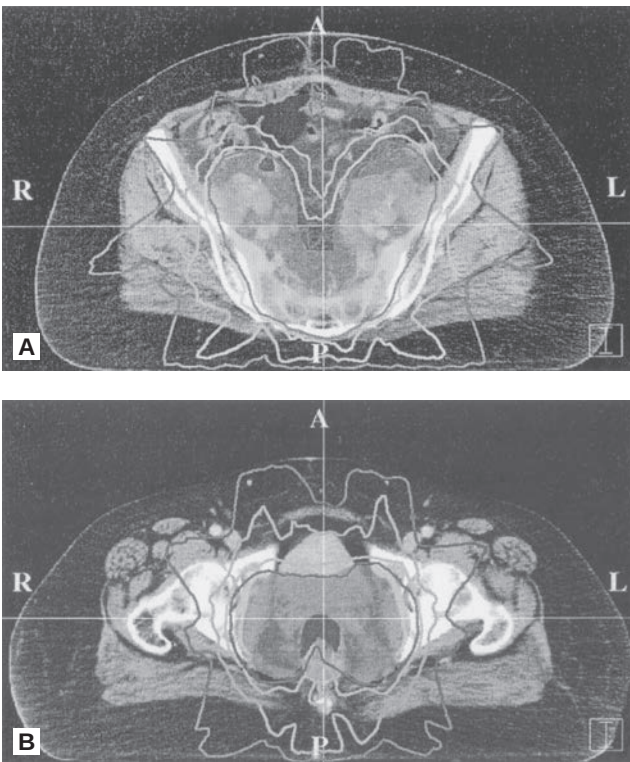


FIGURE 12.18. **A:** Isodose curves from a whole pelvic intensity-modulated radiation therapy plan superimposed on an axial CT slide through the upper pelvis. Highlighted are the 100%, 90%, 70%, and 50% isodose curves. **B:** Isodose curves from a whole pelvic intensity-modulated radiation therapy plan superimposed on an axial CT slide through the lower pelvis. Highlighted are the 100%, 90%, 70%, and 50% isodose curves.
Source: Reprinted from Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 2002;52:1330, with permission from Elsevier.

TomoTherapy units were the first commercially available treatment machines that directly combined CT (MVCT in this case) with highly complex MLCs to deliver IMRT using IGRT. Each day, the patient receives an MVCT, a comparison using 3D fusion to the original treatment plan is made, adjustments to the patient position are made, and IMRT treatment is delivered without the patient needing to change machines. Corrections to the delivered dose can even be modeled based on the patient's current anatomy as visualized by the MVCT built into the TomoTherapy machine. Excellent clinical outcomes have been published with rotational therapy (53). Other linacs are using variation of arc therapy to perform IMRT delivery. Varian (RapidArc®) and Elekta (VMAT) controls gantry speed, aperture shape, and dose rates to generate their arc therapy treatments, a form of volumetric modulated arc therapy (VMAT). Both use the same principle of modulating the beam aperture while the gantry is moving in arc to minimize the time and monitor units while improving dose conformity. In addition to photon beams, many linacs provide the option to treat patients with electron beams of various energies (e.g., 4 to 21 million electron volts [MeV]). Compared to photon beams, electron beams have different depth dose and dose profiles (Fig. 12.22), when electrons, even at the same energy as photons, do not penetrate as far as photons do within tissues. While electron depth doses have a D_{max} that increases with increasing energy, unlike photons, the higher the electron energy, the higher the surface dose to tissue, that is, loss of “skin sparing.” Electrons have been used in the treatment of vulvar and other cancers that involve the inguinal lymph nodes. Great care has to be taken when using electrons in this setting as the inguinal lymph nodes can be very

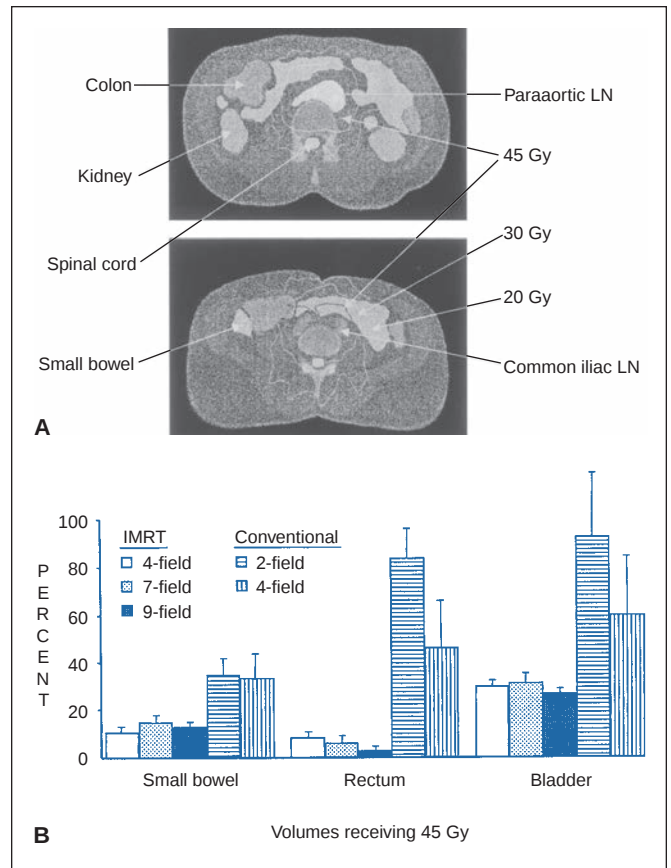


FIGURE 12.19. **A:** Axial views of intensity-modulated radiation therapy dose distribution. **B:** The functional volume of the small bowel, rectum, and bladder receiving ≥ 45 Gy with intensity-modulated radiation therapy and conventional techniques when 100% of the target volume (uterus) receives $\geq 95\%$ of the prescription dose (45 Gy).

Source: Reprinted from Portelance L, Chao KSCC, Grigsby PV, et al. Intensity-modulated radiation therapy (IMRT) reduces small bowel and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys.* 2001;51:261–266, with permission from Elsevier.

deep in women with higher body mass indices (BMI) and will under dose nodes at a depth >3 cm. This resulted in an increased risk of inguinal failures in GOG study (54,56,55). Electrons can be used to treat vulva in patients with close or positive vulvar margins or in combination with higher-energy beams to treat the inguinal nodes in lower BMI patients.

Simulation

The conventional simulator used in radiation oncology departments reproduces all the gantry, collimator, and table rotations used in a linac treatment, and therefore “simulates” the actual treatment. Instead of a therapy (MV) photon beam, the conventional simulator uses a diagnostic (kV) photon beam to simulate the treatment beam. Previously, the conventional simulator (Fig. 12.23) allowed the radiation oncologist to determine beam direction and treatment fields that would be needed for a radiotherapy treatment based on X-ray fluoroscopy. The radiographic visualization of internal structures allowed special shielding (poured blocks) to be constructed. All the geometric parameters of the conventional simulator are nearly identical to the actual treatment linacs. The intersections of the gantry rotation axis, collimator rotation axis (the machine isocenter), and patient location are identified and marked on the patient's skin with removable ink or a permanent series of tattoos. These marks

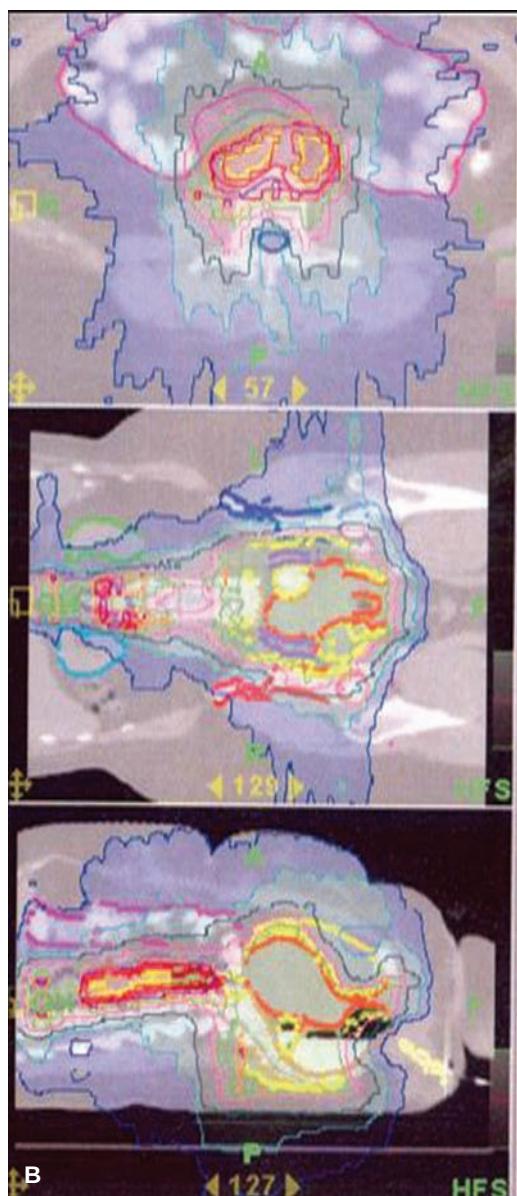
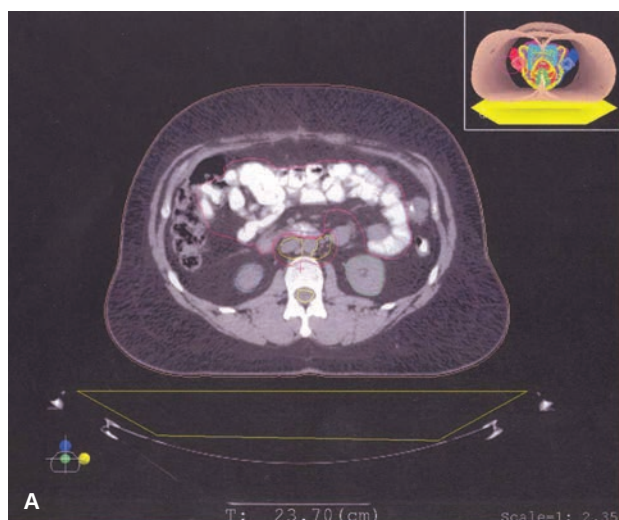


FIGURE 12.20. **A:** Contours of enlarged paraaortic nodes with margin are shown in close proximity to small bowel. **B:** IMRT plan for extended field irradiation in axial, coronal, and sagittal projections.

facilitate the reproduction of the same clinical setup for the patient each day of treatment. Hard-copy radiographs can also be used to document the expected treatment fields for comparison with port films obtained on the treatment linac.

CT-based simulators (“CT Sims”) have largely replaced conventional simulators in most radiation oncology departments. CT Sims (Fig. 12.23) combine a diagnostic CT scanner with a software package that allows for the simulation of the patient setup in the virtual world of the computer. All of the necessary gantry angles and table angles are modeled in the computer. Computer-controlled room lasers tied into the CT Sim software allow the simulator therapist to identify the treatment isocenter in a fashion similar to the conventional simulator. DRRs are created for later comparison to actual treatment images. The treatment isocenter and the full CT images can then be transferred to the computer planning system for further treatment planning. Some departments are also equipped with MR or PET scanners for treatment planning. Fusion of CT images with PET or MR images enables CT-based treatment planning with the benefit of improved tumor definition with PET or MR to reduce margin size or increase dose (36).

Computerized Dosimetry

In a modern radiotherapy department, computers are necessary to accurately calculate the absorbed doses to tissues. These absorbed doses within tissues are termed isodoses, or lines of the same dose. To initiate this process, CT images are acquired of the area of interest at a pretreatment planning session or simulation. These scans are typically obtained on the CT simulator. Treatment targets such as pelvic/para-aortic lymph nodes, the uterus, or vagina are identified through contouring on these images, as are normal tissues such as the rectosigmoid, bladder, large and small bowel, kidneys, stomach, and spinal cord. Dose goals are identified for the targets and normal tissues. A dosimetrist uses this information to design the radiation treatment plan. Treatment beams are planned and the resulting dosimetry is reviewed by the treating physician and a physicist and altered as needed to best address the tumor and avoid the normal organs and tissues. In order for a computer treatment planning system to do all this, the depth dose and dose profiles for all of the treatment beams (photons and electrons) must be accurately entered into the planning system.

There are varying complexities of treatment plans that might be used. For simple targets, such as metastatic cancer to the spine, a simple single field or parallel opposed, two-dimensional (2-D) plan might be all that is required. Complexities of internal anatomy and external surface contours can be ignored while still successfully delivering a palliative treatment plan to the patient. More complicated target definitions might require specific and accurate knowledge of adjacent internal anatomy and the details of the patient’s surface in order to accurately deliver a successful treatment plan. In these cases, a 3-D conformal treatment plan is developed. In still more complicated target/normal tissue regions, IMRT treatment planning might be required in order to give sufficient dose to the target while minimizing the dose to an adjacent normal tissue. The goal for most treatment plans is to treat the target to a specified dose while minimizing dose to adjacent normal tissues.

In all of these examples, the word “target” is used. The goal is to encompass the target with the desired dose. Targets are more formally defined in ICRU 50 (57). Figure 12.24 illustrates the gross target volume (GTV), the clinical target volume (CTV), the planning target volume (PTV), and the treated volume. Each of the target or tumor volumes is larger than the previous target volume by some margin. The CTV includes all of the GTV plus possible microscopic extensions. The PTV includes all of the CTV plus a margin to account for possible geometric uncertainties of the patient or treatment margin. The irradiated volume includes

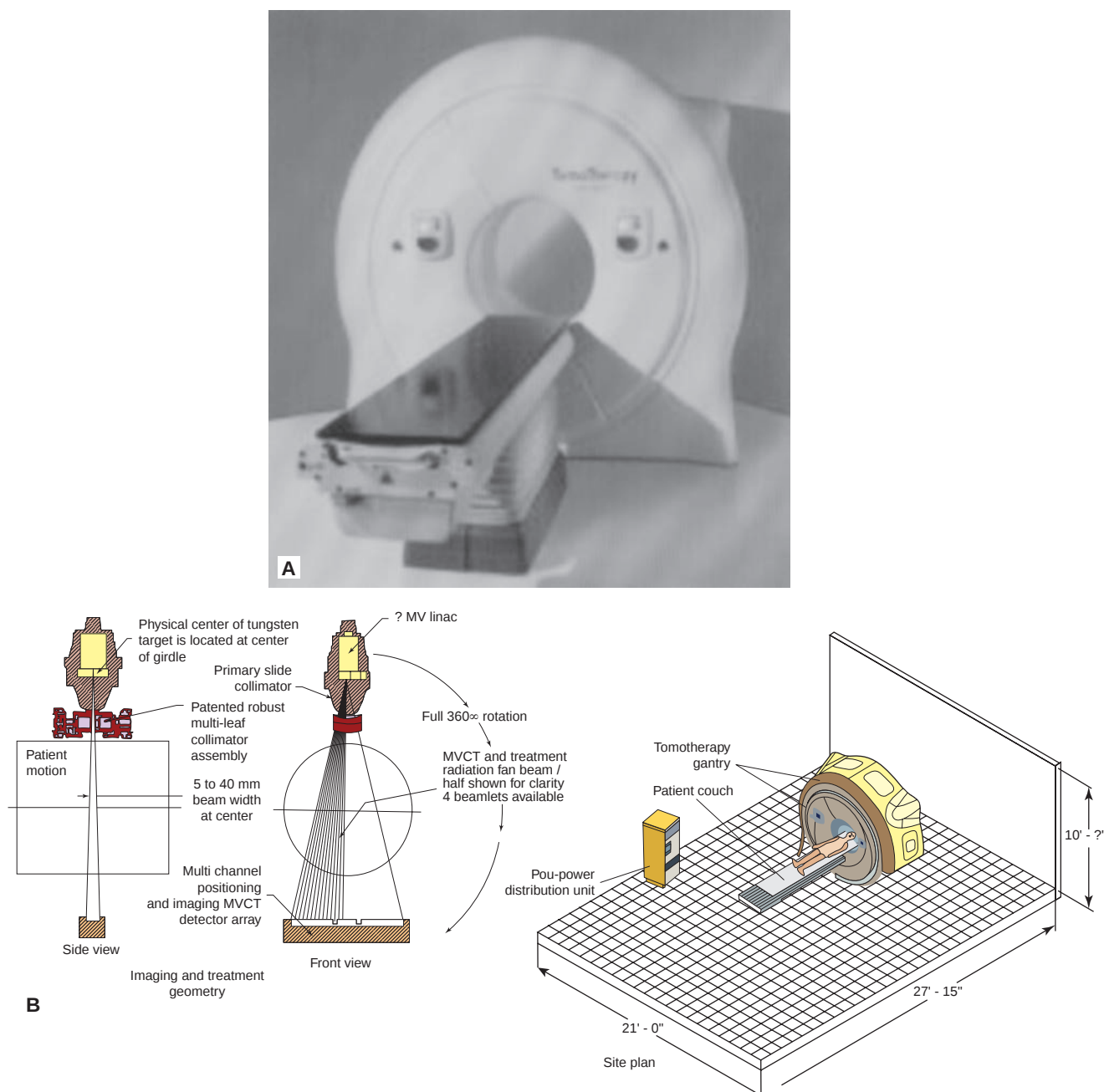


FIGURE 12.21. A: Helical TomoTherapy device commercially available for IMRT. B: Diagrammatic representation of the device.

Source: Courtesy of TomoTherapy Inc., Madison, Wisconsin, USA.

all of the PTV plus any margins that might be included in the treatment plan to provide minimum dose coverage to the PTV.

Brachytherapy Principles

Brachytherapy is a term with Greek roots where “brachy” means “short distance.” With brachytherapy, a highly concentrated dose of radiation is delivered to immediately surrounding tissues within millimeters to several centimeters of the applicators that carry the radioactive sources (58). This allows for a high dose of radiation to be delivered to closely approximated tumor and to relatively spare surrounding normal tissues such as the rectosigmoid, bladder, and small bowel. This is in comparison to teletherapy, where “tele” means “far distance” and refers to external beam irradiation where the radiation source is at a

greater distance from the patient (~100 cm) than with brachytherapy. With external beam irradiation, the tumor and/or tumor bed are typically irradiated along with adjacent tissues at risk such as lymph nodes. External beam irradiation typically is much more penetrating than brachytherapy unless electron beam external irradiation is used. With electron beam therapy, superficial structures such as the skin and or superficial lymph nodes are optimally treated unlike the deep abdominopelvic tissues, which are best irradiated with the penetrating photons produced by a linear accelerator.

There are different types of brachytherapy or radioactive implants (58). Temporary implants are used most frequently and are categorized as interstitial or intracavitary. With interstitial brachytherapy, the radioactive sources are transiently inserted into tumor-bearing tissues directly through placement in hollow needles or tubes. With intracavitary brachytherapy, radioactive

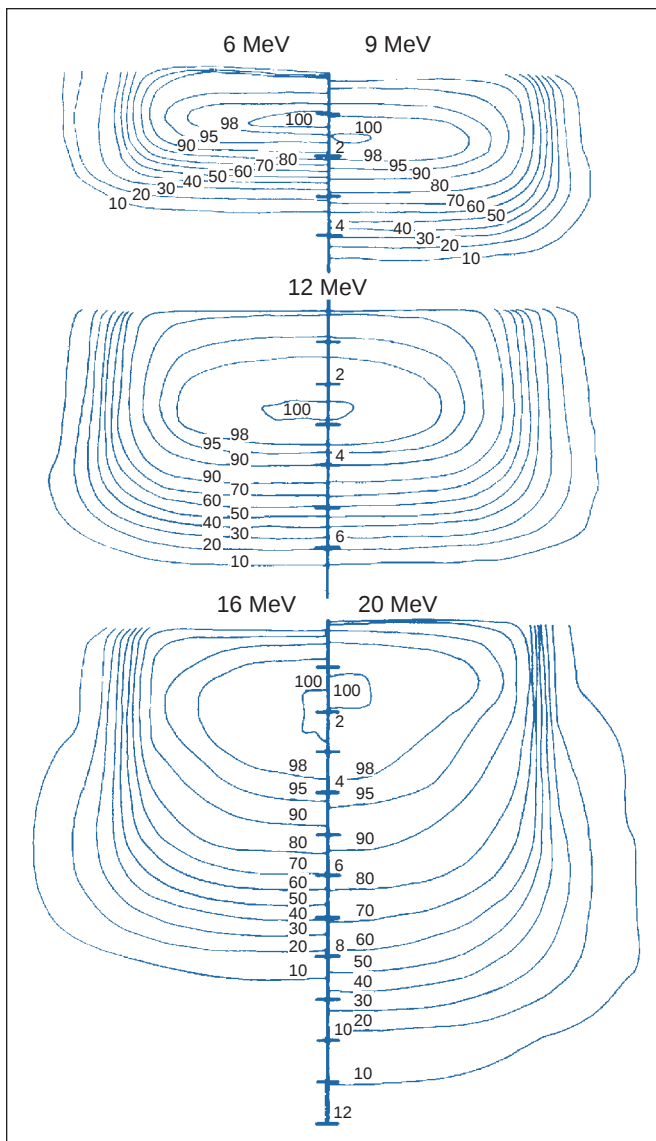


FIGURE 12.22. Electron beam central axis isodose curves for a 10 × 10 cm field at 100 cm SSD. These data are for the Varian Clinac 20 at the Department of Radiation Oncology, Washington University in St. Louis, MO.

Source: From Glasgow GR Purdy JA. External beam dosimetry and treatment planning. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 2nd ed. Philadelphia, PA: JB Lippincott Co.; 1992:208–245, with permission.

sources are placed into naturally occurring body cavities or orifices such as the vagina or uterus using commercially available hollow applicators such as a vaginal cylinder or tandem and ovoids. Temporary surface applications or plesiotherapy for ophthalmic or skin tumors and intraluminal applications in the esophagus, bronchus, and bile duct are other possible approaches. Permanent interstitial implants entail insertion of radioactive seeds (iodine 125 [^{125}I]; gold 198 [^{198}Au]; palladium 103 [^{103}Pd]) directly into tumor-bearing tissues to emit radiation continuously as they decay to a nonradioactive form (58). Radioactive sources are also sealed or unsealed, referring to whether they are solid (^{137}Cs ; ^{192}Ir) or liquid radioisotopes (phosphorus 32 [^{32}P]). The most common sealed radioactive sources used for gynecologic brachytherapy are ^{192}Ir and ^{137}Cs . Historically, unsealed radioactive sources such as ^{32}P have been used to treat the entire peritoneal cavity in ovarian cancer. The limitation of this source was that the beta rays emitted penetrated only a distance of 3 mm, making it useful only for

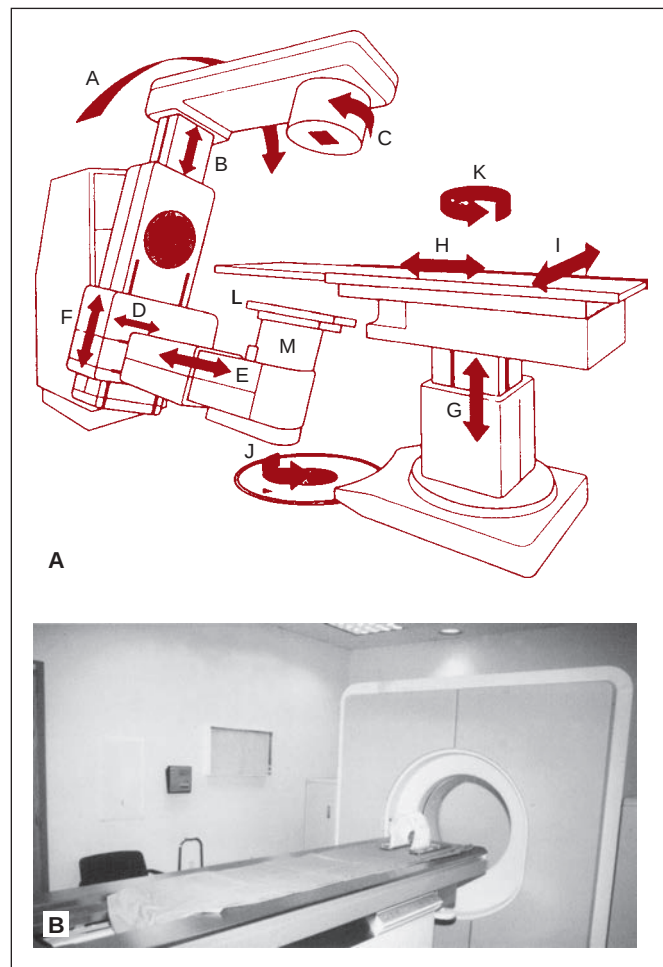


FIGURE 12.23. **A:** The basic components and motions of a radiation therapy simulator: A, gantry rotation; B, source-axis distance; C, collimator rotation; D, image intensifier (lateral); E, image intensifier (longitudinal); F, image intensifier (radial); G, patient table (vertical); H, patient table (longitudinal); I, patient table (lateral); J, patient table rotation about isocenter; K, patient table rotation about pedestal; L, film cassette; M, image intensifier. Motions not shown include field size delineation, radiation beam diaphragms, and source-tray distance. **B:** Three-dimensional simulator that is basically a modified CT scanner with a flat couch suite for treatment planning.

Source: From Van Dyk J, Mah K. Simulators and CT scanners. In: Williams JR, Thwaites DI, eds. *Radiation Therapy Physics*. New York, NY: Oxford Medical Publications; 1993:118 (Fig. 7.3). Reprinted by permission of Oxford University Press.

patients with microscopic or very thin residual tumor deposits following debulking.

Dose rate is also an important variable in brachytherapy. Traditional LDR irradiation has been used for decades in gynecologic cancers using ^{226}Ra and ^{137}Cs sources for intracavitary insertions and low activity ^{192}Ir sources for interstitial insertions. HDR brachytherapy has gradually been introduced over the last several decades and entails the use of a highly radioactive (^{10}Ci) ^{192}Ir source. There are several definitions for the dose rates used in brachytherapy. The ICRU 38 classifies LDR as 0.4 to 2 Gy/hr, MDR (medium dose rate) as 2 to 12 Gy/hr, and HDR as >12 Gy/hr (59). More standard ranges for LDR are 40 to 100 cGy/hr, and for HDR 20 to 250 cGy/min, which is 1,200 to 15,000 cGy/hr. Pulsed dose rate (PDR) is increasingly popular with the scarcity of available new ^{137}Cs sources. Rather than using a high-activity ^{10}Ci ^{192}Ir source with short dwell times as in HDR, PDR uses a medium-strength ^{192}Ir source of 0.5 to 1.0 Ci with dose rates of up to 3 Gy/hr. The radiation with PDR is typically delivered in

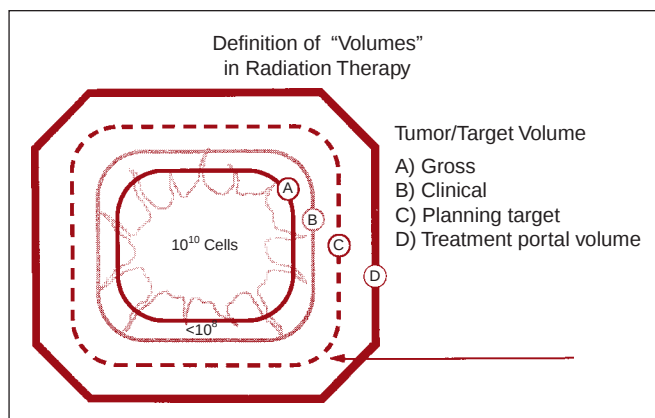


FIGURE 12.24. Schematic representation of “volumes” in radiation therapy. The treatment portal volume includes the gross target volume, potential areas of local and regional microscopic disease around the tumor (clinical), and a margin of surrounding normal tissue (planning).

Source: From Perez CA, Purdy JA. Rationale for treatment planning in radiation therapy. In: Levitt SH, Khan FM, Potish RA, eds. *Levitt and Tapley's Technological Basis of Radiation Therapy: Practical and Clinical Applications*. 2nd ed. Philadelphia, PA: Lea & Febiger; 1992. Modified in Perez CA, Brady LW, Roti JL. Overview. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 3rd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998:1, with permission.

a “pulsed” method over only 10 to 30 minutes of each hour as opposed to LDR techniques, which deliver 30 to 100 cGy/hr continuously over several days (60,61). PDR delivers the same total dose over the same total time at the same hourly rate as LDR, but with an instantaneous dose rate higher than LDR. PDR brachytherapy was developed to combine the isodose optimization of HDR brachytherapy with the biologic advantages of LDR.

The term “afterloading,” whereby an unloaded applicator is inserted first and the radioactive sources introduced later, was popularized by Henschke (62). Nearly every modern brachytherapy exploits afterloading. An ideal implant is established with the appropriate applicator before being loaded with the radioactive sources. This sequence allows for more careful and accurate applicator placement than inherent to earlier “hot loaded” applicators, which were placed in the operating room preloaded with radium. Radiation exposure to medical personnel is reduced and exposure of operating room personnel is totally eliminated. Remote afterloading, which eliminates all personnel exposure, entails the use of a computer-driven machine to insert and retract the source(s), which are attached to a cable. During treatment, the source is transported from its shielded safe to the patient's applicators via a transfer tube. Sources are retracted automatically whenever visitors or hospital personnel enter the room. With modern remote afterloading techniques, a single cable-driven radioactive source is propelled through an array of dwell positions in needles, plastic tubes, or intracavitary applicators within an implanted volume. Through computerized dosimetry, the source stops for a specified duration at a preselected number of locations during its transit, delivering a specified dose to a defined volume of tissue. This dose may be delivered rapidly in a large fraction, as in the case of HDR brachytherapy, or a series of small “pulsed doses” delivered at a given frequency over a period of days, as in PDR brachytherapy (60). Typically, these treatment units are housed in shielded rooms in the hospital (LDR or PDR) or the radiation oncology department (HDR) to further eliminate radiation exposure (58).

Radiation Protection

The amount of radiation that a person other than patients under treatment can receive is governed by state and federal

regulations. The actual values depend on whether the person is considered part of the general public or an occupationally exposed worker. These values can change with different regulations. The National Council on Radiation Protection and Measurements (21) set the following recommendations for limits on exposure to ionizing radiation:

Public exposures <1 mSv or 0.1 rem annually

Occupational exposures <50 mSv or 5 rem annually

Additionally, NCRP Report #91(21) placed limits on embryo-fetus exposures:

Total dose limit <5 mSv or 0.5 rem

Dose equivalent limit in 1 month <0.5 mSv or 0.05 rem

These recommended limits were adopted by the Nuclear Regulatory Commission (10 CFR 20, Standards for Protection against Radiation).

Linacs produce radiation using electrical power. Once the linac is turned “off,” there is little, if any, radiation exposure risk to staff. Radioactive isotopes, used most often for brachytherapy, however, do not have an “off” switch. They are always undergoing radioactive decay with the resultant radiation production of X-rays, γ -rays, electrons, and other particles.

Radiation safety is an important focus for patient and health care workers. All hospitals that house radioactive sources or linear accelerators will have a special department termed radiation safety. Radiation personnel are responsible for monitoring radiation exposure in hospitals and clinics. All health care workers exposed to radiation must wear badges that track radiation exposure. There are three words that encompass all of the important aspects of radiation safety and protection: time, distance, and shielding. All three can be used to reduce radiation exposure. The dose delivered to a target from a radioactive source is directly proportional to the amount of time the target is exposed to the radioactive source (63). The dose delivered to a target is inversely proportional to the square of the distance from the radioactive source double the distance and the dose is reduced by a factor of four:

$$\text{Dose} \sim \text{time}$$

$$\text{Dose} \sim 1/r^2$$

This is the inverse square rule. The relationship between shielding and absorbed dose is more complicated. The simplest explanation is that the absorbed dose is reduced in an exponential relationship to the physical amount of shielding. The exact relationship (μ) depends on the energy of radiation and the specific material, such as concrete or lead, used to provide the protection. More material (x) means more protection. Less energy means more protection for the same thickness (x) of material:

$$\text{Dose} \sim e^{-\mu x}$$

Minimizing time, maximizing distance, and maximizing shielding will reduce one's absorbed radiation dose. Fortunately, there is relatively little exposure to radiation for most health care providers. The linear accelerators in radiation oncology are strategically located and shielded to minimize radiation to anyone other than the treated patient. Many brachytherapy insertions are typically performed with remote afterloading to minimize exposure, and often outpatient brachytherapy can be realized because of HDR techniques. This takes the patient off the hospital ward and thereby avoids exposure to the health professional caring for inpatients. The shielded rooms in the radiation oncology department protect the attendant staff from exposure as well.

CLINICAL APPLICATIONS

Historical Background

The use of radiation in the treatment of gynecologic cancers has a rich history. Roentgen rays were used externally as early as 1902 to treat cervical carcinoma and “radium rays” in 1906. In Europe, the use of intracavitary radium was reported in 1903 for the treatment of inoperable uterine cancers (64). In 1913, Robert Abbe was the first to report a true cure with a patient alive and well after 8 years of follow-up (65). In those early years, there was little knowledge of the biologic effects of radiation on the normal and tumor tissues. Typically, a uterine tandem was used alone without vaginal colpostats. There was little understanding of the dose distribution in the tumor and surrounding normal tissues, and implant duration, and thereby dose, was entirely empirical. Complications and failures were common.

Brachytherapy Systems for the Treatment of Cervical Cancer

Intracavitary brachytherapy for cervical carcinoma was profoundly impacted by the development of various “systems” that attempted to combine empiricism with a more scientific and systematic approach. A dosimetric system refers to a set of rules concerning a specific applicator type, radioactive isotope, and distribution of the sources in the applicator to deliver a defined dose to a designated treatment region (59). Within any system, specification of treatment in terms of dose, timing, and administration is necessary to implement the prescription in a consistent manner. Three systems were developed in Europe, including the Paris system, the Stockholm system, and the Manchester system (66,67,68). The Manchester system principles are an integral part of modern brachytherapy (68).

The Manchester System

The Manchester system was developed in 1932 by Tod and Meredith (68,69,70), and was later modified in 1953 (71) at the Holt Radium Institute. It standardized treatment with predetermined doses and dose rates directed to fixed points in the pelvis. The fixed points A and B were selected on the theory that the dose in the paracervical triangle impacted normal tissue tolerance rather than the actual doses to the bladder, rectum, and vagina. The paracervical triangle was described as a pyramidal-shaped area with its base resting on the lateral vaginal fornices and its apex curving around with the anteverted uterus. “Point A” was defined as 2 cm lateral to the central canal of the uterus and 2 cm from the mucous membrane of the lateral fornix in the axis of the uterus (Fig. 12.25). It often correlates anatomically with the point of crossage of the ureter and uterine artery and was taken as an average point from which to assess dose in the paracervical region. “Point B” was located 5 cm from midline at the level of point A and was thought to correspond to the location of the obturator lymph nodes. To achieve consistent dose rates, a set of strict rules dictating the relationship, position, and activity of radium sources in the uterine and vaginal applicators was devised. The amount of radium would vary based on ovoid size and uterine length such that the same dose in roentgen would be delivered to point A regardless of the size of the patient or the size and shape of the tumor, uterus, and vagina. The vaginal ovoids were available in three sizes: small (2.0-cm diameter), medium (2.5-cm diameter), and large (3.0-cm diameter) and were preloaded or “hot loaded” with radium.

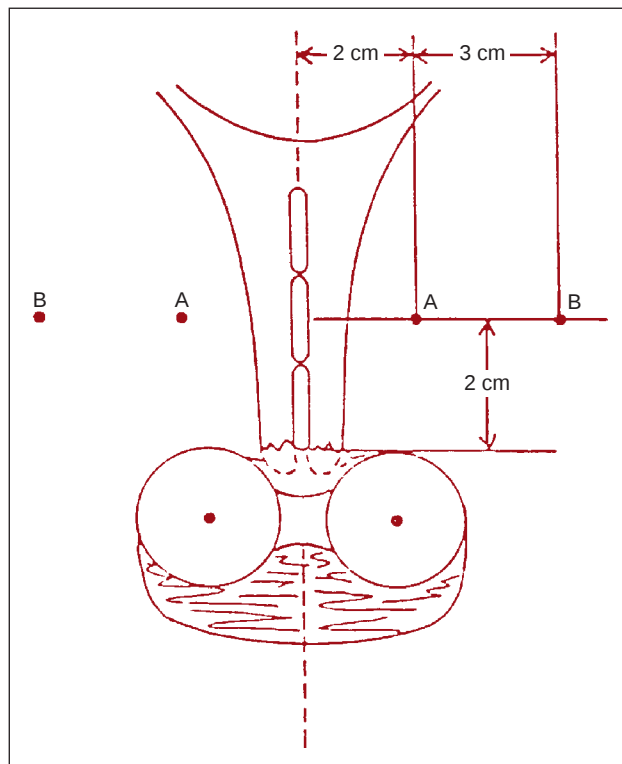


FIGURE 12.25. The Manchester system. Definitions of points A and B in the classical Manchester system are found in the text. In a typical application, the loading of intrauterine applicators varied between 20 and 35 mg of radium and between 15 and 25 mg of radium for each vaginal ovoid. The resultant treatment time to get 8,000 R at point A was 140 hours. Source: From Meredith WJ, *Radium Dosage: The Manchester System*. Edinburgh, UK: Livingstone, 1967, with permission.

The amount of radium per ovoid varied by size to get a uniform dose rate at the ovoid surface. It was recommended to use the largest ovoid size possible and place the ovoids as far laterally as possible in the fornices to carry the radium closer to point B and increase the depth dose. Vaginal packing was used to limit the dose to the bladder and rectum to <80% of point A. Two intracavitary applications of 72 hours with a 4- to 7-day interval between them were given to deliver a dose of 8,000 R at 55.5 R/hr to point A and 3,000 R to point B. External beam irradiation with a midline block in place was later used to deliver a total cumulative dose of 6,000 R to point B.

The Manchester system underlies contemporary intracavitary techniques and dose specification. With current LDR applications using cesium rather than radium, it is considered standard to have a point A dose rate of 50 to 60 cGy/hr and to deliver a total dose of 85 Gy to point A and 60 Gy to point B when combined with external beam therapy while limiting the normal tissues to <80% of the point A dose.

The Fletcher (M.D. Anderson) System

The Fletcher system was established at M.D. Anderson Hospital in the 1940s (72). The Fletcher applicator was subsequently developed and remains an integral part of gynecologic brachytherapy (Fig. 12.26) (73). The initial dosimetric work at M.D. Anderson was done prior to the development of computerized dosimetry in the 1960s (74). As in the Paris system, milligram-hours (mg-hr) were used for dose prescription with the premise that with any geometric arrangement of specified sources, dose at any point is proportional to the amount of

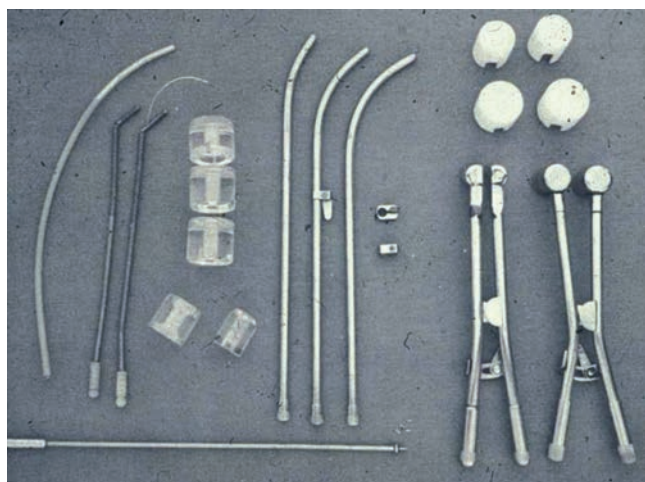


FIGURE 12.26. Fletcher Suit Delclos low-dose-rate applicators. Left to right: Afterloading colpostats, mini ovoids, tandems, cylinders, and source inserters.

Source: Reprinted with permission from Fletcher, Gilbert H, eds. *Textbook of Radiotherapy*. 3rd ed. Philadelphia, PA: Lea & Febiger; 1980:741.

radioactivity and the implant duration. Though previous systems (Paris and Stockholm) had used mg-hr, clinical experience alone determined the amount of radium tolerable to the tissues. Fletcher predicted that better results and less morbidity could be obtained if knowledge of the energy absorbed at various points in the pelvis (“measured data”) such as the bladder and rectum and pelvic lymph nodes could be determined (75). According to Fletcher, a dosimetric approach should meet the following requirements: (a) ensure that the primary disease in the cervix and fornices and immediate extensions into the paracervical triangle are adequately treated; (b) guide treatments in such a way that the bladder and rectum are not overdosed (respect mucosal tolerance); and (c) determine the dose received by the various lymph node groups. Individualization to fit the anatomical situation was an essential aspect of this system (76).

The primary prescription parameter in the Fletcher system was tumor volume, and prescription rules were based on maximum mg-hrs and maximum time, taking into account the total external beam dose and the calculated sigmoid dose. An application was left in place until either of these two maximums was reached. Large mg-hr implants were halted by the mg-hr prescription while smaller mg-hr implants were terminated by time. A set of maxima of mg-hrs was established for combinations with external irradiation, which were published in tables (77,78). Standardized source arrangements and limits on the vaginal surface dose and mg-hrs were all used to help specify treatment.

Despite a more elaborate dosimetry system, the Fletcher system combined many elements of the Paris and Manchester systems, including using the largest size ovoid possible positioned as far laterally and cephalad as possible to give the highest tumor dose at depth for a given mucosal dose. By using a larger ovoid, the radium-mucous membrane distance was increased, allowing a greater increase in the total number of mg-hrs and a greater volume of adequate irradiation (72). The Fletcher colpostats were actually a further evolution of the Manchester ovoids and were made with the same diameters of 2, 2.5, and 3 cm but were more cylindrical than Manchester “ovoids” and were attached to handles, with shielding in the direction of the bladder and rectum. Initially these were preloaded with radium, but later an afterloading model was developed and loaded instead with ^{137}Cs (79,80). Recommended loadings were 15, 20, and 25 mg of radium for the 2-, 2.5-, and 3-cm colpostats,

respectively, and 5 to 10 mg for the mini-ovoids (79). Like the earlier systems, it was also recommended to use the longest tandem available and load the tandem so that sources reached the uterine fundus to give an adequate distribution in the lower uterine segment and paracervical areas and to increase the dose to the obturator lymph nodes. Additionally, a high position of the applicator in the pelvis and a wide separation of the ovoids were thought to increase the dose to the pelvic wall (72,81). Tight packing was also recommended to displace the system upward and centrally and to decrease the dose to the bladder and rectum (72). Recommended tandem loadings were usually 15–10–10 mg of radium with the amount of radium in the tandem usually greater than that in the ovoids (76). The distal source in the tandem was to be positioned to produce an even pear-shaped dose distribution with no drop in dose rate between the tandem and ovoids, without excessive overlap that would cause a hot spot on the adjacent bladder or rectal mucosa. With the ovoids well positioned, this was usually accomplished by placing the physical end of the distal source at or a few millimeters beyond the external os of the cervix. A 10-mg protruding source was recommended if the vaginal ovoids were separated by more than 5 cm or displaced caudally, with each ovoid then decreased by 5 mg.

A careful review of implant films was outlined (Figure 12.27). It was recommended to keep the tandem in the axis of the pelvis, equidistant from the sacral promontory and pubis and the lateral pelvic walls to avoid overdosage to the bladder, sigmoid, or one ureter. The tandem was recommended to bisect the ovoids on the AP films and bisect their height on the lateral films (82). The flange of the tandem was to be flush against the cervix and the ovoids surrounding it, verified by confirming the proximity of the applicators to radio-opaque cervical seeds. Radio-opaque vaginal packing was used to hold the system in place and displace the bladder and rectum. Scrutiny of implant films prior to treatment remains an important tenant of brachytherapy. Two or more intracavitary insertions were thought to make more efficient use of the inverse square law such that the second and third implants would deliver intense radiation to the tumor periphery because of interval tumor regression. A recent retrospective review of implant geometry has confirmed the consistency of the M.D. Anderson approach and the good outcomes achieved when attention is paid to applicator position in the pelvis (83).

The current M.D. Anderson approach to treatment specification reflects a policy of treating advanced cervical carcinoma to normal tissue tolerance (84). This includes integrating standard loadings and mg-hrs with calculated doses to the bladder, rectum, sigmoid, and vaginal surface. The activity in the ovoids is limited by the vaginal surface dose, which is kept below 140 Gy. Calculated bladder and rectal doses are noted and are sometimes used to limit the duration of the intracavitary system, with the combined external beam and implant doses for the bladder kept at <75 to 80 Gy and for the rectum at <70 to 75 Gy. Mg-Ra-eq-hrs are usually limited to 6,000 to 6,500 after 40 to 45 Gy external beam. Though mg-hrs have usually been used to guide and report doses at M.D. Anderson, recent retrospective reviews have also reported point doses, though these have not been used to plan or prescribe treatment. With the implant loadings and durations outlined by Fletcher, typical dose rates at point A are approximately 57 cGy per hour and vaginal surface dose rates are 100 cGy/hour (83,85). The median doses to point B and to the International Commission on Radiation Units & Measurements (ICRU) rectal and bladder reference points averaged 28%, 59%, and 60% of the point A doses, respectively. The median total dose to point A from external beam and intracavitary irradiation was 87 Gy, and the median doses to the bladder and rectum were 68 and 70 Gy. The total dose delivered to the vaginal surface was limited to 120 to 140 Gy or 1.4 to 2.0 times the point A dose. These total doses to

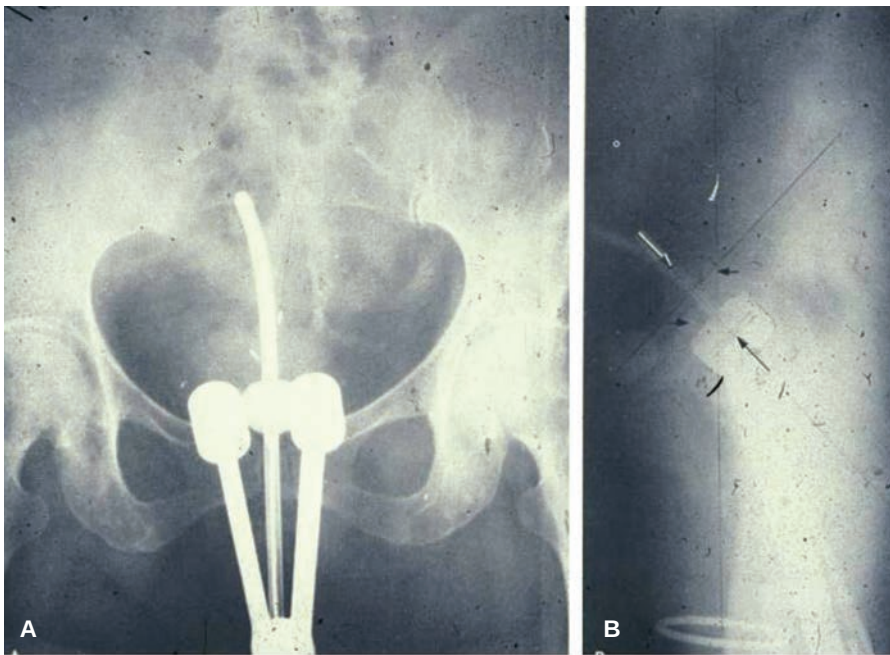


FIGURE 12.27. Ideal position of tandem and ovoid applicator on an AP radiograph **A**: and a lateral radiograph **B**: Note the metallic seeds inserted into the cervix.

Source: Reprinted with permission from Fletcher, Gilbert H, eds. *Textbook of Radiotherapy*. 3rd ed. Philadelphia, PA: Lea & Febiger; 1980:745.

point A and the vagina, bladder, and rectum are used as contemporary guidelines for determining implant duration and, therefore, dose.

Point A Redefined

The failure of localization radiographs to show the surfaces of the ovoids made implementation of the initial definition of point A difficult. The definition of point A was modified in 1953 to be “2 cm up from the lower end of the intrauterine source and 2 cm laterally in the plane of the uterus, as the external os was assumed to be at the level of the vaginal fornices” (Fig. 12.28) (71). This definition of point A is currently used at many institutions (86,87). A seed or marker ball placed near the exocervix and coincident with the tandem flange is used to identify the exocervix on the localization films. This definition, however, becomes problematic when the cervix protrudes between the ovoids (Fig. 12.29). This causes a resultant increase in dose rate at point A because point A lies in the higher dose “bulge” around the ovoids (81). The variation of point A often occurs in a high-gradient region of the isodose distribution. A consistent location for dose specification should fall sufficiently superior to the ovoids where the dose distribution runs parallel to the tandem (Fig. 12.30) (88,89). In patients with deep vaginal fornices, reverting to use of the ovoid surface rather than the exocervix can help to solve this problem (88,89).

Limitations of Brachytherapy Systems: Point A

It has become clear over time that points A and B are not anatomic sites. The actual specification is related to the position of the intracavitary sources rather than to an anatomical structure. Lewis et al. also demonstrated that point A does not maintain a constant relationship to any specific structure and its position varies with the type of applicator, individual tumor anatomy, and age of the patient. No correlation was found between point B and the pelvic wall (90,91). Potish also questions the validity of point A as its position bears no fixed relationship to tumor

or normal tissue anatomy and is in a steep dose gradient and sensitive to displacement (92,93). Point A can be identical for implants that differ in fundamental ways and deliver different overall 3-D dose distributions.

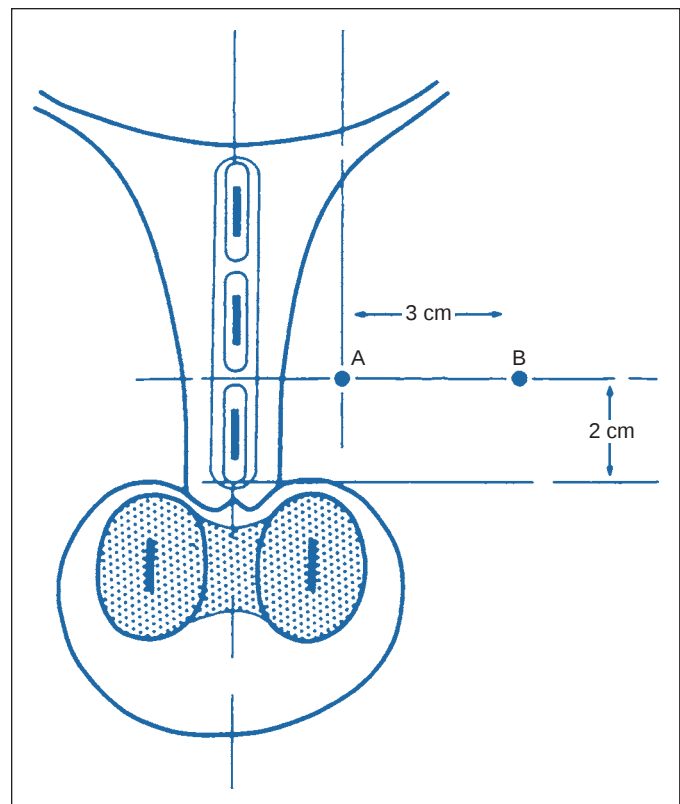


FIGURE 12.28. Revised Manchester system definition of point A.

Source: From Morita K. Cancer of the cervix. In: Vahrson HW, ed. *Radiation Oncology of Gynecologic Cancers*. 1st ed. Berlin, Heidelberg, New York: Springer-Verlag; 1997:185, with permission.

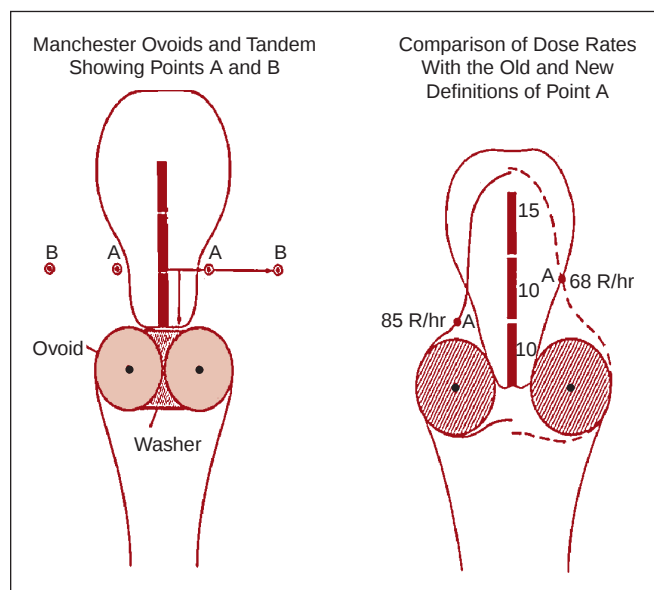


FIGURE 12.29. The definition of point A using the revised Manchester definition becomes problematic when the cervix protrudes between the ovoids, causing an increase in dose rate at point A. Use of the classical Manchester definition of point A (point A defined from the level of the upper vaginal fornices rather than the location of the exocervix) may be helpful.
Source: Reprinted with permission from Batley F, Constable WVC. The use of the Manchester system for treatment of cancer of the uterine cervix with modern afterloading radium applicators. *Am J Roentgenol Rad Ther.* 1967;18:397.

Limitations of Brachytherapy Systems: mg-hr Systems

The use of mg-hr systems also continues at many institutions to guide the choice of source strength and duration of the implant, estimate the risk of complications, compare treatment between patients and institutions, and estimate efficacy (94,95). In the past, little attempt was made to obtain dose information to anatomical structures, and mg-hr prescriptions were not necessarily accompanied by isodose distributions so that the dose prescription was not related to patient anatomy.

Contemporary Dose Specification for Cervical Cancer

The advent of afterloading applicators and computerized dosimetry have brought about a dramatic change in dosimetric analysis (74,96,98). With LDR brachytherapy, the basic principle of 2-D film-based intracavitary prescription is to leave a specific loading of sources in for a definite time, determined by empirical experience, prescription rules, and computerized dosimetry which provides the dose at several anatomic points and isodose distributions (Fig. 12.31). The intracavitary dose is based on the extent of disease and is altered if computer calculations indicated high doses to surrounding critical structures. The rectum and bladder are viewed as tolerance points, compared to point A, which is a treatment dose specification point (97,61). A combination of both mg-hrs and point doses is used at some institutions to guide implant duration (81,101). Though these definitions vary from institution to institution, most will attempt to quantify doses in the paracervical region (point A), and at either point B or the pelvic wall (C or E), and the rectum and bladder (86,87,61). Although intracavitary point dose calculations are not recorded as often for the sigmoid, vaginal mucosa, or cervix, dose evaluation at

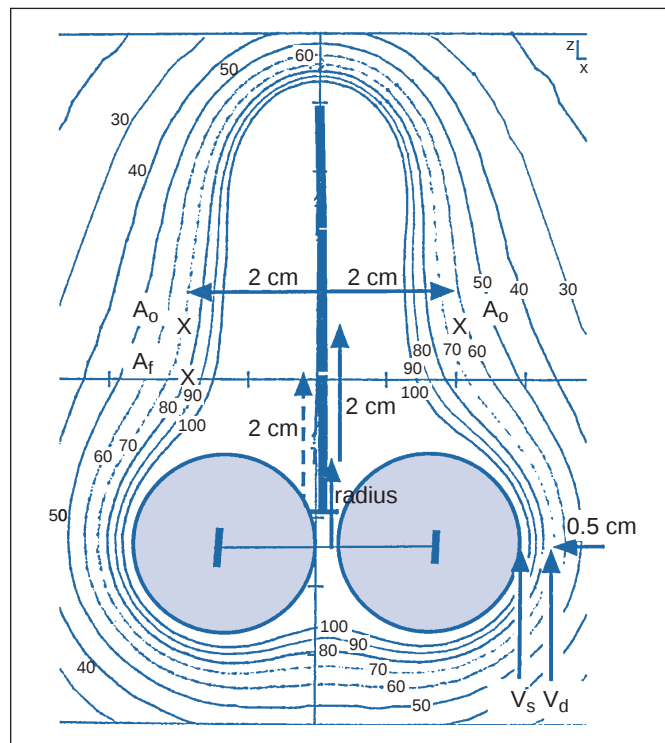


FIGURE 12.30. Variations of point A based on definition. A consistent location for dose specification should fall superior to the ovoids where the dose distribution runs parallel to the tandem and not close to bulge of the pear.
Source: Reprinted with permission from Nag S, Chao C, Erickson B, et al. American Brachytherapy Society recommendations for low-dose rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2002;52(1):38.

these points is also helpful. Maruyama et al. defined a point T (tumor dose) located 1 cm above the cervical marker and 1 cm lateral to the tandem, which is usually 2 to 3 times the dose at point A (99) and has been used at other institutions (100,101). Vaginal surface dose rates, defined at the lateral ovoid surface, will vary based on applicator diameter and available source strengths and should be in the range of 1.4 to 2.0 (the point A dose) (83,102).

It has become increasingly obvious that 2-D orthogonal film-based dose distribution analysis, in which single or multiple reference points are chosen on films at the interface of the organs closest to the applicators and at select dose specification points, is inadequate for gynecologic brachytherapy. Single tumor reference points such as Point A, chosen from localization films, do not give sufficient information about the dose distribution throughout the tumor volume. Nor do the reference points for the bladder and rectosigmoid accurately reflect the dose distribution within these organs. Additionally, there is no recognition of the volume of tumor and normal tissues receiving these doses (28). Increasingly, this 2-D approach is now frequently challenged with the advent of MRI and CT compatible applicators and DICOM image transfer used traditionally for external beam plans. Most radiation oncology departments have CT simulators and some are also acquiring MR scanners, making 3-D image-guided brachytherapy a more common reality. Image-based brachytherapy enables defining both the disease and the organs at risk and then shaping the dose distribution to optimally cover disease and exclude the normal tissues (Fig. 12.32). (103,104,28). Directly relating the intracavitary system to the anatomy through use of CT and MRI is the next step in the lineage of dosimetric systems (Fig. 12.60) (28,103–106).

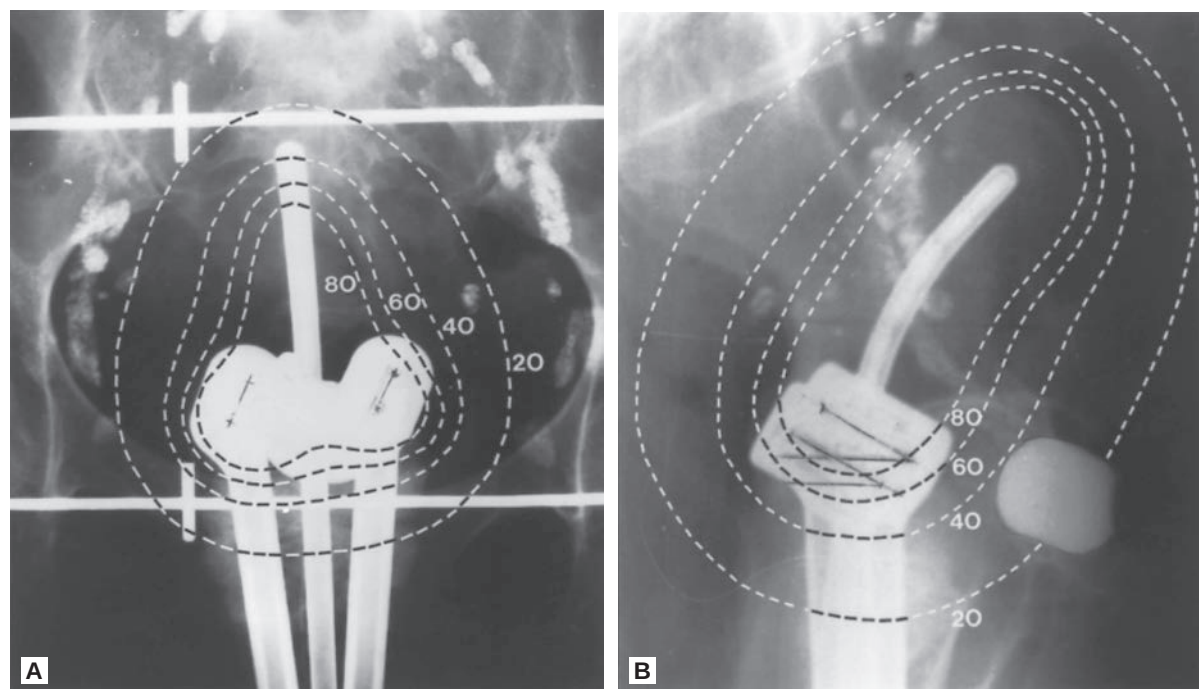


FIGURE 12.31. **A:** Anteroposterior view of intracavitary insertion for carcinoma of the uterine cervix. **B:** Lateral view of same implant. Isodose curves (cGy/hr) are superimposed.

Source: From Perez CA, Grigsby PV, Williamson JF. Clinical applications of brachytherapy. I: Low dose-rate. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*, 3rd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998:487, with permission.

The American Brachytherapy Society (ABS) has been pivotal in developing guideline for the treatment of gynecologic cancers and these will be cited throughout this text for both LDR and HDR brachytherapy. Initially published by Nag et al. (88,89) these have recently been updated and published (107,61). The HDR guidelines, in particular, emphasize the importance of image guidance in brachytherapy planning.

CT is excellent for delineation of the normal pelvic organs, but is poor in defining tumor in the cervix or vagina. With CT-based computerized dosimetry, rectosigmoid and bladder doses can more accurately be determined than with localization films. Even when using CT compatible applicators, however, the boundaries between structures of interest are poorly defined. The value of MR in the imaging of gynecologic cancers lies in its multiplanar capability and superior soft-tissue resolution, compared to CT, enabling delineation of tumor within the cervix, uterus, and vagina as well as within the parametrial and vaginal tissues (108,109). Tumors of the cervix display moderately increased signal on T2-weighted images relative to normal cervical stroma, permitting definition of tumor volume. This is an advantage during brachytherapy as one can assess the proximity of the tumor to the applicator and the subsequent dose distribution throughout the tumor volume. The excellent soft-tissue resolution of MRI allows visualization of residual tumor in relation to the isodose distribution around the MRI compatible brachytherapy applicators (Figs. 12.33 and 12.60) (108–111). The dose distribution can then be optimally conformed to the defined target volume while accurately defining and limiting the dose to the adjacent normal organs at risk. The Gyn GEC ESTRO working group began to develop guidelines for recording and reporting 3-D image-based treatment planning for cervix cancer brachytherapy in 2000. The guidelines were published in 2005, which described a methodology using MR at the time of brachytherapy to define the GTV and CTV (112,113). The gross tumor volume (GTV) at the time of brachytherapy

was defined as residual tumor following external beam on clinical examination as well as the high signal regions on T2 FSE images in the cervix and paracervical tissues. The high-risk clinical target volume (HRCTV) included the GTV as well as the entire cervix and the extracervical tumor spread at the time of brachytherapy. The “high risk” volume refers to tissues with a major risk of local recurrence because of residual macroscopic disease, which require a high dose of radiation, similar to that delivered traditionally to point A. The Intermediate Risk CTV (IR CTV) was defined as encompassing the high risk CTV with a margin of 5 to 15 mm, and refers to tissues carrying a significant microscopic tumor load. Doses of approximately 60 Gy are intended for this volume. With these different regions of risk defined according to physical examination and MR at the time of brachytherapy, dose volume parameters were defined for the GTV, HR CTV, IR CTV, and the organs at risk (OARS). For the rectum, contouring included the outer wall from the anorectal junction to the rectosigmoid flexure and the sigmoid contour continued alone until the sigmoid was approximately 2 cm from the uterus. The small bowel was contoured only if within 2 cm of the uterus. The outer contours of the bladder were also defined (113,110). D100 and D90, as well as V100, were recommended for reporting as well as the minimum dose in the most irradiated tissue volume for 0.1 cc, 1 cc, and 2 cc of the OARS, contouring the outer walls only (110). The radiobiological model equivalent dose (EQD2) is used to sum the external beam and HDR doses together over the course of treatment so that a cumulative biologically weighted dose is available. This allows for systematic evaluation of the doses to the targets and normal organs over the course of treatment and for comparison between centers.

Additionally, the use of dose-volume histogram analysis may add new insight into optimizing local control and decreasing morbidity with a better understanding of the importance of dose-volume relationships. Data from Potter et al. have shown a decrease in complications and an increase in local control

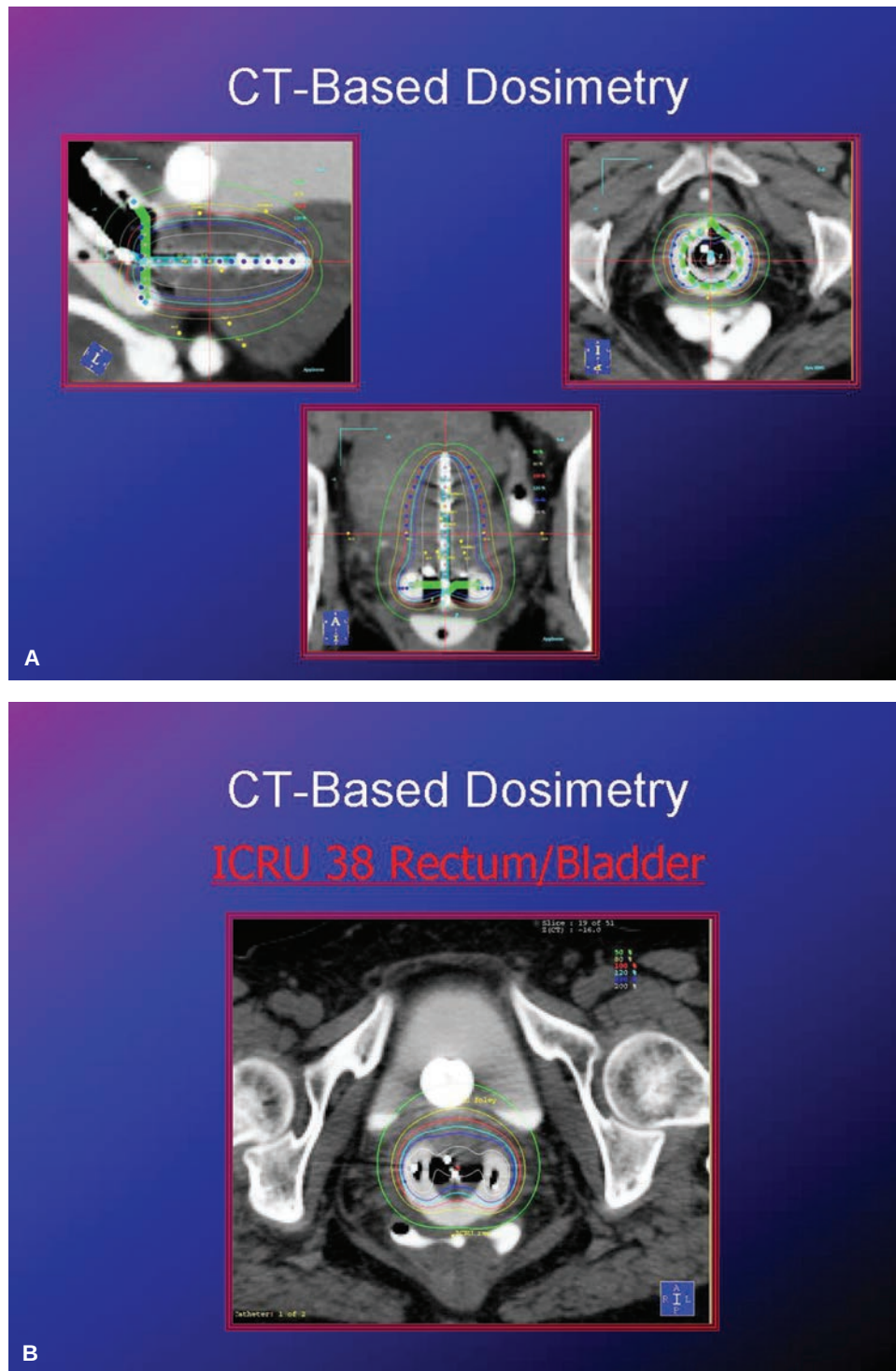


FIGURE 12.32. **A:** Sagittal, coronal, and axial CT images with MRI/CT compatible applicator in place showing the isodose distribution around the applicator and within the surrounding tissues. **B:** Axial CT at the level of the Foley catheter bulb near the traditional ICRU 38 bladder and rectal points. Contrast is present within the bladder and rectum as well as the bladder catheter bulb.

with the use of MRI-guided brachytherapy for cervical cancer (114,115). The ABS supports these guidelines and has incorporated them into its latest guideline document (107). Though frequently confused, the ICRU 38 system (Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology) is a dose reporting system, not a dose specification system

(Fig. 12.34) (59). This was developed so that comparisons could be made between centers using different brachytherapy systems. It provides definitions for determining dose to the bladder and rectum in addition to other characteristics of the implant. Updated ICRU guidelines are forthcoming, with an emphasis on 3D planning and dose specification.

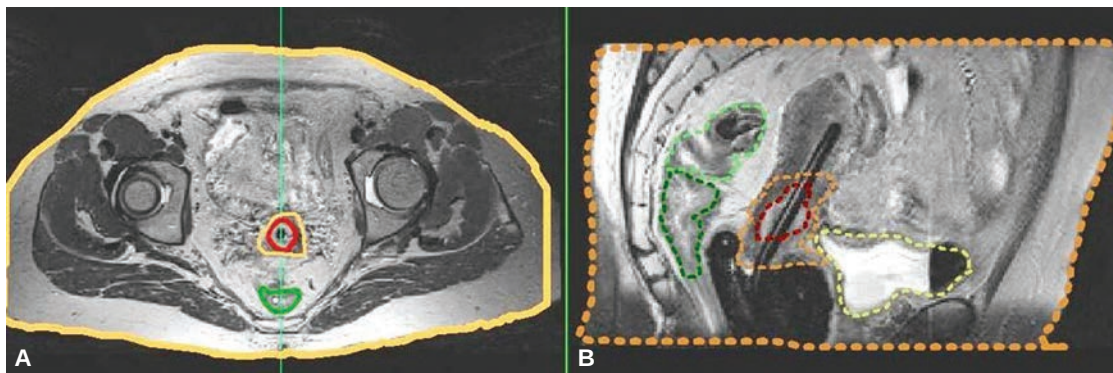


FIGURE 12.33. Axial **A:** and sagittal **B:** MRI images with MRI compatible applicator in place with contours of the gross target volume (GTV) and high risk clinical target volume (HRCTV) as well as the rectum, sigmoid and bladder.

Importance of Brachytherapy in Cervical Cancer

When curative treatment is planned, patients with cervical carcinoma treated with definitive irradiation should receive a combination of external beam irradiation and brachytherapy. As revealed in the Patterns of Care Studies (PCS) and the retrospective series of Perez et al., recurrences and complications are decreased when brachytherapy is used in addition to external beam (85,116–119). Use of an intracavitary implant was the single most important treatment factor in multivariate analysis for stage IIIB cervical cancer with respect to survival and pelvic control in the 1973 and 1978 PCS (120,121). Retrospective series with external beam alone have proven marginal outcomes with this approach (122). Common reasons for avoidance of brachytherapy include inability to negotiate the endocervical canal or poor performance status. Inability to negotiate the endocervical canal should be rare with the use of intraoperative ultrasound, and when this occurs, interstitial implantation is a much better option. Even with IMRT and the ability to customize and escalate the dose to specific volumes, brachytherapy cannot be replaced (123–125). The efficacy of brachytherapy is attributable to the ability of radioactive implants to deliver a higher concentrated radiation dose more precisely to tissues than external beam alone, by treating from the “inside out” due to the close proximity of the radioactive source(s) to the tumor, which contributes to improved local control and survival. At the same time, surrounding healthy tissues such as the bladder and rectosigmoid are relatively spared due to the rapid fall-off of dose around the applicators with distance. With IMRT, dose will necessarily be distributed in the surrounding normal tissues as it makes its way to the cervix as the dose is delivered from the “outside in.” The external beam component of treatment is, however, very important as it addresses tissues at a distance from the brachytherapy applicator such as the pelvic lymph nodes. The external beam also brings about tumor regression in intact cervical and vaginal cancers such that the residual tissue is brought within the range of the pear-shaped or cylindrical-shaped radiation dose distribution around standard applicators (58).

Brachytherapy Applicators

Given the importance of brachytherapy, it is important to select the appropriate applicator to accommodate patient anatomy and the disease and shape the associated isodose distribution to encompass the disease. Tumor volume and patient anatomy are key in this decision. Tumor size and shape are variable, and there is a multitude of applicators available to address these diverse presentations.

INTRACAVITARY APPLICATORS: CERVICAL CANCER

Low Dose Rate

There are varieties of LDR applicators available for intracavitary brachytherapy. The best known are the Fletcher-Suit and Henschke tandem and ovoid (colpostat) applicators (Fig. 12.26) (126). In 1953, Fletcher published an article introducing his preloaded radium applicator, which was designed to produce the largest possible volume of adequate radiation in each of the common directions of spread of disease—the uterine body, parametria, and perivaginal tissues—with relative sparing of the bladder trigone and anterior rectum due to the addition of shielding (72,73). The applicator was modified in the 1960s for afterloading (Fletcher-Suit applicator) (79,80,126) and in the 1970s to accommodate ^{137}Cs sources (80). In the 1970s, the Delclos mini-ovoid was developed for use in narrow vaginal vaults (Fig. 12.26) (79,127). The mini-colpostats have a diameter of 1.6 cm and a flat inner surface. The mini-ovoids do not have shielding added inside the colpostat, and this together with their smaller diameter produces a higher surface dose than

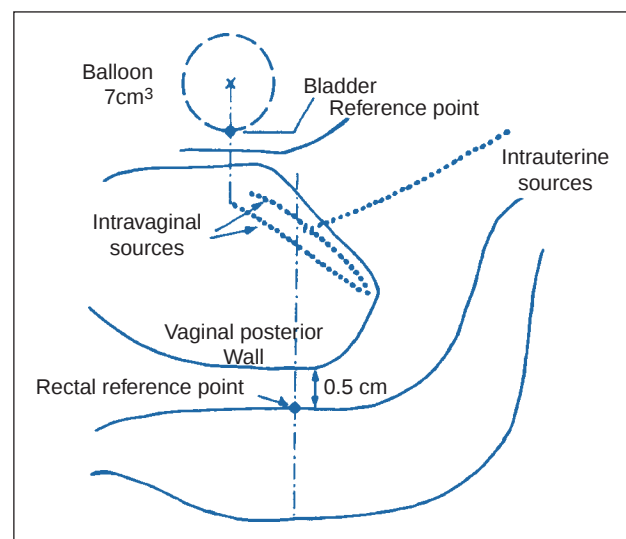


FIGURE 12.34. Reference points for bladder and rectal brachytherapy doses proposed by ICRU.

Source: From Commission on Radiation Units and Measurements. Report 38: Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology. Bethesda, MD: International Commission on Radiation Units; 1985:11, with permission.

regular ovoids with resultant higher doses to the rectum and bladder. Appropriate source strength and treatment duration adjustment are important considerations to prevent complications. Fletcher tandems are available in 4 curvatures, with the greatest curvature used in cavities measuring >6 cm and lesser curvatures used for smaller cavities (Fig. 12.26). A flange with keel is added to the tandem once the uterine canal is sounded, which approximates the exocervix and defines the length of source train needed. The keel prevents rotation of the tandem after packing. The distal end of the tandem near the cap is marked so that rotation of the tandem after insertion can be assessed. PDR adapted applicators are also now available but are much more like HDR applicators than their LDR equivalents (60,61).

The Henschke tandem and ovoid applicator was initially unshielded (126,128) but later modified with rectal and bladder shielding (100,101,61). It consists of hemispheroidal ovoids with the ovoids and tandem fixed together. Sources in the ovoids are parallel to the sources in the uterine tandem (100). The Henschke applicator may be easier to insert into shallow vaginal fornices in comparison to Fletcher ovoids.

The Fletcher-Suit-Delclos tandem and cylinder applicator was designed to accommodate narrow vaginas where ovoids may be contraindicated and to treat varying lengths of the vagina when mandated by vaginal spread of disease. The cylinders vary in size from 2 to 5 cm to accommodate varying vaginal sizes (Fig. 12.26) (127). A narrow vagina poses a therapeutic challenge. Use of vaginal cylinders may lead to a higher rate of local failure as the dose to the lateral cervix and pelvic sidewall is reduced in the absence of ovoids, which produce the optimum pear-shaped distribution. These patients also tend to receive lower total doses due to the proximity of the rectum and bladder (Fig. 12.35) (84). There is less of a dose gradient between the vaginal mucosa and the bladder and rectum than in a patient with a wider vagina (129). Additionally, packing cannot be used with cylinders to decrease the rectal and bladder doses (130–133). Vaginal cylinders increase the length of vagina and rectum treated, with an associated increase in complications. Vaginal fistulae, rectal ulcers, and strictures are reported with increased frequency when vaginal cylinders are used (134–136). Pourquier et al. indicated that doses should be reduced with the use of vaginal cylinders and mini-ovoids to reduce complications as these applicators have no shielding (137,138). Interstitial implantation should also be a

consideration for patients with a narrow vagina or with distal vaginal disease.

The Importance of Optimal Applicator Placement

Geometrically optimal intracavitary implants improve outcome over suboptimal implants. Corn et al. reported an analysis of the 1978 and 1983 PCSs, which attempted to analyze the outcome of cervical cancer patients by the technical quality of the implant. A technically good implant correlated significantly with improved local control, with a trend toward improved survival (139). In a review of the RTOG 0116 and 0128 trials, the quality of applicator placement was statistically related to the risk of local recurrence and disease-free survival (140). Perez et al. observed that “inadequate” insertions increased the incidence of pelvic failures (116) and that the quality of the intracavitary insertion had a measurable impact on the incidence of complications (141). Attention to the details of implant geometry has been linked to improved outcome in the series of Katz and Eifel at M.D. Anderson (83). Prior to afterloading, it was much more difficult to obtain adequate applicator placement due to the need to complete the insertion quickly to avoid excessive exposure to the sources in the preloaded applicators. In the era of afterloading, applicator placement can be more methodical. Orthogonal films or other imaging (CT, magnetic resonance imaging [MRI]) should always be obtained following applicator placement to assess applicator geometry and the need for adjustment to ensure optimum placement. It is imperative that geometrically favorable applicator placement, as described in detail previously by Fletcher, be achieved in as many patients as possible.

Optimum applicator placement is pivotal in maximizing local control. Placement of the brachytherapy applicators in direct proximity to the cervix is necessary to avoid underdosage. There will be a cold spot if the ovoids or other vaginal applicators are displaced away from the cervix (Fig. 12.36). Proper applicator selection is important in avoiding malpositioning. It is extremely important to place metallic markers on the cervix so that the flange of the tandem and the ovoids/cylinder dome are positioned in close proximity to these markers as confirmed on orthogonal check films (83,61).

Likewise, suboptimal applicator placement can increase the risk of complications. Applicators that are too close to the

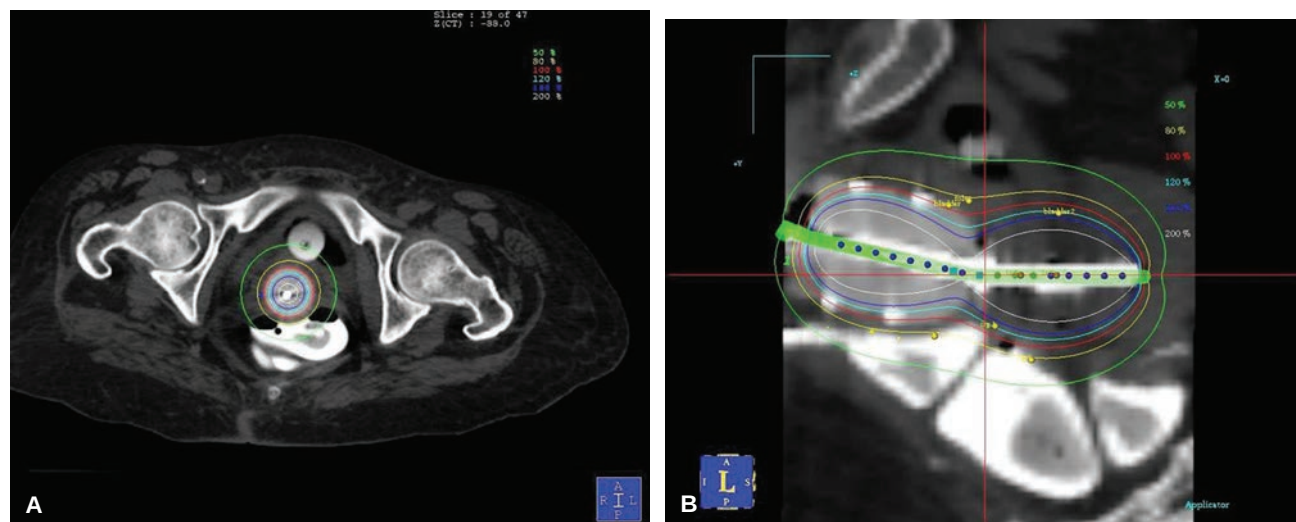


FIGURE 12.35. MRI/CT compatible tandem and cylinder applicator with associated isodose distribution in **A:** axial and **B:** sagittal views, demonstrating the close proximity to the rectum due to the absence of packing or rectal retraction.



FIGURE 12.36. Lateral radiograph of a poorly positioned HDR tandem and ovoid applicator. Note that the tandem does not bisect the ovoids and that the ovoid appears to be displaced inferiorly from the cervical marker balls.

bladder and rectum can increase rectal and bladder complications. Sources in the tandem can give very high doses of radiation to the small bowel (ileum), sigmoid, and upper bladder, often not revealed by orthogonal X-rays. Tandems that have perforated through the uterus can cause tremendous hot spots in the nearby normal organs (82).

Interstitial Applicators: Cervical and Vaginal Cancers—LDR and HDR

The size of the reference pear-shaped isodose achieved with tandem and ovoids is not variable except by increasing the duration (dose) of the implant. The shape of the reference pear-shaped isodose can be altered to some degree by varying the source strengths and applicator type, but it may not be able to encompass a bulky tumor, particularly when there is bulky parametrial or vaginal disease. In these settings, the disease may be better accommodated by an interstitial application (Fig. 12.37) (142). Patients with large, bulky lesions will have a higher rate of local failure because of a decrease in dose to the periphery of the tumor due to the rapid fall-off of dose beyond the relevant pear-shaped distribution. The use of higher doses of external beam prior to implantation and interstitial techniques are important considerations. These patients should not be treated with external beam alone, as achieving the curative radiation doses required may be impossible because of the limited tolerance of the interposed small bowel, rectum, and bladder. Standard intracavitary applications may be suboptimal or prohibited either by tumor bulk or by distorted normal anatomy, and these patients should not be treated with geometrically unfavorable intracavitary implants.

Indications for Transperineal Interstitial Implantation of Gynecologic Malignancies

1. Bulky Disease
 - IB Barrel
 - IIB, III, IVA
2. Anatomical Distortion
 - Narrow/obliterated vagina
 - Obliterated fornices
 - Stenotic/obliterated endocervical canal
3. Recurrent Disease

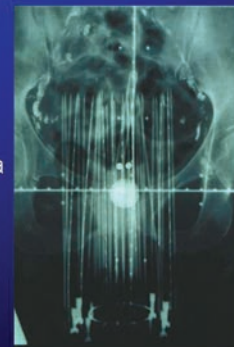


FIGURE 12.37. Indications for interstitial implantation and associated AP radiograph of the implanted needles.

The limitations of intracavitary techniques contrast with the strengths of interstitial techniques in certain settings. Determine which approach is best on a patient-by-patient basis. Interstitial implantation is appropriate in select patients with bulky tumors, anatomical distortion such as an obliterated endocervical canal or narrow vagina, or recurrent disease (142). Interstitial implantation is used in <10% of patients with gynecologic cancers (143). Attention to patient comfort during and after the procedure, integration of appropriate imaging for ideal needle insertion relative to the tumor and dose specification/fractionation, and minimization of both acute and late morbidity are key in achieving a successful outcome. Typically these are performed in higher volume centers through the combined efforts of *Radiation Oncology* and *Gynecologic Oncology* (144). The ABS has recently published consensus guidelines for LDR and HDR interstitial brachytherapy for cervical and vaginal cancers summarizing the most current recommendations (61,145).

The development of prefabricated perineal templates, through which stainless steel needles were inserted and after-loaded with ^{192}Ir or ^{125}I , was pivotal in advancing interstitial techniques for the treatment of cervical and vaginal cancers. With these interstitial techniques, rather than doing a freehand implant, the template concept allows for a predictable distribution of needles inserted across the entire perineum through a perforated template according to an optimum pattern. Commercially available and institution-specific templates are used in these patients to accommodate varying disease presentations. Stainless steel and plastic needles are used, which are after loaded with low- or high-activity ^{192}Ir sources. The MUPIT (Martinez Universal Perineal Interstitial Template, Beaumont Hospital, Royal Oak, Michigan, USA) template (Fig. 12.38) accommodates implantation of multiple pelvic-perineal malignancies (prostate, anorectal, gynecologic) (142,146,147). In this system, one template accommodates many different disease presentations. Recent modifications of this template and needle system enabling HDR implants have become available (148). The Syed-Neblett (Best Industries, Springfield, Virginia, USA) is the other well-known commercially available template system (142,149,150). Currently, there are three LDR Syed-Neblett templates of varying size and shape for use in implantation of gynecologic malignancies (GYN 1-36 needles, GYN 2-44 needles, GYN 3-53 needles), as well as templates for implantation of the anus, prostate, and urethra (142) (Fig. 12.39). There is also a disposable template for gynecologic presentations that accommodates HDR needles (151–153).

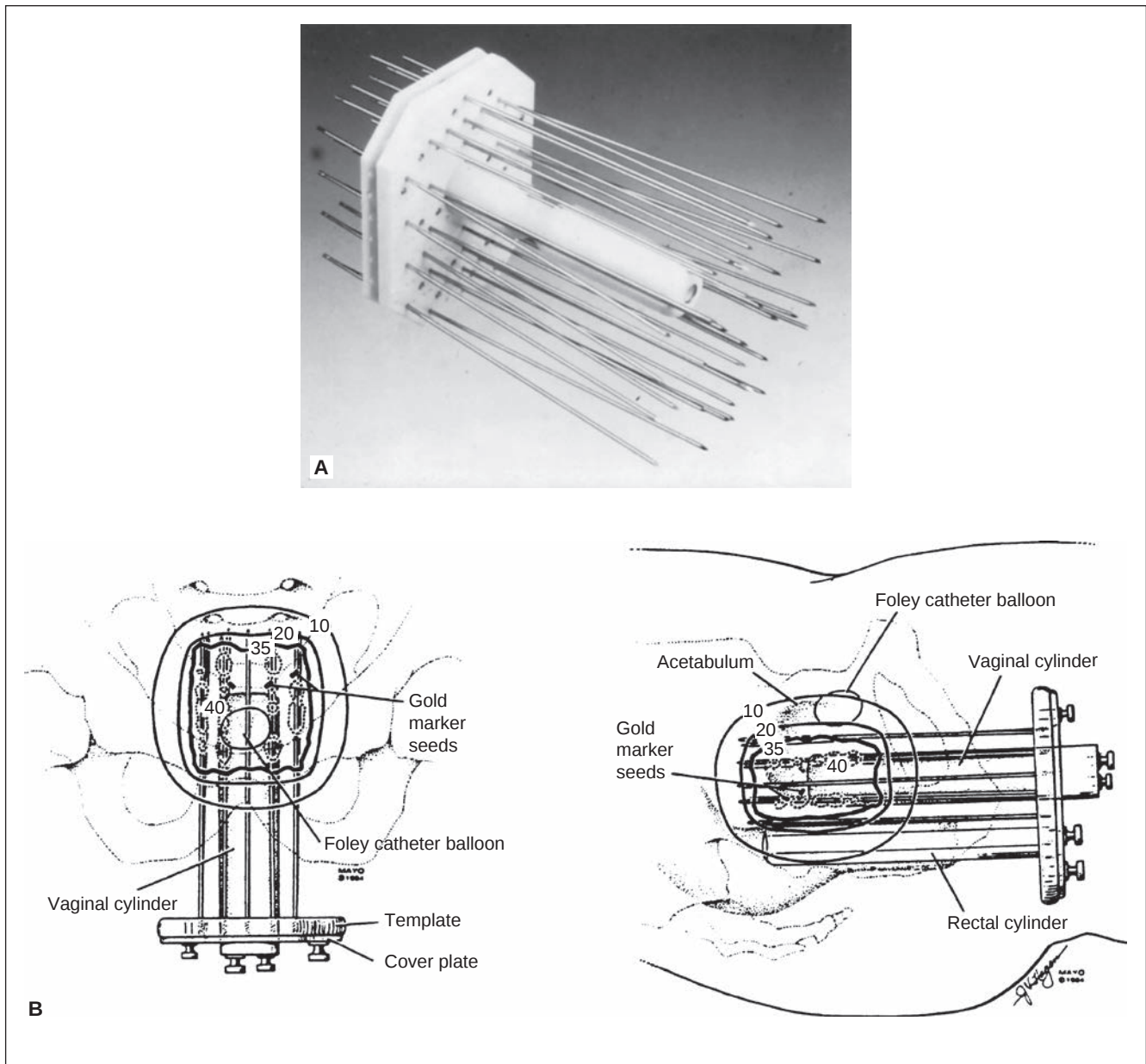


FIGURE 12.38. **A:** Martinez Universal Perineal Interstitial Template (MUPIT).

Source: Courtesy of Dr. Alvaro Martinez, William Beaumont Hospital, Detroit, Michigan, USA.

B: Diagrammatic representation in coronal and sagittal planes of the same template.

Source: Reprinted from Martinez A, Edmundson GK, Cox RS, et al. Combination of external beam irradiation and multiple-site perineal applicator (MUPIT) for treatment of locally advanced or recurrent prostatic, anorectal, and gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 1985;11:391–398, with permission from Elsevier.

The Syed-Neblett and MUPIT templates are particularly suited for treatment of vaginal disease as the vaginal obturator needles can be strategically loaded to encompass disease from the fornices to the introitus. Additionally, the obturator needles can be advanced directly into the cervix, along with a uterine tandem, and may be essential to deliver tumorcidal radiation doses to the cervix by preventing a central “cold spot,” especially if an intrauterine tandem is not used (142,144,145). Use of an intrauterine tandem along with interstitial needles has been statistically associated with an improvement in overall survival in stage IIIB cervical cancer (154). The more peripheral needles are used for implantation of the parametria, which is often underdosed in intracavitary approaches. Modifications of these standard templates have evolved and other innovative templates have been developed for vulvar, vaginal, and cervical

carcinomas (142). Attention to the depth of needle insertion as well as to the number and location of needles is key in achieving an optimum implant (142,149). Additionally, modification of the ring and ovoid applicators to accommodate a limited number of needles to improve tumor coverage has been reported recently, with improved local control in patients with bulky IIB and IIB disease (115,155–157). In these applications, only 10–20% of the dwell time is contributed from source positions in the needles and the remainder by the intracavitary component of the applicator (107). Individualized computer-generated dosimetry is an integral part of interstitial dose delivery. CT imaging following needle implantation has proven very helpful to identify tumor volume and critical normal structures, confirm the adequacy of needle placement in relation to these structures or needed adjustments, analyze and manipulate the

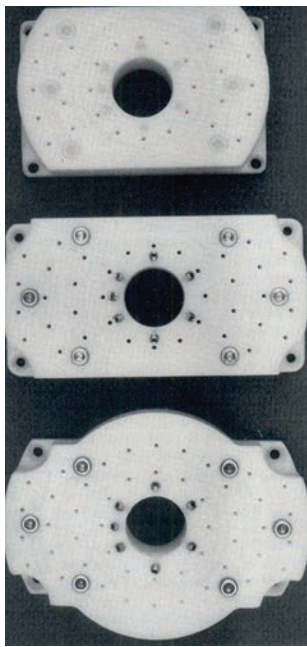


FIGURE 12.39. LDR Syed-Neblett templates (top to bottom)

Gyn 1, Gyn 2, Gyn 3.

Source: Reprinted with permission from Erickson B, Gillin M. Interstitial implantation of gynecologic malignancies. In: Nag S, ed. *Principles and Practice of Brachytherapy*. New York, NY: Futura; 1997:518.

dose distribution related to these structures, and assist with dose specification and the integration of external beam irradiation (142,158). Postprocedure epidural anesthesia provides optimal pain control and allows the needles and tandem to be manipulated outside the operating room if necessary. Modification of the planned source placement based upon the location of specific needles and critical structures can therefore be made before or after source loading (144).

With LDR techniques, traditional LDRs are the goal (142,61), achieved through differential loading (core sources $\leq 1/2$ activity of peripheral sources) of low-activity sources. “Reference” dose rates, of 60 to 80 cGy/hr are optimal. The implant dose rates as well as the dose homogeneity and distribution, can be manipulated by selectively changing the activity associated with a particular needle or needles or by selectively unloading, either immediately or during the implant, strategic needles in the pattern. With HDR techniques, optimization of the dose distribution with predetermined parameters for the reference dose, normal organ doses, and dose homogeneity can produce even more ideal implant dosimetry (Fig. 12.40). Typically, total LDR doses to the tumor volume or reference isodose from the implant range from 23 to 40 Gy over 2 to 4 days for a total dose of 70 to 80 Gy (158,61,142). The total HDR dose will be approximately 60% of the total LDR dose and will be given in divided fractions. There is not a consistent data relative to EQD2 doses when using 3-D image-based HDR interstitial brachytherapy techniques. These seems to be a consensus that the doses are lower than with combined intracavitary HDR and external beam, perhaps on the order of an EQD2 of 75 to 80 Gy (107). With either approach, careful attention to significant hot spots within the implant and doses to the bladder, rectosigmoid, and vaginal surface are requisite to obtaining the best outcome (145,153,142,144).

External whole pelvic irradiation (39.6 to 45.0 Gy) generally precedes implantation. For either LDR or HDR, one or two template implants can be done 1 to 2 weeks following external beam. With HDR, 1 to 2 fractions can be delivered per day over a period of 2 to 5 days, whereas with LDR, continuous hourly



FIGURE 12.40. Axial CT scan with needles inserted into the cervical and paracervical tissues between the bladder and rectum. Isodose curves shown are 80%, 100%, and 120% of the prescription dose.

radiation is delivered. After the implant, selective external irradiation boosting can be done as needed. The total LDR dose to the reference volume from the combined implant and external beam approximates 70 to 85 Gy over 8 weeks (144).

HDR Brachytherapy for Cervical Cancer

Though LDR techniques have been the traditional standard for decades for gynecologic brachytherapy, there appear to be some inherent advantages with the implementation of HDR techniques (159–161). Because the treatment time is very short, treatment is performed on an outpatient basis without the need for several days of bed rest, with greater patient acceptance and comfort. This allows treatment of some patients with medical comorbidities, which would prohibit LDR techniques because of the prolonged bed rest. With the shorter treatment time, the implant reproducibility is superior to traditional LDR approaches as more stable positioning of applicators is possible. The shortened treatment time provides a greater degree of certainty that the sources will remain in the 3D positions documented in the isodose distributions, and that applicator displacement as a function of time will be decreased. The use of external applicator fixation devices allows more constant and reproducible geometry of source positioning (161–163). The newer systems, which allow a single source to “dwell” at a site for a calculated period of time, combined with dose optimization software programs, provide a significant further improvement in the ability to shape the dose distribution. The small source size allows for finer increments in source location and relative weighting for each source location than with the fixed source sizes and activities inherent to the LDR ^{137}Cs sources (89,163,164). This allows for greater precision coupled with greater flexibility and perhaps a reduction in normal tissues doses. Additionally, the rectal retraction devices available with the HDR applicators maximize displacement of the rectum for short periods of time and may give superior and more predictable displacement than traditional vaginal gauze packing (161–163). These 2 factors lead to improved dose

delivery to the tumor relative to surrounding normal tissues. There is also increased integration of external beam with HDR, as external beam irradiation can be given 3 to 4 times per week and HDR 1 to 2 times per week. This can lead to shorter overall treatment duration, which may be pivotal in maximizing cure (165,160). Additionally, due to the small physical size of the ^{192}Ir source, the HDR applicators are lighter and smaller than bulky LDR applicators and are easier to insert, particularly if there is vaginal narrowing. Many institutions use only 1 LDR implant so that if the applicator geometry is poor, there is not the opportunity to perform multiple implants and improve the geometry or change applicators in future insertions as realized with HDR techniques. The remote afterloading also provides a lack of radiation exposure to healthcare providers. Contrastingly, on a radiobiologic basis, HDR lowers the therapeutic ratio compared to LDR, as there may be more late effects of radiation if the rectosigmoid and bladder receive as much radiation as the tumor than with LDR techniques. For HDR to succeed, the geometric advantages must overcome the radiobiologic disadvantages (163). Himmelmann et al. concluded that with HDR regimens, reoxygenation of hypoxic cells can take place between fractions, and this may in fact be a radiobiologic advantage of HDR (166). Disadvantages of HDR may include loss of the radiobiologic advantage of LDR, decreased time for normal tissue repair, a potential increase in late tissue effects with large fraction sizes, and an increase in the number of implants per patient from 1–3 to 3–6 (range, 2–16), which is labor intensive for all involved (160). The need for sedation may still exclude high-risk patients even though bed rest is not required.

Conversion from LDR to HDR

There have been numerous suggestions regarding how to convert total LDR doses to HDR doses in order to implement reasonable dose-fractionation schemes. Efforts have been made by many investigators to compare the biologic effects of LDR with HDR regimens using various dose conversion models. The linear-quadratic model has typically been used, but this does not address the optimal number of fractions. A basic concept is that the total dose with HDR must be less than with LDR and the number of fractions must increase (166–168). This concept comes from early radiobiologic studies. The Equivalent Radiation Dose (ERD) mathematical model can be used to determine the HDR dose per fraction (169,170). The ERD is a biologic dose unit, which utilizes the linear-quadratic model. To determine an appropriate dose for HDR treatments based upon LDR techniques, the ERDs are assumed to be equal. The α/β for tumor is assumed to be 10, while μ is assumed to be 1.4 hr^{-1} . For this calculation, the LDR total dose, LDR dose rate, and desired number of HDR fractions are required to calculate an HDR fraction size. These calculations have shown that one must give approximately 60% to 70% of the LDR dose with HDR. The conversion of doses herein is strictly for the brachytherapy component of the treatment course (159,169,170). More recently, there has been interest in calculating the equivalent dose (EQD2) at 2 Gy per fraction for both the radiation targets (Point A, HR CTV) and the OAR (organs at risk) when adding together both the external beam and the brachytherapy components of treatment. This can be done for LDR, PDR, and HDR. This interactive worksheet is available through the American Brachytherapy website (107).

HDR Applicators

The tandems and ovoids used with HDR are variations of the traditional Fletcher and Henschke LDR applicators but are lighter, narrower, and smaller (Fig. 12.41) (107). The ovoids are 2.0, 2.5, and 3.0 cm in diameter with and without shielding. The



FIGURE 12.41. HDR tandem and ovoids.

Source: Courtesy of Nucletron.

relationship of the colpostat to the handle is different between HDR and LDR colpostats so that the cable-driven HDR source can negotiate the angle between the handle and the colpostat. The Selectron colpostats are angled at 60° to the applicator handles. Standard Fletcher-Suit LDR colpostats are angled most often at 15° and sometimes at 30° with respect to the colpostat handles (Fig. 12.42). This can lead to a different relationship between the tandem and the colpostats and between the colpostats and the cervix, best seen on the lateral orthogonal X-rays taken for dosimetry after applicator insertion. As previously mentioned, these applicators have also been adapted for needle insertion for bulkier tumors (155,156).

The ring applicator, which is an adaptation of the Stockholm technique, has become a popular applicator (164,171–174) (Fig. 12.43). The plastic caps that come with the ring applicator place the vaginal mucosa 0.6 cm from the source path, compared to the caps for the ovoids, which distance the vaginal mucosa from the source path by 1 to 1.5 cm. The short distance from the ring to vaginal mucosa can result in very high surface doses if fixed weighting, nonoptimized techniques are used (161,173). The bladder and rectum may also receive higher doses with fixed weighting nonoptimized dosimetry (172). It is important not to activate all the positions in the ring, as this will increase the dose to the rectum, bladder, and vaginal mucosa (172). Typically, four dwells are activated on each side of the smallest ring (36 mm), five on each side of the medium ring (40 mm), and six on each side of the large ring (44 mm). The tandems are available in lengths of 2 to 8 cm. Four ring-tandem angles are available including 30° , 45° , 60° , and 90° . The shape of the isodose curves comparing the ring with tandem and ovoids will also have a different shape and the volume of tissue irradiated will also differ (172,173). The ring applicator is ideal for patients without lateral vaginal fornices. Its ease of insertion and predictable geometry make it a popular alternative to tandem and ovoids. As previously mentioned, the ring applicator has also been adapted to accommodate needles for patients with bulky tumors (115,157).

Tandem and cylinder applicators are used in the setting of a narrow vagina or vaginal extension of disease and are available in diameters of 2.0 to 4.0 cm (Fig. 12.44). In most cases, rectal and bladder displacement are not possible with this applicator, although some of the cylinders have built-in shielding. A posterior speculum blade to displace the rectum can be used if there is not posterior vaginal disease. As with LDR tandem and cylinder applicators, the bladder and rectal doses may increase with this



FIGURE 12.42. LDR versus HDR ovoid angles. The low dose rate ovoids are positioned at a 15° or 30° angle to the vaginal axis versus 60° in the HDR ovoids.

Source: Courtesy of Nucletron.

applicator, and the dose distribution will be more cylindrical than pear-shaped, which can underdose bulky tumors (Fig. 12.35). Careful attention to normal tissue doses and target coverage is necessary in this setting (107).

HDR Treatment Planning

The dose distribution with HDR tandem and ovoids and tandem and ring applicators model the LDR pear-shaped isodose distribution. Most HDR regimens use a paracervical dose specification point (A) rather than mg-hrs or a volume-based dose specification such as the HR CTV (107). Rectal, bladder, sigmoid, and vaginal surface doses should always be specified or

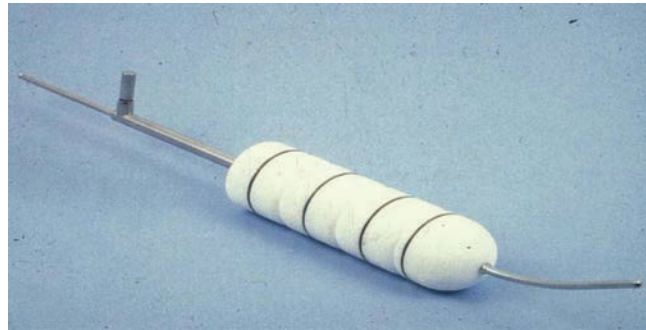


FIGURE 12.44. Tandem and cylinder applicator.

Source: Courtesy of Nucletron.

documented, and some assessment of dose to the pelvic lymph nodes and lateral parametria should be documented.

The HDR system utilizes special vocabulary to describe certain functions and applications. A “dwell position” is a position at which the source is driven to stop or dwell. Dwell positions can be 2.5 and 5 mm apart. An active length will be converted into a number of dwell positions. “Patient points” are points of interest at which the dose is calculated; they are defined on the orthogonal implant films. Examples include bladder, rectum, and sigmoid. “Applicator points” are points of interest at which the dose is calculated; they are defined by manually inputting the coordinates. Typically, applicator points include point A and points on the lateral surface of a ring, ovoid, or cylinder. “Dose points” are points at which the dose is optimized. In general, doses are specified using dose points. The optimization program then attempts to give the prescription dose at each of these points. With the tandem and ring, a similar system is used. The entire ring should never be activated, as this will cause high rectal, bladder, and vaginal doses. For the tandem and cylinder, again, a similar system is used with the exception that at the cylinder interface, dose points are entered laterally from the dwell positions at the distances representing the cylinder surface. Due to the close proximity of the bladder and rectum in women requiring vaginal cylinders because of a narrow vagina, dose specification needs to be done with great care so as not to give excessive doses to the bladder and rectum. Dose specification at point A alone can result in underdosing of target tissue and overdosing of dose-limiting tissues (175–177). If using 2-D planning, in addition to point A, specifying dose at the

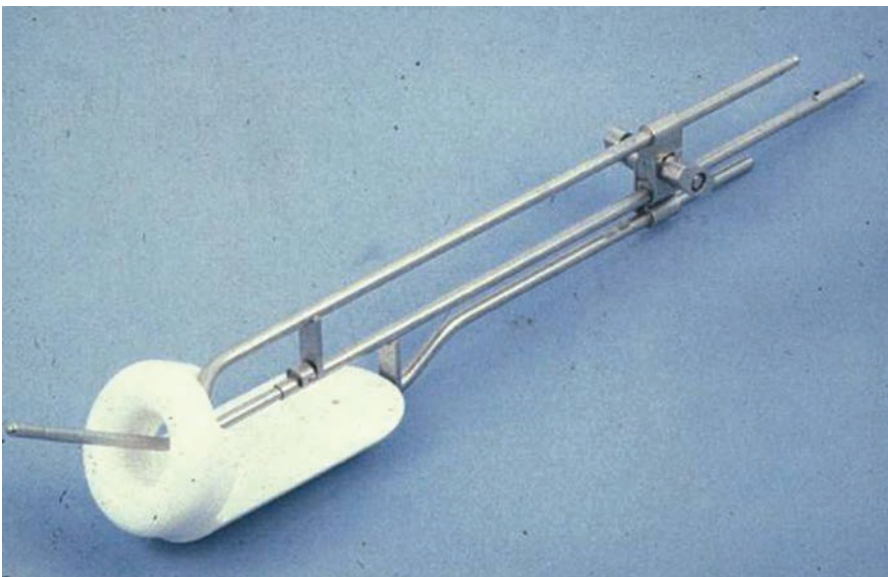


FIGURE 12.43. Tandem and ring applicator with associated rectal retractor.

Source: Courtesy of Nucletron.

vaginal applicator surface is important. If using a volume-based approach, dose specification to the HR CTV while negotiating the doses to 2 cc of the bladder and rectosigmoid is key. With either approach optimization of the dose distribution follows and enables design of a more ideal dose distribution (Fig. 12.45). The term “optimization” refers to the process of achieving certain dose values at points or volumes within the implant. It is not the simple generation of a standard dose distribution by using fixed dose points around the applicator (107). The goal is to match the dose distribution to point A or the HR CTV while simultaneously avoiding the OAR. Inherent to optimization is starting with a standard plan of loading the tandem and the vaginal applicator and then modifying the dwell times and dwell weights to reduce dose to the OAR and ensure optimal tumor coverage (107). Excessive optimization can alter the pear shape to a less desirable configuration with the same point A dose (176,177). When altering the standard dwell times and weights, it is important to also monitor changes in the dose, dose/volume parameters and the spatial dose distribution that result from the modified loading pattern. Reliance on dose volume histograms alone can be dangerous if not also evaluating the spatial dose distribution (107). The entire length of the tandem does not always need to be treated and should be guided by the definition of remaining tumor at the time of brachytherapy seen on MR or CT. This can reduce dose to the OARs (178). Likewise, activation of dwell positions in the vaginal applicator should also be considered carefully in light of the closely approximated bladder and rectum and vaginal target.

HDR Dosimetry Generation

It is important to perform dosimetry for each fraction of an HDR tandem and vaginal applicator regimen even if the same applicator is used, as there may be quite a bit of variation in applicator position with each fraction (179–187,107). There is also applicator deformation of the adjacent structures, which varies with applicator position (182). Variables that impact applicator position are vaginal packing, the presence and effectiveness of sedation/anesthesia, as well as use of the dorsal lithotomic versus legs down position. The bladder and rectosigmoid may also change configuration due to changes in filling and position, and doses to these organs will vary from fraction to fraction. Uterine and sigmoid mobility may also impact the dose distribution in

these organs. Additionally, disease regression and vaginal narrowing will vary from fraction to fraction and can also result in changes in dose distribution. A change in applicator can also result in changes in dose distribution, as can changing the ovoid or ring size, ovoid separation, and tandem curvature. The ovoids may also change in separation and their relative position to the tandem over time if there is not a fixed relationship between the tandem and ovoids (181,183–186). Jones et al. found that when treatment planning was not performed for each fraction and only the initial dosimetry was used, there was increased dose to at-risk normal organs (186). This is also true when using a tandem and ring, even though it has a fixed geometry. The applicator position relative to the pelvic organs is the important factor rather than the relationship of the tandem to the ring (Fig. 12.46).

Dose-Fractionation Schemes

In the 1990 literature review by Fu and Phillips of the randomized and nonrandomized studies of HDR, multiple dose-fractionation schemes were tabulated. Most centers used point A as a reference point, although the definition of point A varied. The dose per fraction at point A varied from 3 to 10.5 Gy, the number of fractions varied from 2 to 13, and the number of fractions per week varied from 1 to 3. At that time, most centers used a schedule of 7 to 8 Gy/fx for three to six fractions. The external beam dose was variable and in most centers was carried out concurrently with or after intracavitary brachytherapy (188). The 1991 Orton et al. survey of 56 institutions reported treatment of over 17,000 cervix patients with HDR and found that the average fractionation scheme was 5 fractions of 7.5 Gy to point A. Fractionation of the HDR treatments significantly influenced toxicity as morbidity rates were significantly lower for point A doses per fraction of ≤ 7 Gy compared with >7 Gy (189,190). Fraction sizes <7.5 Gy were subsequently recommended by the ABS in one of its earlier guideline documents (89). In a literature analysis by Petereit and Pearcey of the HDR fractionation schedules, a dose–response relationship could not be identified for tumor control or complications (191). There is no consensus as to the optimal number of fractions and dose per fraction except that the choice will depend on the external beam dose and on whether central shielding is used, normal tissue doses, medical comorbidities, and the stage of disease. The linear-quadratic model was suggested as a guide to formulate the regimens chosen at each institution (89,192). Currently, Gynecologic Oncology Group (GOG) protocols define a dose/fractionation scheme of 5.6–6.3 Gy $\times$ 5 to point A with whole pelvis doses of 41.4–45 Gy. Radiation Therapy Oncology Group (RTOG) protocols allow fraction sizes of 5.3 to 7.4 Gy when using 4 to 7 fractions, depending on the external beam dose. Tables for combining various external beam doses with varying HDR fractions using the linear-quadratic formula and normal-tissue-modifying factor have been provided with these protocols (192). There has been increasing concern that 6 Gy times 5 to point A may result in excessive toxicity to the rectum and sigmoid when combined with whole pelvis doses of 45 Gy and a dose of 5.5 Gy times 5 to point A may be more reasonable (193,107). In the United States, the most common HDR intracavitary regimen prescribes 2 fractions per week for a total of five fractions, with 5–6 Gy per fraction (194). Internationally the most common dose per fraction was between 5–7 Gy with the higher dose per fraction associated with a decrease in fraction number (3–5 fractions) (143). When using volumetric image-guided brachytherapy, the dose at Point A can still be tracked but the goal is to guide coverage of the HR CTV with acceptable OAR doses for an EQD2 of 80–90 Gy, depending on the volume of disease remaining at the time of brachytherapy. The EQD2 limit to the D2cc (the minimum dose in the most irradiated 2 cm³ normal tissue volume for the rectum and sigmoid is 70–75 Gy and for the bladder, 90 Gy (107).

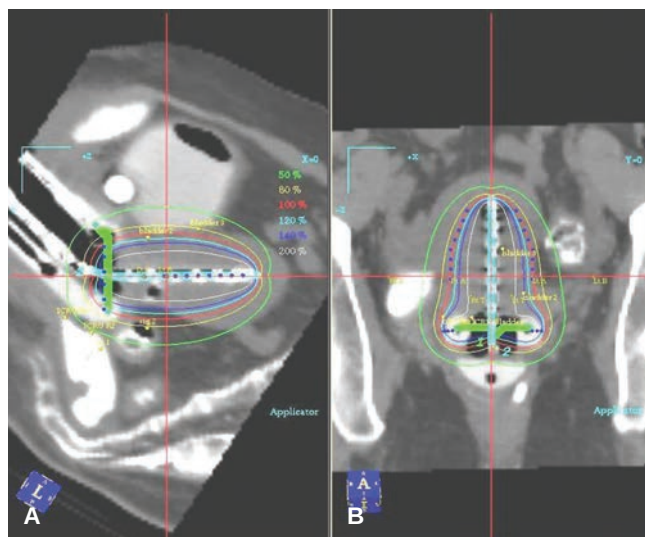


FIGURE 12.45. Dose distribution around a tandem and ring applicator in **A:** sagittal and **B:** coronal projections with dose specified at the ring surface and at the level of point A.

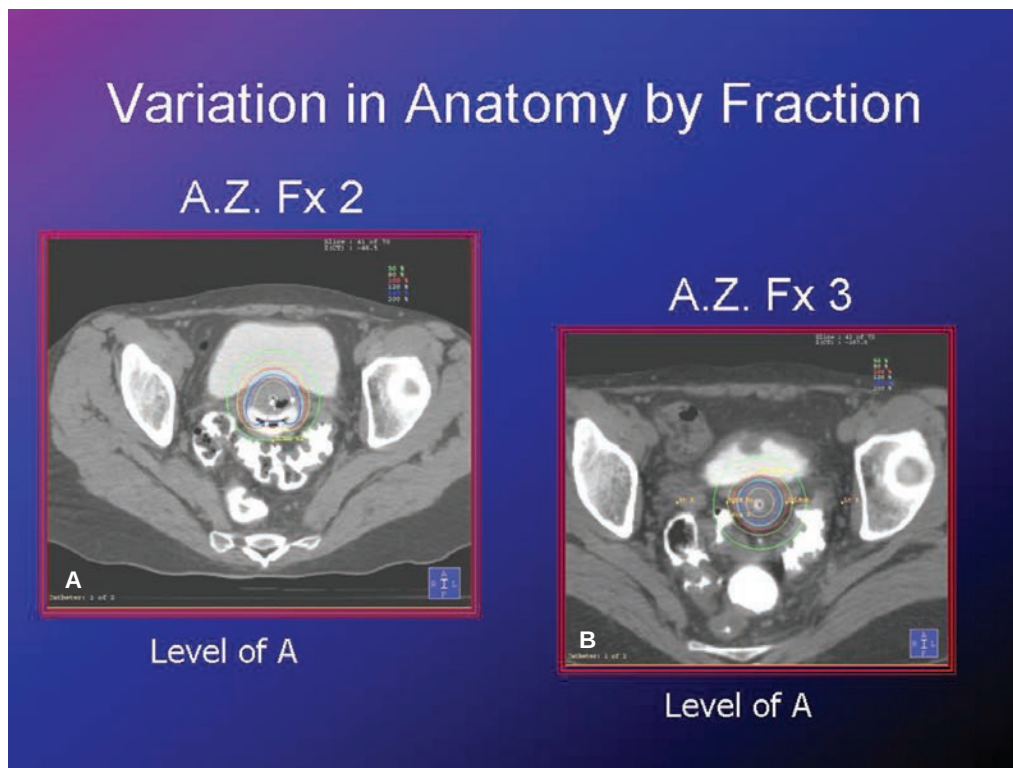


FIGURE 12.46. Variation in anatomy between fraction 2 **A:** and fraction 3 **B:** of a 5-fraction high-dose-rate course. Note the difference in the position of normal organs at the level of point A between fractions 2 and 3.

Sequencing with External Beam

In nonbulky disease presentations, HDR insertions are often integrated early in the treatment course after approximately 20 Gy of external beam RT. Alternatively, some institutions choose to take the whole pelvis to 40 to 45 Gy initially, preceding the five HDR insertions, unless the patient has very early disease or evidence of early vaginal stenosis. This allows for maximum disease regression prior to brachytherapy. When delivering 40 to 45 Gy to the whole pelvis before initiation of HDR, it is important to avoid treatment prolongation by giving two HDR fractions per week to complete the radiation within 50 to 56 days (107). Compressing the duration of treatment to <60 days may be desirable (165,194–196).

Brachytherapy for Endometrial Cancer

Hysterectomy is the cornerstone of treatment for endometrial carcinoma. Selective use of vaginal brachytherapy, external beam irradiation, or both in the postoperative setting is based on the histopathologic risk factors identified in the tissues removed at the time of surgical staging. Vaginal brachytherapy is typically performed using Fletcher colpostats, or a variety of vaginal cylinders (Delclos, Burnett). Both LDR and HDR techniques are used (197,198,199) (Fig. 12.48). The choice of ovoids versus cylinders is individual and both have relative advantages and disadvantages (194). Vaginal ovoids are available in diameters of 2 to 3 cm with associated caps and shielding. Vaginal cylinders are available in diameters of 2 to 5 cm, with or without shielding. Vaginal ovoids generally require sedation for insertion, whereas cylinders do not. The length of the vagina treated with vaginal ovoids is approximately the upper third, whereas vaginal cylinders can treat a portion of or the entire vagina. Though rare, when present, distal vaginal metastases tend to be located in the periurethral area (200,201). Poorly differentiated tumors may

recur earlier and present in the distal vagina or distant disease sites, whereas well-differentiated lesions tend to recur later and are often in the upper vagina (202). Distal vaginal recurrences or metastases, however, are rare after radiation and occurred in 0.5% to 1% of patients when the upper vagina was treated (203). It is therefore not suggested to treat more than the upper half of the vagina routinely. Typically, the length of vagina treated with vaginal cylinders is between 4 and 5 cm, perhaps favoring a longer length when using brachytherapy alone (197,198). Packing is typically used to displace the rectum and bladder with ovoids and not with cylinders. Due to the longer length of vagina treated and the lack of packing, a larger volume of rectum and bladder will be treated with cylinders. Vaginal ovoids may be prohibited in a narrow vagina, whereas vaginal cylinders may not be in close approximation with all of the vaginal mucosa in the setting of a wide vaginal apex or if the cuff has been closed with “dog ears” rather than in a cylindrical shape.

Most vaginal brachytherapy for endometrial cancer is performed with vaginal cylinders using HDR techniques (Fig. 12.48) (197,198). The dose distribution should ideally conform to the shape of the cylinder (204,198). Dose is typically specified either at the vaginal applicator surface (mucosal surface) or at a depth of 0.5 cm from the applicator or vaginal mucosal surface. Dose prescription at 0.5 cm can lead to excessively high mucosal doses and surface doses should also be tracked (205,206,198). Additionally, careful assessment of dose to the rectum and bladder through use of computerized dosimetry should also be performed for the first fraction of radiation delivered (Fig. 12.48). CT-based planning allows for an excellent assessment of the doses to the bladder and rectum as well as evaluation of air gaps at the interface of the applicator surface and vaginal mucosa, but is only needed for the first fraction (Fig. 12.48) (207,208,198). Choo et al. have revealed that 95% of the vaginal lymphatic channels are located within 3 mm of the vaginal surface and that dose prescription to a depth of less than 5 mm may be adequate (209). For LDR insertions, dose

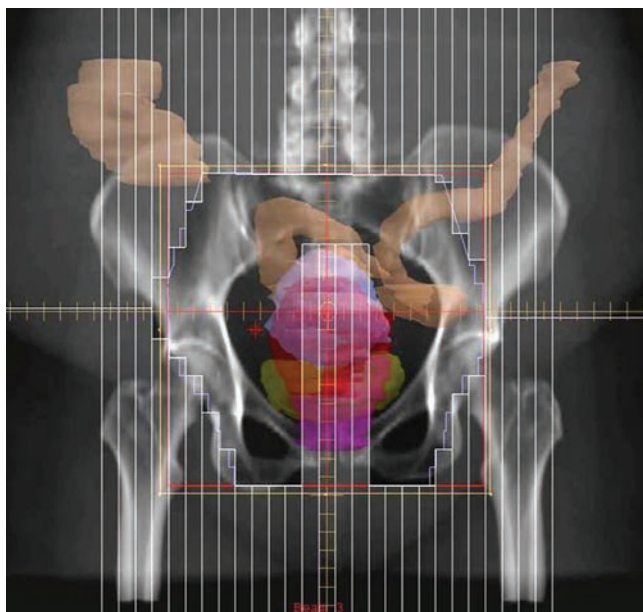


FIGURE 12.47. Midline blocks: A midline block defined by the leaves of the multileaf collimator used to shield the central pelvic structures. Note the unblocked bladder and sigmoid that may get some of the brachytherapy dose and all of the external beam dose.

rates at the surface of the applicator should be in the range of 80 to 100 cGy/hr, and perhaps 50 to 70 cGy/hr if the prescription is at 0.5 cm (204). Total vaginal surface doses of 50 to 80 Gy are reported most frequently in the literature. When used with external beam, cumulative doses of 60 to 100 Gy at the vaginal surface are reported in the literature. Doses in excess of 80 Gy to the vaginal mucosa are not necessary in the setting of adjuvant therapy and can be associated with increased morbidity. For a vaginal recurrence of endometrial cancer, doses of 80 Gy and higher may be needed when combining external beam and brachytherapy (210).

Vaginal brachytherapy alone is generally considered an option for patients treated with hysterectomy, with either no or selective lymph node sampling, who are thought to be at low risk for lymph node metastases. These patients typically have grade 1 or 2 disease without significant myometrial invasion (<1/3) (211,212,198). Additionally, vaginal brachytherapy alone is considered an option at some institutions in the setting of a negative pelvic lymph node dissection, even when high-risk factors such as high grade or deep myometrial invasion are present (212–214,198).

There is great debate about whether a vaginal cuff boost is routinely necessary in addition to external beam irradiation for early-stage endometrial cancer and little data to support it (215,216,198). Practice patterns are based more on institutional tradition and individual preference rather than prospective randomized trials. The rationale for use of a vaginal boost is the supposition that there may be a critical dose needed at the vaginal apex to optimally decrease the likelihood of a vaginal apex recurrence. Doses in excess of the 45 to 50 Gy typically delivered with external beam may be necessary if there are microscopic tumor cells embedded in the hypoxic vaginal cuff.

There are some clinical situations in which more complex brachytherapy procedures are required in the treatment of endometrial cancer. Patients with bulky stage II endometrial cancers may benefit from preoperative radiation with external beam alone, brachytherapy alone, or a combination of the two. Tandem and ovoids or tandem and ring or cylinder applicators are used in this setting. Medically inoperable endometrial cancer is a rare phenomenon in the current era of aggressive surgical staging.

When encountered, it can require the use of sophisticated radiation techniques. Either external beam alone or brachytherapy alone or a combination of the two may be appropriate for some patients. Tandem and ovoids or a tandem and ring or cylinder may be appropriate if the uterine cavity is small. If the uterus is large or if there is more extensive disease, special uterine applicators such as dual and triple tandems or Heyman-Simons capsules may be helpful (Fig. 12.49). There is better coverage of the entire endometrial cavity with these applicators, and dose can be delivered through the uterine wall to the serosa of the uterus (217–219). HDR and LDR techniques can be used.

Patients with recurrent endometrial cancer usually benefit from both external beam and brachytherapy. Doses in excess of 80 Gy may lead to better local control in these patients (210). In patients with residual vaginal disease less than 0.5 cm in maximum thickness, vaginal cylinders or ovoids can be used, whereas in patients with thicker lesions following external beam, interstitial techniques are needed. For apical lesions, laparotomy or laparoscopy may be required for optimum needle placement and to avoid small bowel tethered to the pelvic floor (142,220–222).

EXTERNAL BEAM IRRADIATION FOR GYNECOLOGIC CANCERS

Cervical and Vaginal Cancers

In cervical and vaginal cancers, the role of external beam irradiation is to shrink bulky tumor prior to implantation to bring it within range of the high-dose portion of the intracavitary dose distribution, improve tumor geometry by shrinking tumor that may distort anatomy and prevent optimal brachytherapy, and sterilize paracentral and nodal disease that lies beyond reach of the intracavitary system (77). Some institutions maximize the brachytherapy component of the treatment regimen and perform the first intracavitary insertion after 10 to 20 Gy with subsequent external beam delivered with a central block (222). Other institutions treat the whole pelvis to 40 to 50 Gy and perform brachytherapy once the external beam is completed. The total dose at point A or the HR CTV, however, should remain the same, stage for stage. Implementing brachytherapy early with subsequent reliance on only the implant to treat the central disease may be considered an advantage as a greater portion of the central dose is delivered with the implant, with relative sparing of the bladder and rectum, perhaps permitting delivery of a higher central dose over a shorter period of time (223). More reliance, however, is placed on the extremely complex match between the intracavitary

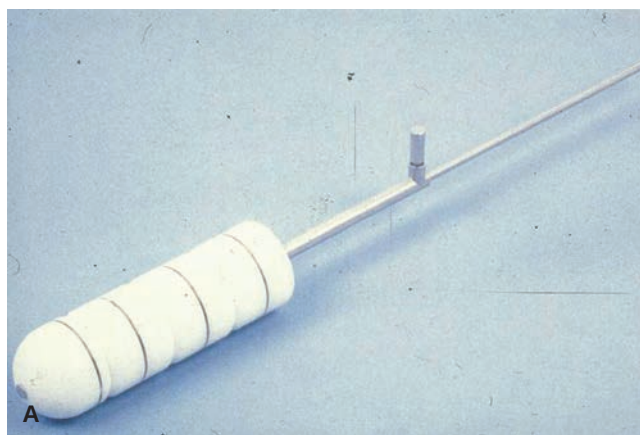


FIGURE 12.48. A: High-dose-rate domed vaginal applicator.

Source: Courtesy of Nucletron.

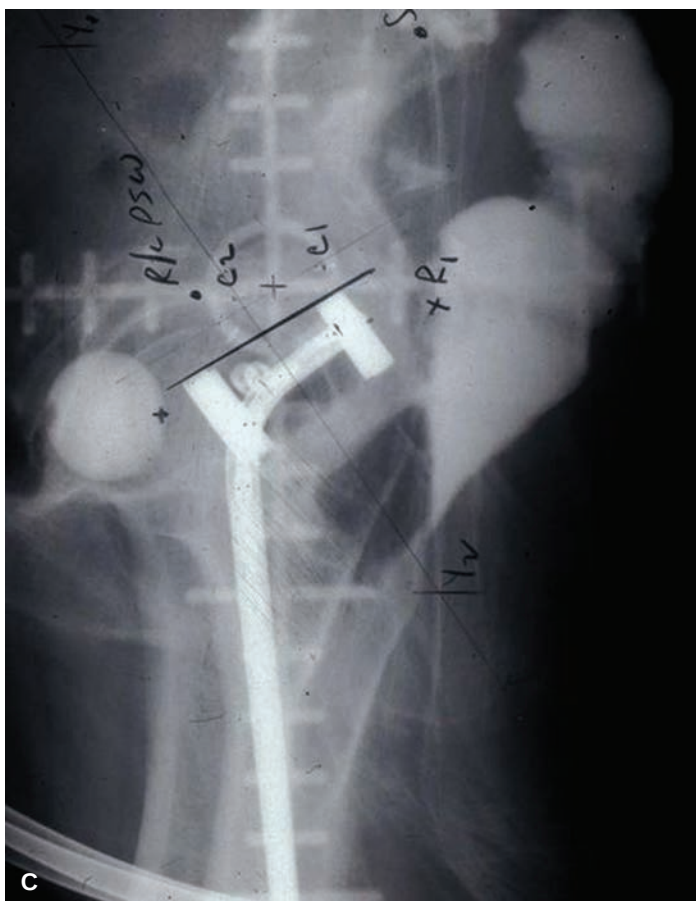


FIGURE 12.48. (continued) **B:** Low-dose-rate Fletcher ovoids with associated radiograph. Lateral radiographs are shown of cylinder **C:** and ovoids **D:** with bladder bulb contrast in both and rectal contrast in **C:**. CT-based dosimetry for a vaginal cylinder revealing the relationship of the dose distribution to the cylinder surface and adjacent bladder and rectum.

system and the edge of the midline block, making good implant geometry imperative when brachytherapy contributes a large portion of the central dose. Those who prefer to deliver an initial 40 to 45 Gy of external beam first believe that the ability to deliver a homogeneous distribution to the entire region at risk for microscopic disease and the ability to have more shrinkage of central disease prior to intracavitary irradiation outweigh other considerations. The brachytherapy dose is accordingly decreased to respect normal tissue tolerance. In addition to causing regression of central disease, the external beam fields are also directed at the regional lymph nodes at risk. In cervical and vaginal cancer, the risk of pelvic lymph node involvement is related to the stage of disease, tumor size, and lymphatic vascular space invasion. Other histomorphologic factors influencing lymph node involvement in cervical cancer include pathologic tumor diameter, depth of stromal invasion, uterine body involvement, parametrial spread, and the number of cervical quadrants involved by tumor (224). Early necropsy studies reported the lymphatic pathways for patients with cervical cancer (225). The primary lymphatic pathway is to the parametrial and paracervical nodes, and the obturator and internal and external iliac nodes. Secondary spread can occur to the sacral and common iliac nodes, with subsequent spread to the paraaortic nodes. Unlike in endometrial cancer, paraaortic lymph node involvement in the absence of pelvic lymph node involvement is rare. Inguinal lymph node involvement occurs with distal vaginal spread of disease or via the round ligament if there is extensive involvement of the corpus. The cervical lymphatics are located in 3 plexuses in the mucosa, muscularis, and serosa of the cervix and anastomose extensively with the lymphatics of the uterine isthmus. This interconnected lymphatic supply is one of the reasons why the entire uterus should be within the external beam fields when treating cervical cancer. Additionally, there may also be lower uterine segment and endometrial extension of tumor. There are lymph vessels running posteriorly in the uterosacral ligaments to lymph nodes located in the sacrum between the rectum and internal iliac vessels. These posterior nodes may terminate in the common iliac, subaortic, or paraaortic lymph nodes (224,226,227). Recent CT studies have added further information on the location of these lymph nodes and variants of spread (228).

For all gynecologic cancers, these patterns of lymphatic spread influence the external beam field borders. Traditionally, design of “standard” pelvic fields, as shown in many radiation oncology textbooks, has been thought to be quite simple and straightforward and based primarily on skeletal landmarks. The skeletal landmarks are not sufficient for field design (229–231). Traditionally, many institutions have used the “four-field box” technique to treat the pelvis with typical AP–PA field sizes of 15 × 15 cm and lateral field widths of 8 to 9 cm (Fig. 12.50) (82). The intent of the 4 fields is to use rather narrow lateral beams to avoid some of the small bowel anteriorly and a portion of the rectum posteriorly. As radiation technique must be “predicated on knowing where things are as opposed to where they ought to be,” there exist no such entities as “standard” radiation treatment volumes, “standard” portal design, or “standard” field sizes. Surgical and imaging series using CT, MRI, and Lymphangiogram (LAG) have revealed that fields of these sizes can easily miss the primary tumor and its extensions and the regional lymphatics at risk, and design of the pelvic fields needs to be done with care and use of confirmatory imaging (230,232–238). Plain films do not visualize the important soft tissues such as the cervical tumor and its extensions, the uterus, or the lymph nodes at risk. Additionally, bladder and rectal contrast and a vaginal obturator or cervical markers have been used to guide field design but are not sufficient (234,239). As with the brachytherapy component of treatment, the adequacy of the external beam fields and margins has a direct relationship with local and regional control (233). What may be considered a mysterious failure following definitive irradiation, perhaps caused by

“radiation resistance,” may actually be the result of a marginal miss due to external beam field design. Placement of radiation fields must take into account the alteration of the spatial relationship between the tumor and normal anatomy due to individual anatomic, tumor-induced, or treatment-related positional variations of the uterus and cervix, as well as knowledge of the location of the regional lymphatics (234,236). Radiation oncologists must be aware of these patterns of disease spread as well as have an in-depth understanding of CT anatomy when designing radiation fields following CT simulation. Identification and contouring of enlarged nodes in nodal regions at risk, as well as identification of the iliac vessels, which serve as surrogates for the location of unenlarged lymph nodes, are important in subsequently defining radiation field borders (Fig. 12.51). Additionally, contouring of the entire uterus and portions of the vagina will also ensure that these tissues are included in the radiation fields (Fig. 12.51). Reliance on bony anatomy alone for radiation field design rather than on CT-defined targets is discouraged. Generally, the superior border of the pelvic fields is at the S1–L5 interspace for early-stage disease (i.e., nonbulky IB or IIA) or at the L4–5 interspace for more advanced disease. The latter is used if one wants to cover the common iliac lymph nodes. Interestingly, Greer et al. evaluated “standard” pelvic fields (Anterior–Posterior [AP] - Posterior–Anterior [PA], 15 × 15 cm; lateral, 8 to 9 cm wide) for the treatment of cervical cancer in relationship to intraoperative findings. Based on intraoperative measurements of the location of the aortic bifurcation and the bifurcation of the common iliac arteries relative to the lumbosacral prominence (the anterior caudal border of L5), Greer et al. concluded that anterior and posterior treatment fields with a superior border at the L4–5 interspace are required to cover the internal iliac, external iliac, and obturator nodes as the bifurcations of the common iliac arteries were above the lumbosacral prominence in 87% of the patients studied. Coverage of the common iliacs could require extending the upper field border to the L3–4 interspace or even the L2–3 interspace in some patients (240). In a later series, Greer et al. treated 38 patients with cervical carcinoma with these expanded fields (AP–PA fields: median length and width of 20 and 17.5 cm; lateral fields: median width of 16.5 cm, posterior border including the entire sacrum), with an acceptable late actuarial severe complication rate of 14.8% (239). Obviously, with CT-based dosimetry, it is imperative to outline the vessels and/or nodes in these areas to determine the appropriate field borders as unnecessary irradiation of bowel could occur if all patients were treated to the L2–3 interspace based on this assumption (Fig. 12.51). CT is an excellent tool to either identify pathologically enlarged nodes, multiple small lymph nodes that by increased number rather than size are suspicious, or in the absence of nodes, the aortic and iliac bifurcations and the iliac vessels (228,230). Finlay et al., using CT-based planning, found that 79% of patients treated with conventional fields had inadequate coverage. For adequate coverage, the superior border may need to be as high as L3–4 to cover the common iliac nodes. Using CT-based planning, Finlay et al. reported that 95.4% of the patients who had “conventional” pelvic fields had inadequate coverage of nodes when these were contoured on treatment planning CT scans (241). The inferior border of the pelvic field is usually at the bottom of the ischial tuberosities or 3 to 4 cm below the most distal vaginal component of disease. Inguinal nodes are included if there is distal vaginal spread, in which case treatment of the vaginal introitus with margin would also be required. MRI is especially helpful in imaging vaginal tumor extension (234). The lateral borders of the AP–PA fields are important to design carefully as the 1.5- to 2.0-cm margin from the pelvic brim standardly recommended may be too narrow. Using lymphangiography, Pendlebury et al. found that in order to cover the lymphatic channels in the pelvis in 90% of cases, the lateral margins of the AP–PA fields would need to be 2.5 cm lateral to the pelvic brim

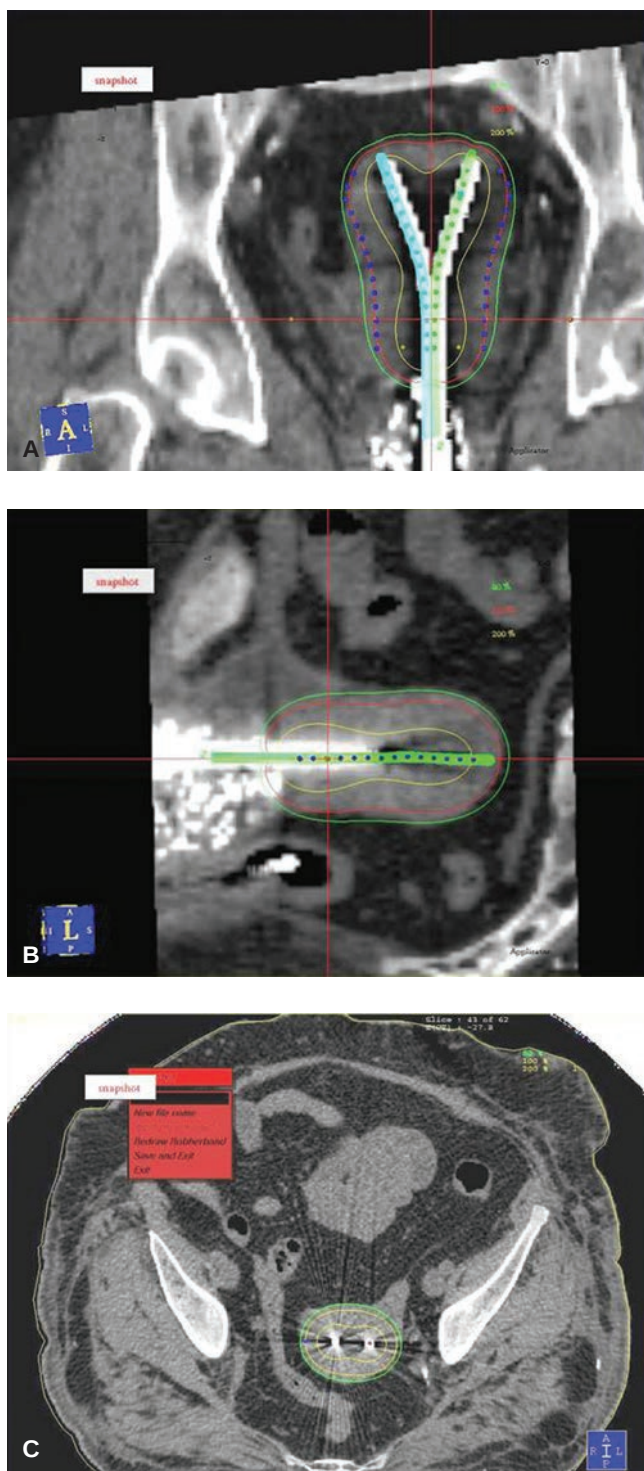


FIGURE 12.49. Brachytherapy plan for a patient with medically inoperable endometrial cancer in **A**: coronal, **B**: sagittal, and **C**: axial dimensions. Note dual tandems on the coronal image **A**.

(range of medial margins to cover lymph nodes, 0.5 to 3.0 cm) (231), and Bonin et al. found a margin of 2.6 cm (229). Intraoperative measurements have confirmed these findings (240). The lateral fields are even more prone to marginal misses than the AP-PA fields, as demonstrated in multiple series that have compared the standard textbook lateral fields (8 to 12 cm wide) to fields designed based on CT and MRI images (Fig. 12.52) (230,232,233,235–237,242). For the lateral fields, a commonly employed guideline is to place the posterior border in a

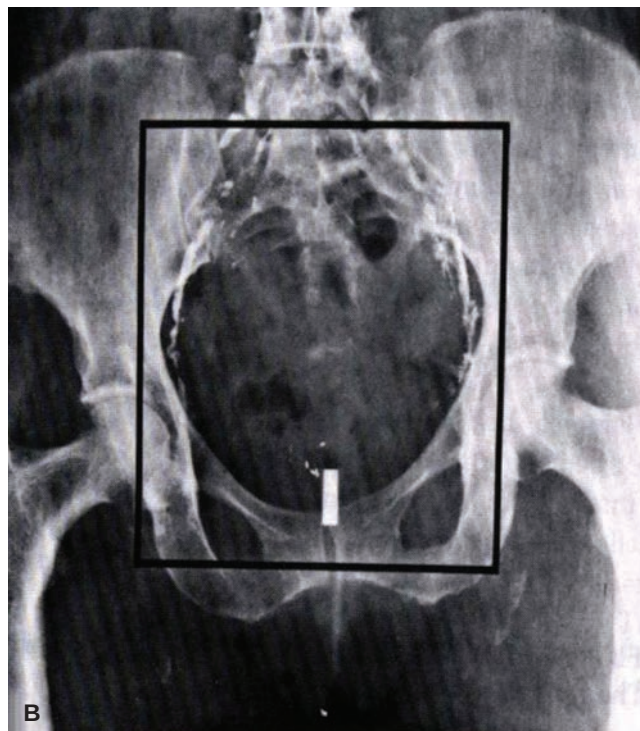


FIGURE 12.50. Traditional four-field pelvic box technique with short and narrow fields with the potential to miss the uterine fundus and the pelvic lymph nodes.

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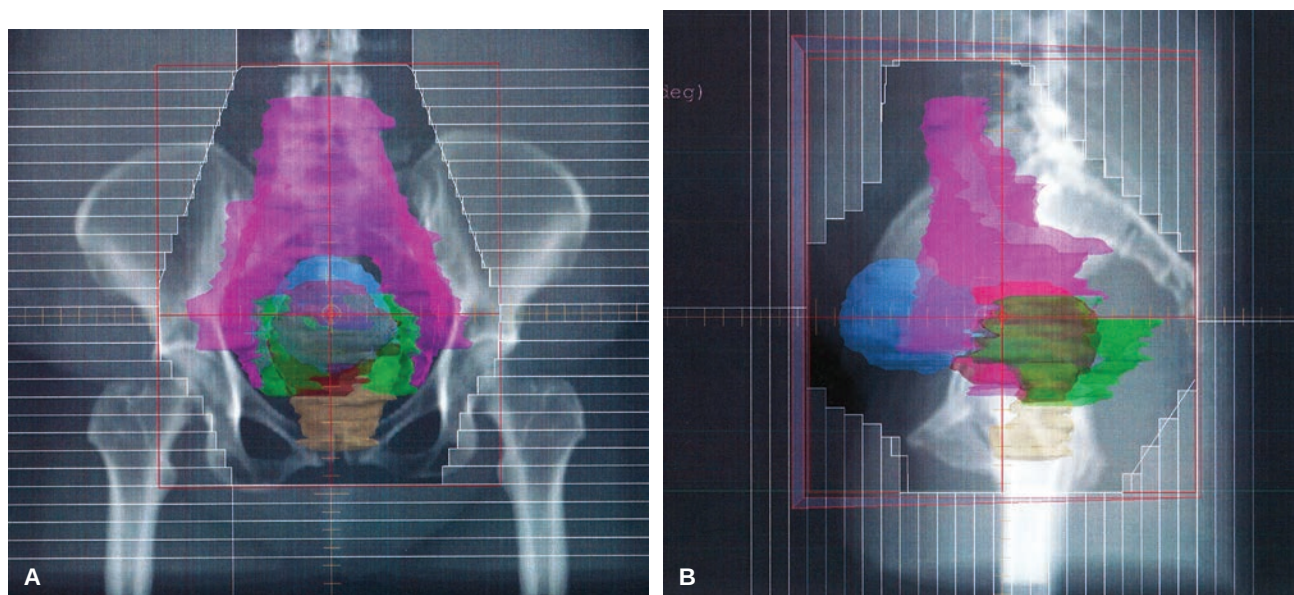


FIGURE 12.51. Digitally reconstructed AP **A:** and lateral **B:** radiographs with associated contoured targets including the pelvic lymph nodes and uterus/cervix/parametria and vagina. Note the multileaf collimator leaves defining the field shape in accordance with coverage of the targets of interest.

horizontal line, parallel to the treatment couch that divides the mid-rectum and intersects the sacrum between the second and third sacral segments (S2–3 interspace), and the anterior border by a horizontal line, parallel to the treatment couch from the anteroinferior lip of L5 to the anterior aspect of the pubic symphysis (235). These “standard” lateral fields are too narrow. For the lateral fields, careful consideration needs to be given to the anterior border to include the external iliac nodes. Based on lymphangiography, Pendlebury et al. found that to cover the external iliac nodes, the anterior border of the lateral field was sometimes as much as 2 cm anterior to the pubic symphysis (231), which was later confirmed by Bonin et al. (229). Chun et al. found that based on CT definition of the external iliac lymph nodes, when using standard lateral fields, only 50% of the patients studied had adequate coverage of these nodes (230). Additionally, the anterior border must also be drawn to include the entire uterus, given the interconnecting lymphatics of the uterus and cervix and the possibility of lower uterine segment/endometrial extension (Fig. 12.52) (227,232,236). Enlargement of the uterine fundus by the presence of hematomata or massive fundal extension of cancer can displace the fundus anteriorly and cephalad, as can an anteverted or retroverted uterus (232,237,243). The prone position may accentuate this displacement (234,236). The anterior field border should be based on CT or MRI delineation of the tumor and/or normal anatomical variants to avoid underdosing of these structures (230,232,234,235,237,242,243). The posterior border of the lateral fields must be designed carefully. Based on intraoperative findings, Greer et al. showed that the cardinal and uterosacral ligaments extend posterior to the rectum and sigmoid in their attachments to the sacrum. As part of the parametria, these tissues often contain nodes, even in early disease (IB and II, 22.5%) or are involved by direct extension and need to be covered in most patients by including the entire sacrum in the lateral fields (239). If there is uterosacral ligament involvement, it is especially important to include the entire sacrum in the lateral fields, although some institutions will use this as a criterion for AP–PA fields alone (226). The internal iliac lymph nodes can also lie very close to the rectum and splitting of the rectum can result in a marginal miss of these nodes (Fig. 12.53) (228). For posterior cervical lesions, there can also be direct extension to the superior rectal nodes or sacral lymph nodes (224). Tumor can also

extend directly around the rectum. Kim et al. found that the most common site of an inadequate margin was near the portion of the lateral field blocking the rectum. On CT, it was found that tumor often fell along the lateral aspect of the rectum. The second most common site of inadequate margin was the posterior border at the S2–3 interspace (232). Zunino et al. also found inadequate posterior border margins when the uterus was both retroverted and anteverted (Fig. 12.52) (237). The reason for narrow lateral fields is typically concern over the rectum and the small bowel. Russell et al. have included the entire sacrum in the lateral fields of all patients with cervical cancer treated at their institution, and they have reported no increase in acute or late morbidity. When present, all rectal injuries observed have been on the anterior rectal wall due to the proximity of the implants used in the definitive management of these patients (235). Greer et al. also reported no increase in late rectal complications when including the entire sacrum in the field (239). It may also be a mistake to avoid the chance of a marginal miss by treating just with anterior and posterior fields, as in most cases some of the small bowel can be omitted from the lateral fields when using imaged-based planning (235). Gerstner et al. found that by using beam’s eye view–based 3D treatment planning, though the rectal volume treated increased to avoid a marginal miss, there was an overall reduction in the lateral field treatment volume as compared to standard treatment fields due to beam shaping to exclude portions of the bladder and small bowel and bladder distention (242). MRI has been found to be an invaluable tool for delineating normal anatomy and the extent of cervical tumor involvement because of its superior soft-tissue contrast when compared to CT. MRI also allows direct imaging in sagittal, coronal, and transverse plains (237). Sagittal MRI images are exceedingly helpful in designing radiation fields (Fig. 12.52). Design of the anterior and posterior borders of the lateral fields can be especially influenced by these images (234–237,243). Thomas et al. performed MRI rather than CT in the treatment position, and found better delineation of the tumor volume due to the superior contrast resolution (236). Lymphangiograms are very helpful in defining the location and architecture of lymph nodes when designing radiation fields, and are especially helpful in designing the lateral fields and subsequent nodal boost fields (229,231,237,244). They do not routinely image the internal iliac lymph nodes, although sometimes these will fill

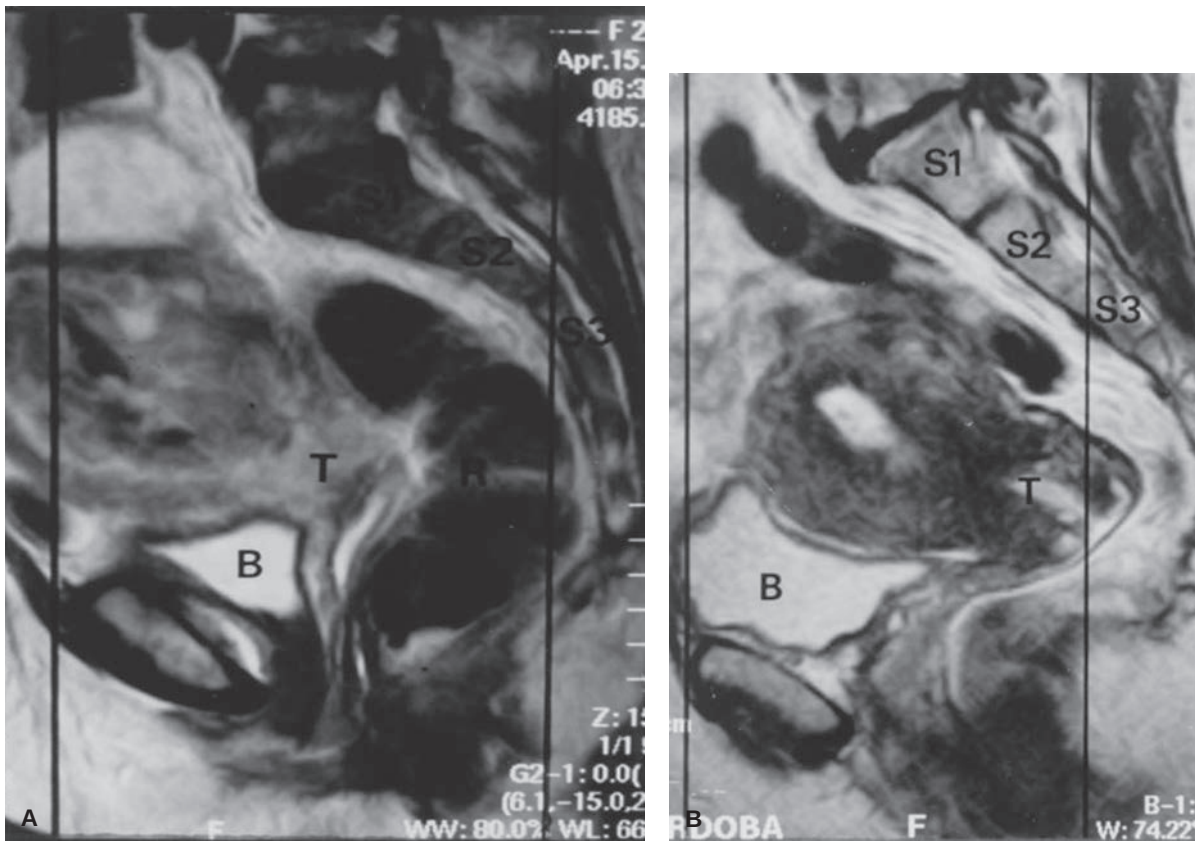


FIGURE 12.52. (A–B): Traditional lateral fields are superimposed on sagittal MRI scans to evaluate target coverage with traditional fields. Note in **A**: that the traditional lateral fields would not completely cover the uterine fundus, and that in **B**: the traditional lateral field would cut through cervical tumor within the anteverted uterus.

Source: Reprinted with permission from Zunino S, Rosato O, Lucino S, et al. Anatomic study of the pelvis and carcinoma of the uterine cervix as related to the box technique. *Int J Radiat Oncol Biol Phys*. 1999;44(1):56–57.

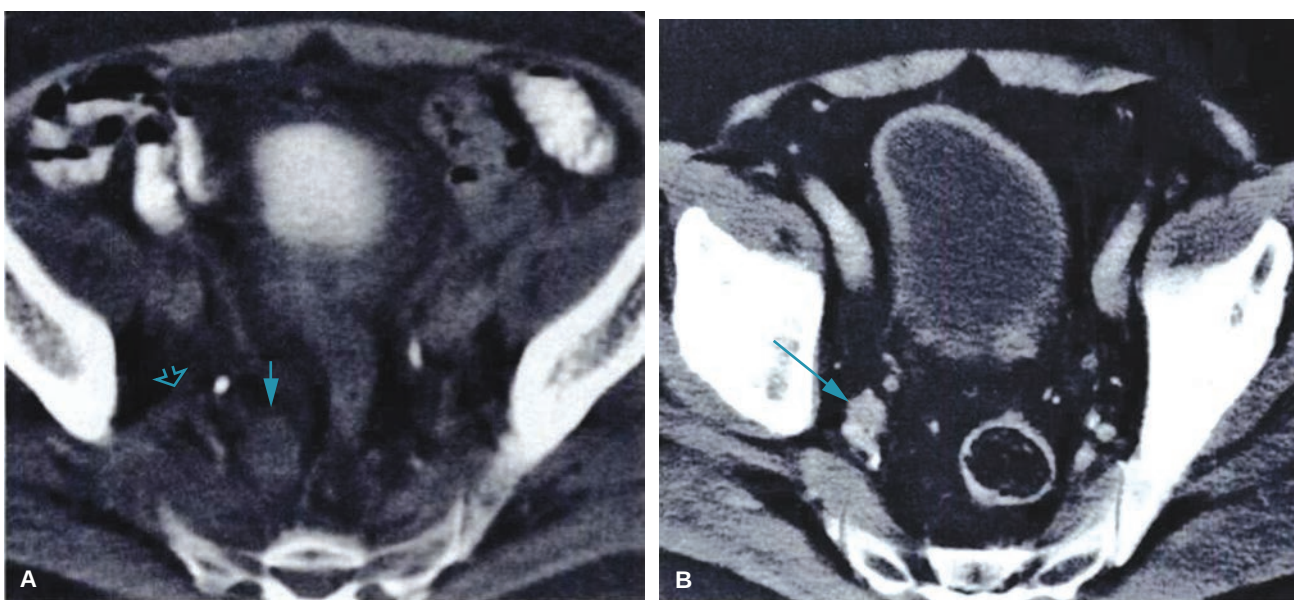


FIGURE 12.53. A: The location of the presacral lymph nodes mandates including the entire sacrum to cover disease in the uterosacral and cardinal ligaments and superior rectal (pre-sacral) nodes. The right lateral sacral node (*solid arrow*) is medial to the hypogastric vessels (*open arrow*). **B:** Note the proximity of the internal iliac lymph node (*solid arrow*) to the rectum. This spatial relationship would exclude partial blocking of the rectum on the lateral fields.

Source: Reprinted with permission from Park J, Chamsangavej C, Yoshimitsu K, et al. Pathways of nodal metastases from pelvic tumors: CT demonstration. *Radiographics*. 1994;14(6):1311.

in a retrograde manner. Unfortunately, lymphangiography is available at only a few institutions due to the fact that it is time consuming for both the radiologist and patient, and fewer radiologists are trained in such procedures (229). Positron emission tomography (PET)/CT scans have largely replaced lymphangiograms at most institutions with Medicare approval in 2005 and can detect involved pelvic and paraaortic lymph nodes better than CT alone (245–248). PET does not rely on lymph node size alone, unlike CT; rather, it relies on metabolic alterations for detection of disease. PET has better accuracy than can be achieved with CT or MRI with a sensitivity of 85% to 90%, a specificity of 95% to 100%, and overall accuracy of 90% to 95%. Nodes as small as 6 mm can be imaged with PET, providing information to guide therapy and predict outcome.

Midline Blocks

Midline blocks are used at variable points in time at many institutions (Fig. 12.47). It is important to understand when the midline block is placed as this will influence the HDR fraction size. Higher whole pelvis doses can be utilized without a midline block (162,163), but the HDR doses have to be appropriately reduced. HDR and external beam fractions should not be given on the same day. Use of midline blocks is controversial as there can be an increased risk of rectosigmoid, bladder, and small bowel complications if careful attention is not given to tracking and limiting the total dose in these OAR (254–256).

A midline block may be used during external beam to avoid regions of excessive dose adjacent to the brachytherapy implant and to deliver an adequate dose to potential tumor-bearing regions outside of the implant. When using a midline block early in the treatment course, more reliance is placed on the extremely complex match between the intracavitary system and the edge of the midline block. Some institutions customize the midline shield for each patient by defining the block edges as the contour of the isodose line passing through point A (249), or the 50% isodose line. Other institutions further customize this by stepping or altering the block thickness at specific isodose level intervals to achieve a dose “feathering” effect between the external beam and brachytherapy doses. The step-wedge or variable thickness transmission block used at Mallinckrodt (MIR) was initially designed to correspond to the various isodoses of the intracavitary insertions with various tandem and ovoid configurations (141,250,251). Over time, a customized step-wedge was not fabricated for each patient, but a number of standard prefabricated sizes were made available for repeated use. Several other institutions have published use of customized step-wedge midline blocks based on individual implants (252). Most institutions use rectangular blocks 4 to 5 cm in width rather than production of blocks based on the isodose distributions (Fig. 12.47) (249,253).

There are some important safety issues when using midline blocks (254–256). The midline block position should be based on films with similar isocenters. If patients receive external beam irradiation in the prone position, it may be wise to simulate them in the supine position for their parametrial boosts so that they are in the same position as they are for their implants. Midline blocks can be positioned to account for applicator deviation. Wolfson et al. found that most institutions using the standard rectangular midline blocks align the superior–inferior central axis of the block along the midplane of the patient’s pelvis, while those using customized midline blocks usually align the midline block along the axis of the tandem (249). Aligning along the midplane of the patient can be problematic if the tandem is deviated. The step-wedge corrects for the lateral gradient of the intracavitary system and not the rapid dose gradient anterior and posterior to the plane of the implant or for variations in the positions of the implants. The contribution of scattered radiation may increase the dose under narrow midline blocks, which

may exceed the anticipated 5% of the primary pelvic dose when using a 5 to 6 half-value layer (HVL) midline block. Midline blocks that are too narrow may not adequately shield the bladder and rectosigmoid given their ability to move in and out of the blocked field. Filling and emptying of these organs may also alter their position relative to the block. Eifel et al. point out that the distance between the distal ureters is usually 4 to 5 cm. A narrow block may fail to shield a portion of the ureters during external beam (257). Reviewing the M.D. Anderson experience, Eifel et al. detected an increase in complications in patients with midline blocks (4 cm) used throughout the course of external beam. Since the ureters are typically 2 to 3 cm from midline, the explanation for the ureteral stenosis could have been an overlap between the external beam fields and the high-dose region of the intracavitary implants (257). A margin of 0.5 cm lateral to the lateral ovoid surface is recommended in designing the width of the midline block for each patient to protect the implanted volume. If the intracavitary system is broad, a wide midline block may potentially shield the external iliac lymph nodes. If tissues immediately adjacent to the colpostats and tandem tip are not shielded, portions of the ileocecal junction and rectosigmoid may be overdosed (258,259). Huang et al. recommended avoiding a combination of parametrial boost doses of ≥ 54 Gy and a cumulative rectal biologically effective dose (CRBED) ≥ 100 Gy₃ to decrease the risk of radiation-induced bowel complications (259). Chun et al. also found increasing rectal complications with parametrial boosts >55 Gy (257). When a midline block is inserted prior to 40 Gy, it should not extend to the top of the field since it will shield the common iliac and presacral lymph nodes, which will be underdosed (249). Kuipers notes that the uterus can be displaced cranially toward the sigmoid during intracavitary irradiation because of vaginal packing. It may be important to make the midline block high enough to protect the sigmoid so that it does not receive further radiation during external beam (260). The inferior edge of the midline block should be coincident with the caudal aspect of the whole pelvis fields to avoid overdosage of the distal vagina (249). When there is suspicion of uterosacral ligament involvement, it is safer to avoid early placement of the midline block, which will shield disease lying posterior to the implant (226). Due to concern over rectal tolerance, the rectum is shielded after a certain amount of external beam radiation therapy, which can block tumor in the perirectal area and uterosacral space. The geometric configuration of the intracavitary implant emphasizes lateral rather than posterior coverage and does not effectively treat the perirectal and uterosacral space effectively. This can lead to underdosing of tissues in this area and an increased risk of central recurrence. Higher whole pelvis external beam doses, interstitial implantation, or addition of a supplemental posterior oblique external beam boost may offer ways to compensate dose in this area (226). Given the potential for risk, some would advocate abandoning the midline block in favor of other options (254–256). As there may be some disparity in implant position if multiple fractions are used over time, such as with HDR, it is necessary to reassess the midline block configuration after each implant (261).

Parametrial/Nodal Boosting in Cervical Cancer

Parametrial boosting is often recommended for patients with bulky parametrial or sidewall disease, after completion of the whole pelvis field and midline block fields, as the parametria are a common site of failure. The need for boosting is usually based on the status of disease regression following whole pelvis irradiation. MRI may be helpful in making this assessment both before and during radiation. Mayr et al. found MRI imaging useful in the localization of parametrial tumor extension and enlarged their parametrial boost fields based on these MRI

images to include the disease and exclude small bowel (234). Logsdon and Eifel suggest boosting residual lateral pelvic wall disease after 40 to 45 Gy whole pelvis to 60 to 62 Gy to small volumes (85). Perez et al. found a trend toward increased pelvic control with point B doses (defined at 6 cm lateral to the central axis) >45 Gy (116,262). In the 1973 and 1978 PCS, there was no relationship between lateral dose >60 Gy and either infield pelvic control or survival, but the lateral dose did impact complications with an increase above 50 Gy (118,120,121). There was a trend toward decreased failure with increasing parametrial doses in stage III disease (119). Perez et al. found that the incidence of pelvic recurrence was correlated with tumor size and dose of irradiation delivered to the lateral parametrium. There was an increase in the incidence of pelvic recurrence in patients receiving less than 50 Gy, but no correlation with increasing doses of irradiation (263). Doses needed to eradicate parametrial disease in the literature are typically around 60 Gy, combining the external beam doses with the implant doses. The proximity of small bowel can make this a risky proposition. Perez et al. noted that with doses below 50 Gy to the lateral pelvic wall, the risk of small bowel complications was about 1% and somewhat higher with larger doses (141). In a later series, grade 3 small bowel sequelae were 1% with doses of 50 Gy and 2% to 4% with doses over 60 Gy ($p = 0.04$) (264). At present, Perez et al. recommend limiting the small bowel doses to less than 60 Gy. Ferrigno et al. found an increase in small bowel complications when parametrial boosts were above 59 Gy. They recommended dropping the superior border of the parametrial fields to the S2–3 level and limiting the total dose to 54 Gy (194). The use of concurrent chemoradiation may allow a decrease in these doses, but data is too preliminary to conclude what this dose should be. When there is uterosacral space involvement, thought should be given to the use of a supplemental posterior oblique external beam boost (226). Grigsby et al. used PET/CT scans to evaluate lymph node size, irradiation dose, and patterns of failure. The parametrial and lymph node boost doses used were in the range of 9.0 to 14.4 Gy following large field doses of 50.4 Gy. Radiation dose and lymph node size were not significant predictors of lymph node failure. The risk of an isolated lymph node failure was <2% (265). A reoperation series following definitive irradiation and chemotherapy was reported by Houvenaegel et al. After 45 Gy and whole pelvis and selective parametrial or nodal boosting to 55 to 60 Gy, 15.9% of patients had biopsy-proven residual disease in the pelvic nodes and 11.7% of paraaortic nodes (266). Use of IMRT may be a method to increase dose

to bulky nodes or residual parametrial disease while sparing adjacent normal structures (35,47,46).

Endometrial Cancer

For endometrial cancer, many of the same nodes are at risk as in cervical cancer, but the spread of disease is not as predictable with the paraaortic nodes independently at risk. The presacral nodes are also not at risk unless there is cervical involvement. Both the pelvic and paraaortic nodes are at risk in all sites of uterine involvement, and grade, myometrial invasion, and lymphatic vascular space invasion are more predictive of risk than location (267–271). Cervical and lower uterine segment involvement also increases the likelihood of pelvic and paraaortic lymph node metastases compared to fundal location, as do increasing histologic grade and myometrial invasion. In the surgical staging series of Boronow et al., 18 of 222 patients had lower uterine segment involvement and 6 (33%) had pelvic lymph node metastases (270,272). In the final GOG surgical staging series report, by location, patients with fundal lesions had a 4% risk of paraaortic and 8% risk of pelvic lymph node involvement, whereas patients with lower uterine segment involvement had a 16% risk of pelvic and 14% risk of paraaortic lymph node involvement (274).

In endometrial cancer, external beam irradiation is generally recommended for patients thought to be at significant risk for lymph node metastases and/or a vaginal cuff recurrence. Traditionally, this has been recommended in the absence of a lymph node dissection or a limited lymph node sampling. External beam irradiation is also still delivered at many institutions in the setting of a negative lymph node dissection when high risk features such as deep myometrial invasion, high grade, lymphatic vascular space invasion, lower uterine segment involvement, or cervical invasion are present (273,274).

External beam irradiation typically covers the upper one-half to two-thirds of the vagina, the pelvic lymph node regions, and the surgical bed (Fig. 12.54). External beam field design must necessarily include the pelvic lymphatics with exclusion of as much small bowel as possible. Treatment of the patient in the prone position with a full bladder will help to exclude at least some small bowel in most patients unless these loops are fixed in the pelvis (Fig. 12.55). It is important, however, for the lateral fields to also cover the course of the external iliac nodes, which are quite anterior in the pelvis and require inclusion of some

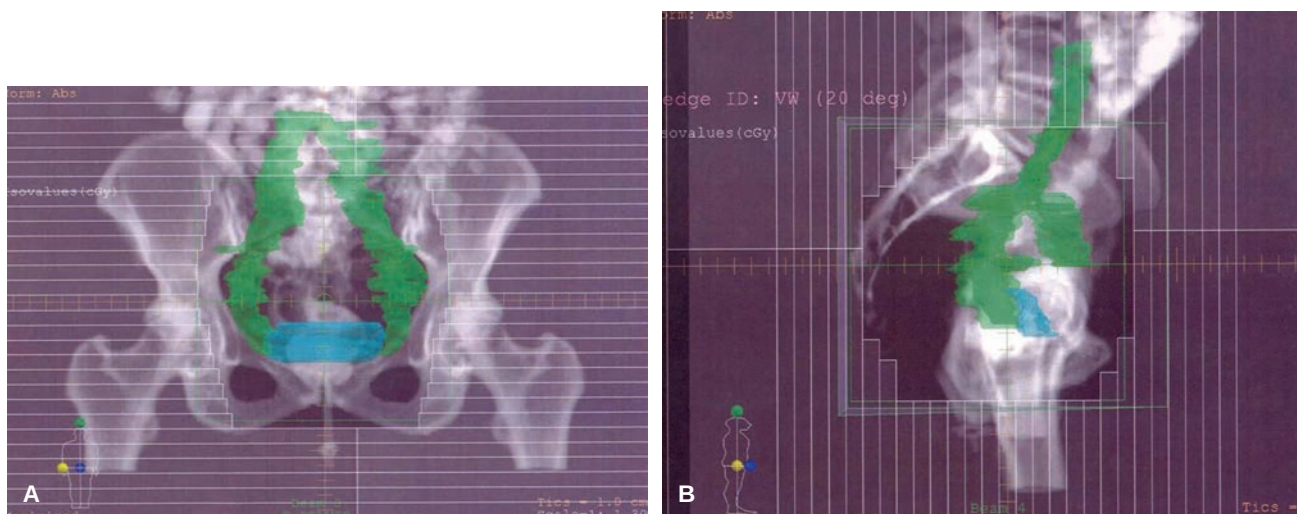


FIGURE 12.54. Digitally reconstructed AP **A:** and lateral **B:** radiographs with nodal volumes contoured as well as the vaginal apex and the fields defined by the leaves of multileaf collimator. This is a standard field design for patients with endometrial cancer.

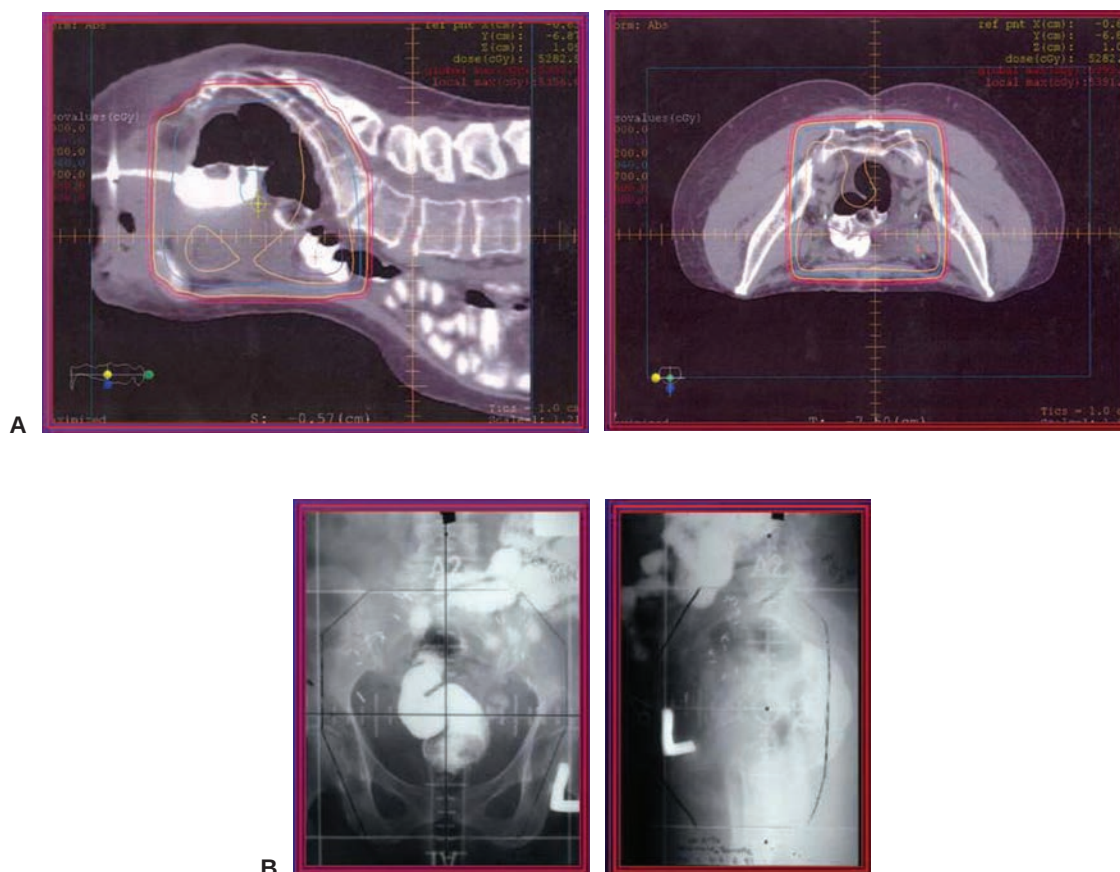


FIGURE 12.55. **A:** Utility of the prone technique for small bowel displacement as shown on a sagittal and axial CT scan of a patient with endometrial cancer planned in the prone position. **B:** Radiographs of the pelvis showing significant amount of small bowel in the radiation fields.

small bowel in the lateral fields to be adequately covered. Doses of 45 to 50.4 Gy are typical, with some institutions treating to 40 Gy and as high as 60 Gy to reduced fields in the setting of nodal disease. Whole pelvic fields are generally reduced or a midline block is added after variable doses.

Prone techniques have been used in the treatment of many other pelvic malignancies to attempt to exclude small bowel from the field. Use of a belly board device to further enhance small bowel displacement has become standard practice for many pelvic malignancies (275–277). Use of prone position with or without a belly board for the treatment of patients with cervical cancer has been reported in a few series, in the postoperative (275,276,278–280) and definitive settings (275–277,280,281). Prone positioning with the belly board has been used extensively for patients with rectal cancers when using a PA and two lateral fields. Concern over use of this technique for patients with gynecologic malignancies when adding a fourth field (AP) to cover the external iliac nodes has been raised by Ghosh et al. due to the uncertainty in source to skin distance (SSD) and variation in tissue thickness from the anterior field. In patients who underwent postoperative irradiation for cervical cancer, they observed that the small bowel was best excluded from the AP-PA fields when the patient was positioned prone without the belly board, thereby compressing the small bowel laterally out of the AP-PA fields. They recommended an alternating routine (278). Bladder distention can also help to optimally displace bowel when using the belly board (275,277). Concern over use of the belly board in patients treated with definitive versus postoperative irradiation for cervical cancer is also raised due to the potential change

in position of the uterus when prone, the impact and variability of bladder filling, and the potential daily variation in the setup (278,280,281). There is also some concern that, in patients with intact uteri, the prone position may increase the volume of the rectum treated (280). CT-based dosimetry has documented that the prone position, particularly with bladder filling, can alter the position of the uterus within the radiation field (234,236,281). Hence, if patients are simulated prone, it is even more imperative to use CT- or MRI-based dosimetry in the prone position to make sure that the entire uterus is in the pelvic fields, and it is also imperative to consistently fill or empty the bladder (281,282). IGRT may also be helpful in ensuring that the daily setup is reproducible and reliable.

Extended Field Irradiation

Extended field irradiation refers to inclusion of both the pelvic and paraaortic nodes in the radiation fields. Common indications for extended field irradiation in gynecologic cancers include patients with positive paraaortic nodes or those with positive pelvic nodes or bulky primary lesions feared to be at risk for microscopic paraaortic disease (Fig. 12.56). Extended fields include more normal organs than pelvic fields alone. Limitation of dose to the small bowel, kidneys, liver, stomach, and spinal cord are essential. Three-dimensional conformal techniques are helpful in achieving an acceptable therapeutic ratio. Use of IMRT has recently been piloted in this setting with further attempts to decrease acute and late toxicity (Fig. 12.20).

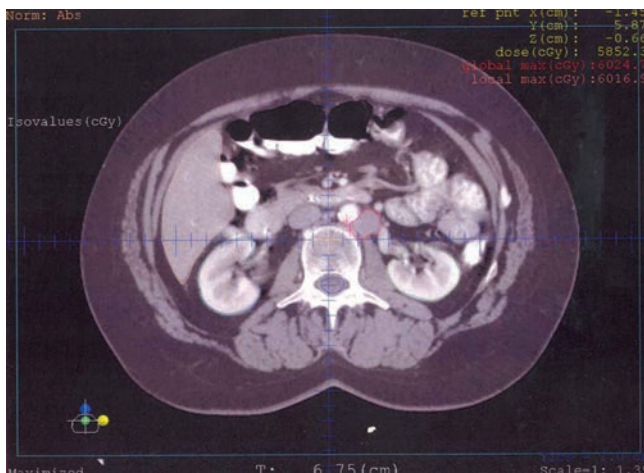


FIGURE 12.56. Axial CT scan demonstrating an enlarged periaortic lymph node near the left renal hilum.

Selective boosting of gross nodal disease may allow for safer dose escalation (45–47).

Pelvic and Inguinal Irradiation

External beam fields will necessarily include the inguinal lymph nodes in patients with vulvar cancer or distal vaginal cancers or when cancer of the cervix or endometrium involves the distal vagina. Risk of femoral head necrosis or femoral neck fractures is increased in this setting. Recent use of IMRT to treat vulvar and vaginal cancers has been published with success (50).

Whole-Abdominal Irradiation

Whole-abdominal irradiation is used to cover the entire abdominopelvic cavity in ovarian cancers or high-risk uterine cancers such as those with positive peritoneal washings or adnexal involvement (IIIA disease). This requires limiting the radiation dose to a maximum of 30 Gy to the entire abdomen and using lower fraction sizes of 150 to 170 cGy. This will reduce both acute and late toxicities. Careful attention to and limitation of the dose of radiation delivered to the liver and kidneys requires selective blocking of these structures at different doses (283,284). IMRT techniques are also being explored for whole-abdominal irradiation to reduce doses to the GI tract, liver, kidneys, and bone marrow and increase dose to the peritoneal surfaces and lymph nodes (48,49).

Radiation-Induced Tissue Effects

Side effects that develop during the course of radiation and persist for 3 months or less following completion of radiation are termed acute side effects. Those toxicities that develop later than 3 months after the completion of radiation are termed late or chronic effects. The late effects of radiation are due to damage at the capillary level where there is endothelial cell proliferation resulting in less diffusion of oxygen into the tissues with resulting fibrosis. There is less resistance to infection, trauma, or functional stress due to this change in vasculature and circulation (285,286). When treating gynecologic cancers, the normal tissues most often incidentally irradiated in the pelvis

are the rectosigmoid, small bowel, bladder, vagina, and pelvic bones and bone marrow. In the upper abdomen the kidneys, liver, stomach, small bowel, large bowel, and spinal cord may be in the radiation field. The response of a tissue or organ to radiation depends on two factors: (a) the inherent sensitivity of the individual cells, and (b) the kinetics of the population as a whole of which the cells are a part. These factors combine to account for the substantial variation in response to radiation characteristic of different tissues (1). Additionally, the volume of tissue irradiated as well as the dose, dose rate, and fractionation scheme will affect both acute and late toxicities. The addition of chemotherapy or other systemic agents may impact toxicity, as may other medical comorbidities such as diabetes, hypertension, collagen vascular diseases, Crohn's disease, and ulcerative colitis, as well as social risk factors such as smoking. The most comprehensive data describing the effects of radiation on the normal tissues was published by Rubin and Casarett and later updated by Emani et al. (286,287). Rubin and Casarett defined tolerance doses (TD) for almost all of the tissues. The TD 5/5 is defined as the probability of a 5% risk of complications within 5 years of the completion of radiation, and TD 5/50 as the probability of a 50% risk of complications within 5 years (286). More recently, the QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) guidelines have been published with updated recommendations (288,289).

Skin

When treating abdominopelvic tumors with radiation, often there will be minimal skin reactions due to the skin-sparing quality of the high-energy radiation beams used to treat these sites deep within the body. Contrastingly, when treating the vulvar and inguinal regions, where electrons or lower energy X-rays are more often used, there can be marked skin reactions. Skin reactions are also more likely to develop in skin folds such as the inguinal creases or intergluteal fold. The cells in the basal layer of the skin are very sensitive to radiation, but because of the time required for these differentiating cells to move from the basal layer to the keratinized layer of skin, there is a 2- to 3-week delay between the start of radiation and the appearance of skin reactions. Erythema is the first visible skin reaction due to dilation of the small capillaries and is usually seen about the third week of radiation. Other skin reactions include dry desquamation and moist desquamation occurring after the 4th week of radiation. Moist desquamation occurs with transient loss of the epidermis and exposure of the dermis. Serous fluid often oozes from the exposed and inflamed dermis (286,290). These effects may be enhanced by the combination of irradiation and some chemotherapeutic agents, particularly actinomycin D and doxorubicin (Adriamycin) (293). It is also well known that chemotherapy agents such as Adriamycin or gemcitabine can “recall” radiation reactions after the original reaction has subsided (291,292). Radiation-induced skin reactions are treated with various topical ointments and creams as well as with sitz baths and special emphasis on cleansing all stool and urine gently from the perineum. Additionally, if the distal vagina or vulva is in the radiation field, patients may also complain of dysuria or painful defecation, which is due to the caustic effects of the urine and stool on the denuded epithelium of the distal vagina, perianal area, and vulva. Diarrhea control and use of barrier creams to protect the irritated skin from stool and urine will help to minimize discomfort and hasten skin healing. Sulfa-based creams and Domeboro soaks can be used to expedite healing. Return of the epidermis can take 10 to 14 days. Residual surviving basal cells form islands of regeneration, which proliferate to re-epithelize the area. Islands of skin forming in the desquamated skin herald skin renewal. The new skin is thin and pink with gradual return to normal

in 2 to 3 weeks (286). Late manifestations of radiation on the skin include depigmentation, subcutaneous fibrosis, dryness and thinning with loss of apocrine and sebaceous glands, thinning or loss of hair, and telangiectases. Necrosis of the skin is rare and generally occurs only with very high doses of radiation in excess of 60 Gy (286,293).

Bone Marrow/Pelvic Bones

The lymphocytes are the most radiosensitive cells in the bone marrow. The rate of fall of the various components of the marrow is a function of the half-lives of the mature cells. These half-lives are as follows: erythrocytes, 120 days; granulocytes, 6.6 hours; and platelets, 8 to 10 days (286). Pelvic irradiation may cause transient lymphopenia. This is even more of an issue when whole-abdominal or extended-field irradiation is used due to the increased bone marrow in the radiation fields. This decrease in lymphocytes is thought to be the result of irradiation of the lymphocytes circulating through the vascular bed and may not be indicative of bone marrow reserve depletion. Prior or concurrent chemotherapy will also lead to increased bone marrow toxicity. Frequent monitoring of the CBC is considered standard of care with pelvic or abdominal irradiation. Permanent chronic changes are noted even when small segments of the bone marrow are irradiated to doses over 30 Gy, and recovery may take up to 18 months or longer in a proportion of patients with good reparative capacity.

Insufficiency fractures can also develop in irradiated pelvic bones (293,294,295). These most commonly involve the sacrum and ileum, followed by the pubic bones, and rarely the acetabulum. Patients may complain of sudden onset of back or groin pain, which worsens with weight bearing and changes in position. MRI is the best imaging modality to detect them and also rule out recurrent disease. Sometimes edema will be reported in the absence of actual fractures, and in other cases, actual fractures will be seen. It is important not to confuse these changes with metastatic disease, as further palliative irradiation would worsen the integrity of the bone. Symptoms from these changes in the pelvic bones will often improve over time, but patients may also suffer future symptoms from exacerbation of these fractures or development of new fractures over time. Sacroplasty can be used if patients remain symptomatic. Narcotics and changes in activity are often required. Femoral neck complications can include avascular necrosis as well as fracture. This is a rare complication following irradiation of the inguinal nodes. Hip replacement surgery is required to resolve this problem (296).

Liver

During whole-abdominal irradiation or paraaortic irradiation, the liver is in the radiation field and dose must be limited to this critical organ. Clinical and pathologic studies have shown that the liver is not a radioresistant organ. Venooclusive disease is the pathologic entity caused by radiation. Necrosis and atrophy of the hepatic cells result from this change in blood supply. CT scanning following radiation can show changes in perfusion of the liver corresponding to the radiation fields. These changes are not always associated with toxicity. The clinical course and liver changes depend on the dose-fractionation scheme and volume of irradiation as well as the presence of chemotherapy and preexisting liver disease. During radiation, the liver enzymes may be elevated. This can continue following completion of radiation. Signs of radiation hepatitis can include a marked elevation of alkaline phosphatase (3 to 10 times normal), with much less elevation of the transaminases (normal to 2 times normal) (286,297). Liver enlargement and varying amount of ascites can also evolve. If the doses and volumes are high enough, liver failure can occur.

The TD 5/5 for whole liver is 30 Gy in 2 Gy fractions (286,287). Small portions of the liver can receive up to 70 to 90 Gy. Mean liver doses of <28 to 32 Gy at 2 Gy per fraction are recommended (298).

Kidney

The kidneys are very sensitive to small doses of radiation, and a common goal is to avoid greater than 18 to 20 Gy whole kidney dose. When delivering whole-abdominal irradiation, the kidneys are at risk and must be blocked at acceptable doses to prevent renal failure. When delivering paraaortic irradiation, the kidneys are also at risk and treatment planning CT scans can help to define which beam angles are best to irradiate the nodal regions yet miss, in part, the kidneys. When planning radiation fields, sometimes one kidney will need to be irradiated more than the other and the equivalent of one kidney must be spared. Chemotherapy can lower kidney tolerance to radiation as can increasing age. Irradiation of only one kidney does not necessarily reduce the risk of renal complications (299). Functional renal studies prior to radiation are important in documenting unexpected perfusion or excretion abnormalities and in determining how much each kidney contributes to total renal function. Functional changes have been described after exposure of the kidney to more than 20 Gy, and signs and symptoms of renal dysfunction can follow including hypertension, leg edema, and a urinalysis showing albuminuria and low specific gravity (299). A normocytic, normochromic anemia may also appear. Renal function studies will ultimately show decreased blood flow and filtration rates. CT scans may reveal a small kidney if one kidney has been preferentially irradiated to protect the other (286). Current dose-volume recommendations are found in the QUANTEC data (299).

Ovaries

In premenopausal patients treated with definitive irradiation, the ovaries will be irradiated incidentally and ovarian failure will occur. Hot flashes and other menopausal symptoms can begin to develop during radiation. Hormone replacement therapy is an important consideration in women younger than 50. Alternatively, midline oophorectomy has been used in young women requiring irradiation for Hodgkin's disease in an effort to spare the ovaries. The ovaries can also be elevated out of the radiation field and placed above the true pelvis to attempt to avoid them when treating cervical cancer. The radiosensitivity of the ovarian cells varies considerably with age. The dose necessary to castrate a woman depends on her age. A larger dose is required during the period of more active follicular proliferation. A single dose of 4.0 to 8.0 Gy or fractionated doses of 12 to 20 Gy (depending on age) are known to produce permanent castration and sterility in most patients (285,286,293).

Vagina

There are few noticeable acute reactions when treating the upper two-thirds of the vagina with radiation. Some patients may notice a white-yellow vaginal discharge, which is due to mucositis of the vaginal mucosa. This can be evident during radiation and can continue for several months after radiation (286). The lower third of the vagina, however, will become quite irritated when irradiated, in part due to irradiation of the vulva and urethra as described above. The distal vagina is less tolerant of radiation than the proximal, and the tolerance doses are in the range of 80 to 90 Gy versus 120 to 150 Gy, respectively (300). There are, however, no studies that have successfully correlated

DVH parameters with morbidity (301). Vaginal narrowing and shortening is a late sequela of radiation, which can alter and impede sexual function. Combined brachytherapy and external beam irradiation will cause more late effects than either modality alone. Use of a vaginal dilator or intercourse 2 to 3 times/week can help to keep the vagina open. Use of lubrication with intercourse as well as estrogen creams to build up the vaginal mucosa can also make intercourse more comfortable (293,302). Rarely, with excessive doses of radiation, patients can develop vaginal necrosis. This is due to a change in blood supply to the vaginal tissues and is much more common at the introitus than at the vaginal apex, perhaps due to the vascular supply of the vagina. The posterior vaginal wall is most frequently involved (300). Interstitial implants are more likely to cause necrosis than intracavitary implants. Hydrogen peroxide douches, antibiotics, and hyperbaric oxygen therapy can help the vaginal tissues to heal (303,304). Narcotics are often necessary to control the associated pain until healing has occurred. Trental (pentoxifylline) can also help soft-tissue necrosis to heal (305). The uterus is very resistant to high doses of radiation as is evident in patients treated with external beam and brachytherapy for cervical cancer. Rare cervical necrosis can occur and will respond readily to hyperbaric oxygen treatments and pentoxifylline (286,304,293). There may be an increased risk of this in patients using cocaine. Necrosis can also be caused by recurrent tumor, and distinguishing recurrent disease from necrosis can be very difficult and sometimes will mandate surgical intervention (286).

Stomach, Small and Large Intestine

The stomach is lined with a mucous membrane, which is columnar epithelium and sensitive to radiation. Like the small and large bowel reactions, the stomach lining develops erosions and thinning and subsequent edema and ulceration. Symptoms can include nausea, vomiting, reflux, and pain. Use of prophylactic antiemetics and proton pump inhibitors can decrease the acute effects of radiation. Acid production can be decreased during radiation and for up to 1 to 2 years after. Late effects can include gastritis and ulceration with associated bleeding. Progressive fibrosis can lead to gastric outlet obstruction and rarely perforation, all of which are dose and volume dependent (286). The entire stomach can tolerate doses of 45 to 50 Gy, but data on maximum tolerated doses are inadequate (306).

The acute effects of radiation on the small intestine are due to the inherent radiation sensitivity of the rapidly dividing undifferentiated crypt of Lieberkuhn cells. The normal lining of the GI tract is a self-renewing tissue. These undifferentiated stem cells normally migrate and differentiate upward from the lower half of the crypts to the tips of the intestinal villi as they mature, providing a continuous supply of surface cells as they divide. Their function is to primarily form absorptive cells but also mucous-secreting goblet cells and endocrine cells (285,286,290). The mature cells at the surface of the villi are repeatedly sloughed and replaced by the cells, which originate in the crypts. These undifferentiated crypt cells are the most sensitive to radiation and are preferentially depleted, leading to loss of mature replacement cells at the surface of the villi. When these mature mucosal cells cannot be replaced, the villi shorten and the loss of absorptive function of the small intestine occurs. This loss of function results in fluid and nutrient wasting, diarrhea, and dehydration. This constellation of symptoms is termed acute radiation enteritis. Fortunately, re-epithelialization occurs within several days due to recovery of the rapidly dividing crypt cells (290). Mucosal healing will occur within 10 to 14 days if radiation is terminated, and symptoms will accordingly improve and resolve in most patients. It is common to observe watery diarrhea with intermittent abdominal cramping starting in the second or third week of abdominal or pelvic irradiation.

Increased peristalsis, disturbance of the absorption mechanisms, and a decreased transit time also occur. Patients will report increased flatulence and noisy bowel sounds. Rarely patients will report nausea. Implementation of a low residue diet, hydration, and use of antimotility agents can be very helpful. Some patients may be lactose and fat intolerant as well. Judicious use of narcotics to calm the bowel can also be helpful. Concurrent 5-FU or gemcitabine can worsen small bowel toxicity with diarrhea from the 5-FU often appearing before the radiation enteritis has had time to evolve. The late effects of radiation on the small bowel can be a continuation of the acute effects. Some patients will experience chronic diarrhea that will require a permanent change in diet. Certain foods may trigger diarrhea such as those high in fiber or fat. Spicy foods and MSG may also trigger diarrhea. Areas of narrowing corresponding to regions of high dose or adhesions can occur in the small bowel loops and lead to partial obstruction of the small bowel. Patients may report abdominal pain and distention followed by diarrhea and relief of these symptoms. A complete bowel obstruction would also be characterized by abdominal pain and distention in addition to vomiting and lack of bowel movements. Small bowel obstructions occur in approximately 5% of irradiated patients and surgical intervention is required in some to relieve these obstructions. Prior surgeries or a history of a perforated appendix or pelvic abscess as well as inflammatory bowel disease can increase the risk of small bowel toxicity as can the use of chemotherapy. Hypertension and diabetes can also be risk factors as can thin body habitus. Radiation to large volumes of bowel or high doses to even small volumes of bowel can lead to bowel obstructions. The ileum is the most common loop of bowel involved (286). Malabsorption of fats, carbohydrates, protein, B₁₂, and lactose can occur in some patients. Excessive bile salts can reach the colon and act as a cathartic, and medications such as cholestyramine can be helpful in controlling the resultant loose stools.

Small bowel doses should be limited to 45 to 50 Gy with 60 Gy maximum (264). Current recommendations for small bowel dose/volume constraints are as follows: The absolute volume of small bowel receiving >15 Gy should be <120 cc when delineating individual loops of bowel. If the entire peritoneal space is defined, the volume of small bowel receiving >45 Gy should be <195 cc (306).

The rectosigmoid mucosa is also a rapid renewal system similar to the small bowel. When the rectum is included in the irradiated volume, there is rectal discomfort with tenesmus and mucous production, sometimes mixed with blood in the stools. Patients may report frequent and sometimes painful evacuations of only small amounts of stool mixed with mucus. Hemorrhoids may worsen during radiation. This constellation of symptoms is termed "proctitis." Medications to decrease the number of stools as well as antispasmodic agents can be helpful. Suppositories or foams with steroids can be helpful, as can topical perianal skin ointments and lotions. Uncontrolled radiation enteritis can worsen radiation proctitis due to frequent stooling through the irritated rectum. For late effects, if the dose of radiation is large enough, it may cause temporary or permanent ulceration and bleeding due to telangiectasias (Fig. 12.57). Cortisone-containing rectal suppositories and foams or sulfasalazine instillations can also help to heal the bleeding and ulcerated rectal mucosa as can argon laser ablation of the telangiectasias.

Hyperbaric oxygen therapy can be helpful in controlling bleeding when severe (304,307,308,309). Fibrosis, stenosis, perforation, and fistula formation are rarer (Fig. 12.58). In general, doses in excess of 60 Gy are necessary to produce this more advanced radiation damage to the small bowel and rectosigmoid (310). Fecal diversion may be necessary in the setting of stenosis, necrosis, or fistula formation. Retrospective analyses have shown that limited volumes of the rectum can tolerate about 75 Gy (external beam and brachytherapy) with acceptable morbidity (257,264).

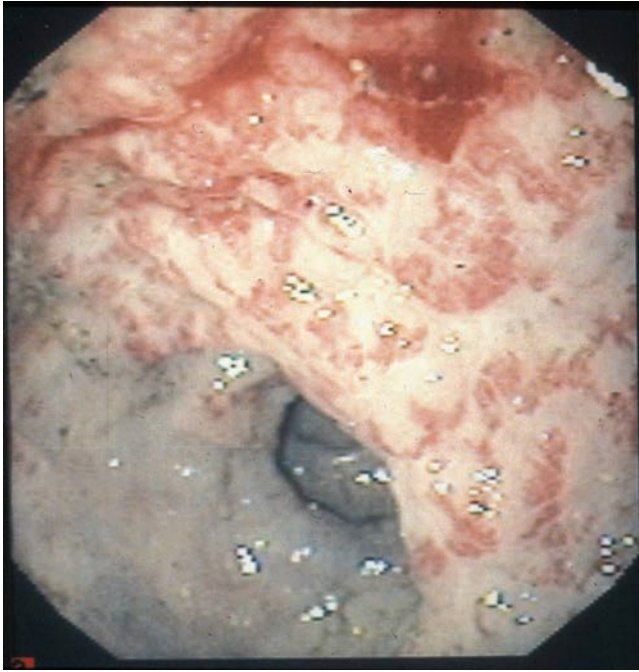


FIGURE 12.57. Radiation-induced telangiectasias of the rectum consistent with radiation proctitis.

Bladder/Ureters/Urethra

The bladder and ureters have a rapidly renewing transitional epithelium. The effect of radiation is early denudation similar to the skin due to injury to the rapidly dividing basal cells. Epithelial desquamation leads to focal ulcerations, hyperemia, and edema of the bladder wall, which is visible at cystoscopy (286,290,311). Acute and transient radiation cystitis may be observed with moderate doses of irradiation (>30 Gy) and usually requires no specific treatment. Patients will report urinary frequency and urgency as well as mild dysuria, as well as decreased bladder capacity. However, with higher radiation

doses, more severe symptoms of cystitis develop, such as severe dysuria and hematuria, which may require treatment. Agents such as Pyridium may help lessen these symptoms. Significant spasms of the bladder musculature, which may be improved with administration of smooth muscle relaxants, may also occur. It is important to rule out the presence of a concomitant bacterial infection, which may exacerbate the symptoms. Infections are seen at an increased rate in irradiated patients, perhaps in part due to radiation-induced diarrhea and contamination of the perineum. Urinalysis and urine cultures obtained under sterile conditions, when indicated, should be obtained before institution of antibiotic therapy. Radiation cystitis is characterized by the presence of white cells and red cells without bacteria on urinalysis.

With doses above 60 Gy, chronic cystitis and hematuria may be observed due to telangiectasias, which can develop in the bladder lining (85,312). With higher doses, more severe chronic cystitis, fibrosis, and decreased bladder capacity can occur. Rarely, bladder neck contractures as well as fistulas may occur, which can necessitate surgical intervention. Fistulas are more likely to occur if there is invasion of the bladder wall by tumor or in the setting of interstitial implants. Surgery may be required to deal with some of these complications (286). Hyperbaric oxygen therapy can be very helpful with hemorrhagic cystitis, as can the drug pentosan polysulfate (Elmiron), which has been used for interstitial cystitis (304,307,313). The ureters are quite resistant to radiation and rare ureteral stenosis is reported in some series (257,286,311,314). This can require stenting or rarely diversion. Interstitial implants are more likely to cause this than intracavitary implants, as can early placement of a narrow midline block (257). Urethral stenosis is also rare and is also more likely to occur with interstitial than intracavitary approaches. Careful dilation can be helpful in sustaining bladder outflow (311).

Bladder and Rectosigmoid—LDR

The bladder and rectosigmoid are the organs of concern in the setting of combined external beam irradiation and brachytherapy. Dose and volume are considered two important variables related to complications. Dose has been thought to be an

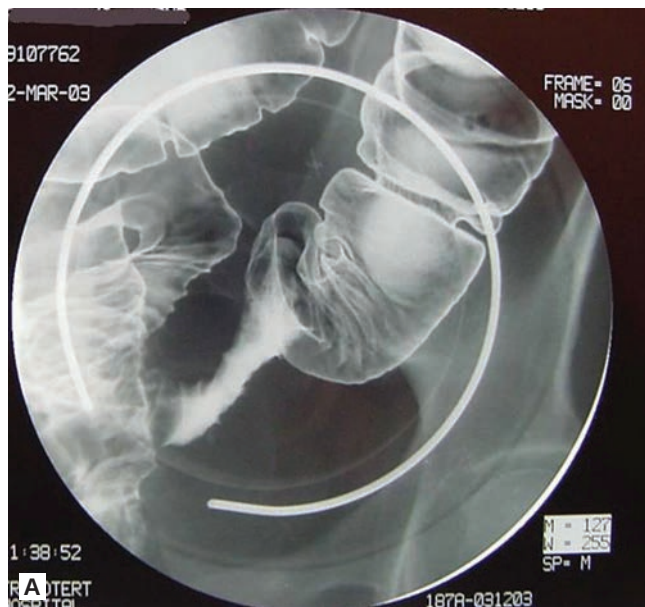


FIGURE 12.58. Radiation-induced sigmoid stricture noted on a contrast study. **A:** full view, **B:** magnified view, following definitive chemoradiation.

important determinant of normal tissue complications. Attempts have been made to determine the maximum tolerable normal tissue dose with an acceptable risk of complications. There is no consensus as to what these values should be. Point doses may or may not coincide with complication risk, as they do not account for the volume of organ irradiated. They are also not defined consistently. Maximum bladder point doses of 75 to 80 Gy and rectal doses of 70 to 75 Gy are guidelines (82,264,312,310). The ratio of dose to the rectal point and bladder point and dose to point A is also important with a low incidence of rectal (0.3% vs. 5%) and bladder (2% vs. 2% to 5%) complications when this ratio was less than 80% (264). Other factors such as external beam dose and intracavitary dose rate are also important in the etiology of complications. The volume of rectum and bladder irradiated is an important variable in the development of complications in addition to the cumulative dose (315). Both external beam and use of tandem and cylinder applicators can increase the volume of bladder and rectum treated (130,316). Stage, patient age, and medical comorbidities such as hypertension, diabetes, diverticulitis, or inflammatory bowel disease may also increase the risk of complications, as can the administration of chemotherapy. Individual radiosensitivity may also impact complication risk (317).

Bladder and Rectosigmoid—HDR

Acceptable normal tissue doses are even more debatable in HDR than LDR. Using HDR techniques, the therapeutic range is narrower and the risk of complications seems to rise faster than the rate of improved tumor control. Available clinical data also suggests that in addition to total HDR dose, the most important factor in late complication development is the dose per fraction and the number of fractions (162,317,318). The organ most at risk for complications is the rectosigmoid, whereas the bladder complication risk is comparatively low (188,319,320). Rectal and sigmoid complications occur earlier than bladder complications (317,318). Rectal bleeding is the most frequent rectal morbidity occurring in approximately 30% of patients (257,319,320,321). To avoid excessive morbidity, better physical dose distributions must be achieved with HDR to reduce doses to critical normal structures. This implies the use of rectal and bladder displacement. Fowler has speculated that if only 80% of the tumor dose is received by the critical normal tissues, then 4 to 6 HDR fractions can be used safely, whereas 12 to 16 fractions would be required if the normal structures receive 90% of the point A dose, and 30 fractions if the normal structures received 100% of the HDR dose (162,322). Rectal retractors have become an integral component of insertion techniques and perhaps improve the effectiveness and reproducibility of rectal displacement over gauze vaginal packing (162,161,163). Whatever the case, a rectal retractor, vaginal speculum blade, or gauze packing should be used to displace the rectum (170,189).

Various disparate recommendations concerning normal tissue fraction size and total dose exist in the literature. Sakata et al. found that the probability of rectal complications increased dramatically above a maximal rectal dose (D_{eq}) of 60 Gy (323). Cheng et al. found that patients with >62 Gy of summed external beam and intracavitary doses to the proximal rectum and >110 Gy maximal proximal rectal BED had significant increase in complications (324). Takeshi et al. noted that radiation dose significantly impacted rectal dose complication rate with an increase above 65 Gy (325). Various recommendations for rectal and bladder tolerance doses are in the literature using point doses and time–dose fractionation (TDF) and biologically equivalent dose (BED) values (194,257,259, 320,326–332). When using point doses, it is very important to choose points related to critical structures very carefully on the orthogonal films. Rectum above the level of the vaginal applicators and rectal retractor

should be identified and sigmoid in addition to rectal points should be evaluated, as should bladder and vaginal points. Various methods for determining normal tissue doses have been described. When possible, the doses to the normal critical structures should be less than the dose at point A, perhaps in the range of 50% to 80%. The portions of the rectum and sigmoid that are above the range of the rectal retractor are most often the hot spots, and every effort must be made to decrease the dose to the rectosigmoid relative to the point A dose. Consideration to decreasing the dwell times or turning off dwell positions in the tandem should be given. To avoid underdosing endometrial extension of tumor, at least treating 4 cm above the exocervix so that point A is not in a region of dose constriction may be wise. Tandem lengths of 6 to 8 cm are typical. If there is endometrial extension, a longer tandem may be needed. Additionally, use of a tapered tandem will decrease sigmoid, bladder, and small bowel doses (175). Contrast in the sigmoid is helpful in making these decisions. CT scanning after applicator placement is exceedingly helpful and much more reliable in assessing the proximity of the sigmoid to the tandem and in manipulating the dose distribution (Fig. 12.59). Assessment of the anterior and posterior uterine wall thickness measured on CT with the applicator in place, along the course of the tandem, as well as the measured distances from the tandem to the rectosigmoid, small bowel, and bladder, can help to guide dose prescription and potentially decrease toxicity if the distribution is altered appropriately (105). Sigmoid doses can often be higher than the rectal ICRU doses (324). Van Lancker and Storme have not found point A or normal tissue dose points helpful as predictors of complications, but rather that volume calculations were extremely helpful in predicting complications, and they found a significant correlation between rectal complications and the ICRU reference 60 Gy isodose volumes (333). Dose volume data appears to be more helpful than point dose data in predicting for complications. Using CT or MR based volume planning, the EQD2 limit to the D2cc (the minimum dose in the most irradiated 2 cm³ normal tissue volume for the rectum and sigmoid is 70–75 Gy and for the bladder, 90 Gy (112,113,115,107). Georg et al. found that for the rectum, a significant dose effect was found for all DVH parameters for any grade of complication as well as for G2 to G4 side effects with the exception of the D0.1cc. For G2 to G4 rectal toxicity, a threshold of 60 Gy (EQD2) was observed with a 10% incidence at 78 Gy and a 20% incidence at 90 Gy. For bladder, no significant dose response was observed for G1 to G4 side effects, but for complications of >G2, dose effect curves could be generated for all DVH parameters that were statistically significant. For bladder, there was a 5% risk of G2 to G4 morbidity with a D2cc of 70 Gy, a 10% risk of G2 to G4 morbidity with a D2cc of 101 Gy, and a 20% risk of G2 to G4 morbidity with a D2cc of 134 Gy (334,335). Late bladder sequelae have been infrequent in patients with such doses but longer follow-up is needed to be certain as the late effects in the bladder can be quite delayed in their appearance (115). Georg et al. and Kook et al. also found a correlation between rectal dose volume parameters and endoscopically defined mucosal changes as well as clinical side effects (337,336).

FUTURE FOCUS

Reduction of morbidity and improvement in local control and cure is a common goal in the treatment of patients with gynecologic cancers. Use of 3-D and functional imaging will be increasingly important to define tumor and normal tissues. This can perhaps allow escalation of dose to the tumor and reduction of dose to the critical normal tissues. There has been, however, a reluctance to vary from traditional dose specification as good outcomes have been published at institutions skilled in the care of gynecologic

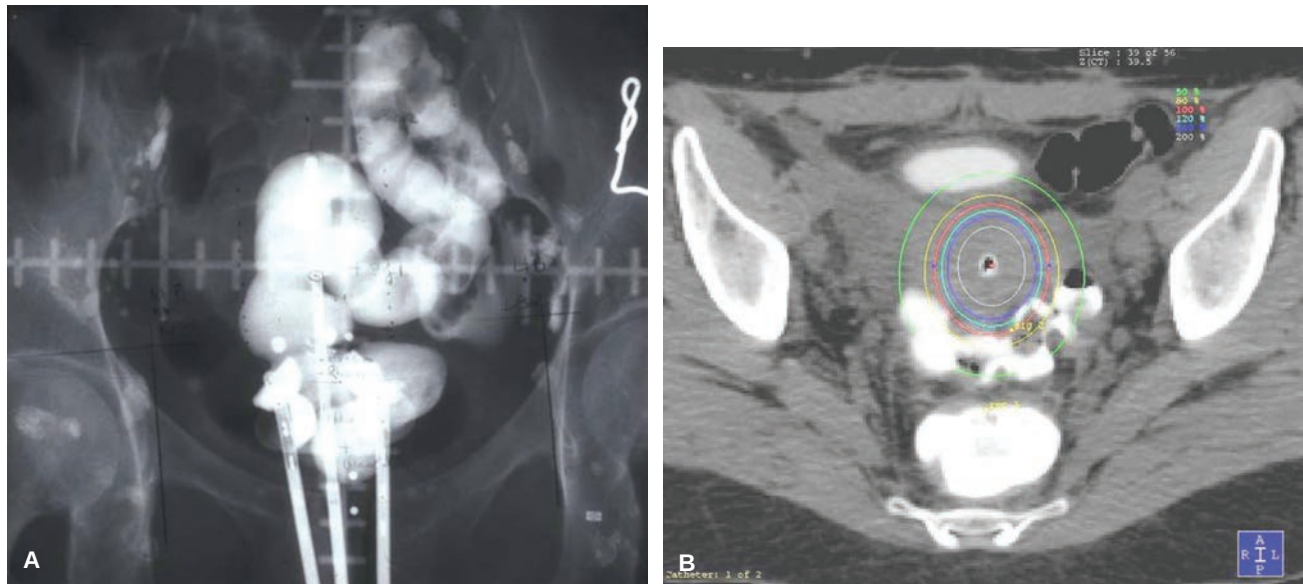


FIGURE 12.59. Radiograph of the pelvis with a tandem and ovoid applicator in place demonstrates the circuitous course of the sigmoid **A**. The axial CT scan **B** demonstrates a more accurate relationship of the sigmoid to the uterine tandem and the need to limit dose to this loop of sigmoid positioned very close to the high-dose region of the implant.

patients. It is potentially dangerous to optimize therapy to such an extent that the dose distribution looks dramatically different from the traditional “pear shape,” which effectively encompasses the primary tumor and parametria in cervical cancer presentations. Making this pear too narrow to avoid critical structures may lead to a higher rate of local recurrence. Yet it is important to treat the disease and not just strive for an ideal dose distribution. Preliminary studies using CT indicate that we underestimate normal tissue doses with the present 2-D dosimetric analysis used at most institutions (103,317,106). Whether this information should change the way we prescribe doses remains debatable. Directly relating the intracavitary system to the anatomy through use of CT and MRI seems to be the next step in the lineage of dosimetric systems (Fig. 12.60) (103,104,106). The GEC ESTRO GYN Working Group has developed guidelines for defining and contouring tumor volumes and normal tissues on MRI scans with the brachytherapy applicators in place (112,113). These guidelines are now incorporated into the EMBRACE study, which is actively accruing patients in a large registry to study the impact of image-based brachytherapy on tumor control and normal tissue toxicity. The excellent soft-tissue resolution of MRI allows visualization of residual tumor in relation to the isodose distribution around the MRI compatible brachytherapy applicators (Figs. 12.33 and 12.60) (108,111). Data from Potter et al. have shown a decrease in complications and an increase in local control with the use of MRI-guided brachytherapy for cervical cancer (114,115). Additionally, the use of dose-volume histogram analysis may add new insight into optimizing local control and decreasing morbidity with a better understanding of the importance of dose-volume relationships. This may be a powerful tool to help improve the therapeutic ratio in patients with gynecologic cancer and will best be achieved through collaboration of radiation oncologists, gynecologic oncologists, and diagnostic radiologists.

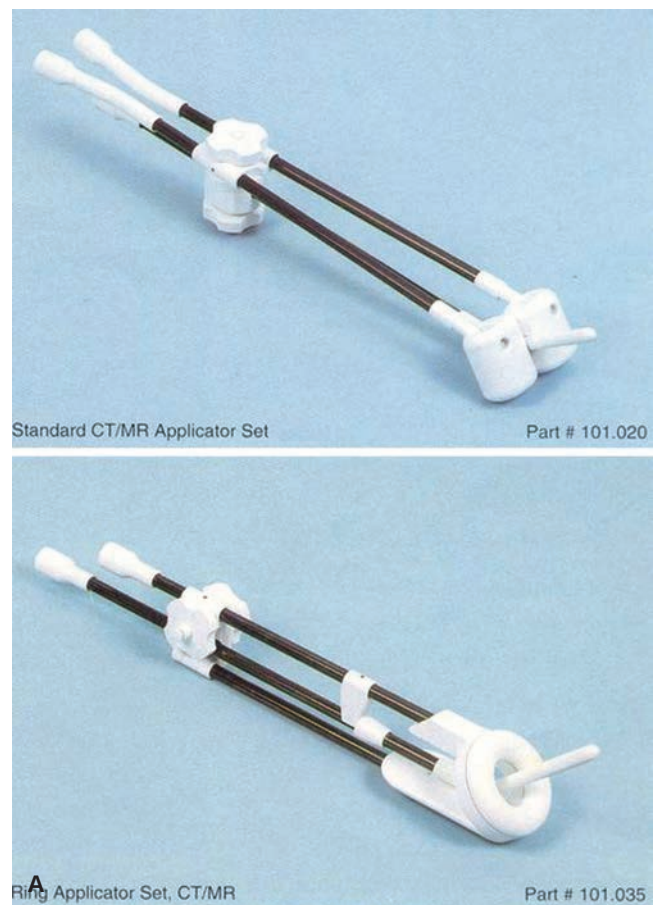


FIGURE 12.60. **A:** MRI compatible applicators.

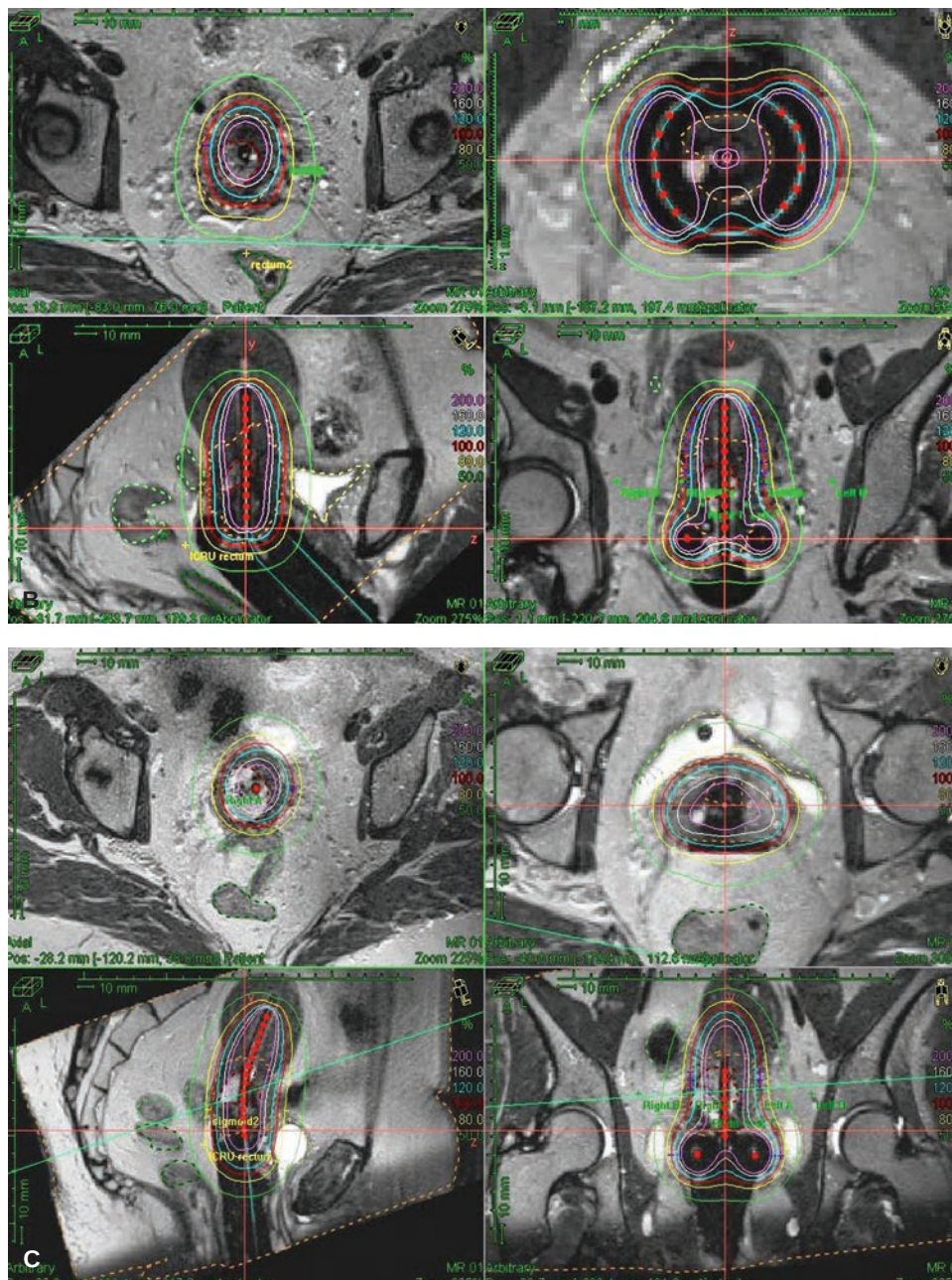


FIGURE 12.60. B, C: MRI of the pelvis with an MRI/CT compatible applicator ring B: and ovoids C: in place. Note the associated dose distribution relative to visible tumor within the cervix and the bladder, rectum and sigmoid.

REFERENCES

- Hall EJ, Garcia AJ. *Radiobiology for the Radiologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
- Warders RL, Hofer KG, Harris CR, et al. Radionuclide toxicity in cultured mammalian cells: elucidation of the primary site of radiation damage. *Curr Top Radiat Res Q*. 1978;12(1-4):389-407.
- Hawkins RB. The influence of concentration of DNA on the radio sensitivity of mammalian cells. *Into J Radiat Once Boil Phys*. 2005;63(2):529-535.
- Cremer C, Cremer T, Zorn C, et al. Induction of chromosome shattering by ultraviolet irradiation and caffeine: comparison of whole-cell and partial-cell irradiation. *Mutat Res*. 1981;84(2):331-348.
- Hatayoglu SE, Orta T. Relationship between radiation induced dicentric chromosome aberrations and micronucleus formation in human lymphocytes. *J Exp Clin Cancer Res*. 2007;26(2):229-234.
- Garaj-Vrhovac V, Fucic A, Horvat D. The correlation between the frequency of micronuclei and specific chromosome aberrations in human lymphocytes exposed to microwave radiation in vitro. *Mutat Res*. 1992;281(3):181-186.
- Silva MJ, Carothers A, Dias A, et al. Dose dependence of radiation-induced micronuclei in cytokinesis-blocked human lymphocytes. *Mutat Res*. 1994;322(2):117-128.
- Ewing D. The oxygen fixation hypothesis: a reevaluation. *Am J Clin Oncol*. 1998;21(4):355-361.
- Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *Int J Radiat Oncol Biol Phys*. 1991;20(3):429-432.
- Li CY, Nagasawa H, Dahlberg WK, et al. Diminished capacity for p53 in mediating a

- radiation-induced G1 arrest in established human tumor cell lines. *Oncogene*. 1995;11(9):1885–1892.
11. Davis TW, Wilson-Van Patten C, Meyers M, et al. Defective expression of the DNA mismatch repair protein, MLH1, alters G2-M cell cycle checkpoint arrest following ionizing radiation. *Cancer Res*. 1998;58(4):767–778.
 12. Kachnic LA, Wu B, Wunsch H, et al. The ability of p53 to activate downstream genes p21(WAF1/cip1) and MDM2, and cell cycle arrest following DNA damage is delayed and attenuated in scid cells deficient in the DNA-dependent protein kinase. *J Biol Chem*. 1999;274(19):13111–13117.
 13. Canman CE, Lim DS, Cimprich KA, et al. Activation of the ATM kinase by ionizing radiation and phosphorylation of p53. *Science*. 1998;281(5383):1677–1679.
 14. Wang X, Khadpe J, Hu B, et al. An overactivated ATR/CHK1 pathway is responsible for the prolonged G2 accumulation in irradiated AT cells. *J Biol Chem*. 2003;278(33):30869–30874.
 15. McCabe MT, Azih OJ, Day ML. pRb-Independent growth arrest and transcriptional regulation of E2F target genes. *Neoplasia*. 2005;7(2):141–151.
 16. Knudson AG, Hethcote HW, Brown BW. Mutation and childhood cancer: a probabilistic model for the incidence of retinoblastoma. *Proc Natl Acad Sci USA*. 1975;72(12):5116–5020.
 17. Huang PS, Patrick DR, Edwards G, et al. Protein domains governing interactions between E2F, the retinoblastoma gene product, and human papillomavirus type 16 E7 protein. *Mol Cell Biol*. 1993;13(2):953–960.
 18. Kneale GW, Stewart AM. Mantel-Haenszel analysis of Oxford data. I. Independent effects of several birth factors including fetal irradiation. *J Natl Cancer Inst*. 1976;56(5):879–883.
 19. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol*. 1997;70:130–139.
 20. International Commission on Radiological Protection. <http://www.icrp.org/>. Accessed October 1, 2007.
 21. *Recommendation on Limits for Exposure to Ionizing Radiation*. Report no. 91. Bethesda, MD: National Council on Radiation Protection and Measurements; 1987.
 22. Johns HE, Cunningham JR. *The Physics of Radiology*. 4th ed. Springfield, IL: Charles C. Thomas; 1983.
 23. Khan FM. *The Physics of Radiation Therapy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.
 24. Bouchard M, Nadeau S, Gingras L, et al. Clinical outcome of adjuvant treatment of endometrial cancer using aperture-based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1343–1350.
 25. Hasselle MD, Rose BS, Kochanski JD, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys*. 2011;80(5):1436–1445.
 26. Jhingran A, Winter K, Portelance L, et al. Efficacy and safety of IMRT after surgery in patients with endometrial cancer: RTOG-0418 Phase II study. *Int J Radiat Oncol Biol Phys*. 2011;81(2):S45.
 27. Mell LK, Tiriyaki H, Ahn K-H, et al. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1504–1510.
 28. Erickson B, Lim K, Steward J, et al. Adaptive radiation therapy for gynecologic cancers. In: Hendee R, Li X, ed. *Imaging in Medical Diagnosis and Therapy: Adaptive Radiation Therapy*. Boca Raton, FL: Taylor & Francis Group; 2011:351–368.
 29. Small Jr W, Mell L, Anderson P, et al. Consensus guidelines for the delineation of the clinical target volume for intensity modulated pelvic radiotherapy in the postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;71(2):428–434.
 30. Small W, Mundt A. *Gynecologic Pelvis Atlas*. RTOG Radiation Therapy Oncology Group. <http://www.rtog.org/gynatlas/main.html>. Accessed January 9, 2009.
 31. Gay H, Barthold H, O'Meara E, et al. Pelvic normal tissue contouring guidelines for Radiation Therapy: a Radiation Therapy Oncology Group Consensus Panel Atlas. *Int J Radiat Oncol Biol Phys*. 2012;83(3):e353–e362.
 32. Taylor A, Rockall A, Reznick R, et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1604–1612.
 33. Martinez-Monge R, Fernandes P, Gupta N, et al. Cross-sectional nodal atlas: a tool for the definition of clinical target volumes in three-dimensional radiation therapy planning. *Radiology*. 1999;211:815–828.
 34. Jhingran A, Salehpour M, Sam M, et al. Vaginal motion and bladder and rectal volumes during pelvic intensity-modulated radiation therapy after hysterectomy. *Int J Radiat Oncol Biol Phys*. 2012;82(1):256–262.
 35. Kochanski J, Mell L, Roeske J, et al. Intensity-modulated radiation therapy in gynecologic malignancies: current status and future directions. *Clin Adv Hematol Oncol*. 2006;4(5):379–386.
 36. Kidd EA, Siegel BA, Dehdashti F, et al. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010;77(4):1085–1091.
 37. Lim K, Kelly V, Stewart J, et al. Pelvic radiotherapy for cancer of the cervix: is what you plan actually what you deliver? *Int J Radiat Oncol Biol Phys*. 2009;74(1):304–312.
 38. Beadle B, Jhingran A, Salehpour M, et al. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys*. 2009;73(1):235–241.
 39. Haripoteponkul NH, Nath SK, Scanderbeg D, et al. Evaluation of intra- and inter-fraction movement of the cervix during intensity modulated radiation therapy. *Radiation Oncol*. 2011;98:347–351.
 40. Chan P, Dinniwel R, Haider MA, et al. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study. *Int J Radiat Oncol Biol Phys*. 2008;70(5):1507–1515.
 41. Tyagi N, Lewis JH, Yashar CM, et al. Daily online cone beam computed tomography to assess interfractional motion in patients with intact cervical cancer. *Int J Radiat Oncol Biol Phys*. 2011;80(1):273–280.
 42. Lim K, Small W Jr, Portelance L, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys*. 2011;79(2):348–355.
 43. Holmes T, Das R, Low D, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. *Int J Radiat Oncol Biol Phys*. 2009;74(5):1311–1318.
 44. Hartford A, Palisca M, Eichler T, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for intensity-modulated radiation therapy (IMRT). *Int J Radiat Oncol Biol Phys*. 2009;73(1):9–14.
 45. Beriwal S, Gan GN, Heron DE, et al. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys*. 2007;68(1):166–171.
 46. Ahmed R, Kim R, Duan J, et al. IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. *Int J Radiat Oncol Biol Phys*. 2004;60(2):505–512.
 47. Esthappan J, Chaudhari S, Santanam L, et al. Prospective clinical trial of positron emission tomography/computed tomography image-guided intensity-modulated radiation therapy for cervical carcinoma with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys*. 2009;72(4):1134–1139.
 48. Hong L, Alektiar K, Chui C, et al. IMRT of large fields: whole-abdomen irradiation. *Int J Radiat Oncol Biol Phys*. 2002;54(1):278–289.
 49. Duthoy W, Gersem W, Vergote K, et al. Whole abdominopelvic radiotherapy (WAPRT) using intensity-modulated ARC therapy (IMAT): first clinical experience. *Int J Radiat Oncol Biol Phys*. 2003;57(4):1019–1032.
 50. Beriwal S, Heron D, Kim H, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. *Int J Radiat Oncol Biol Phys*. 2006;64(5):1395–1400.
 51. Oelfke U, Nill S. Computed tomography-based image-guided radiation therapy technology. In: Hendee R, Li X, eds. *Imaging in Medical Diagnosis and Therapy: Adaptive Radiation Therapy*. Boca Raton, FL: Taylor & Francis Group; 2011:141–156.
 52. Potters L, Gaspar L, Kavanagh B, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for image-guided radiation therapy (IGRT). *Int J Radiat Oncol Biol Phys*. 2010;76(2):319–325.
 53. Schwarz JK, Wahab S, Grigsby PW. Prospective phase I-II trial of helical tomotherapy with or without chemotherapy for postoperative cervical cancer patients. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1258–1263.
 54. Peterit DG, Mehta MP, Buchler DA, et al. Inguinofemoral radiation of NO, N1 vulvar cancer may be equivalent to lymphadenectomy if proper radiation technique is used. *Int J Radiat Oncol Biol Phys*. 1993;27(4):963–967.
 55. Koh W-J, Chiu M, Stelzer KJ, et al. Femoral vessel depth and the implications for groin node radiation. *Int J Radiat Oncol Biol Phys*. 1993;27(4):969–974.
 56. Stehman FB, Bundy BN, Thomas G, et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group Study. *Int J Radiat Oncol Biol Phys*. 1992;24(2):389–396.
 57. *International Commission on Radiation Units and Measurements, Prescribing, Recording, and Reporting Photon Beam Therapy*. ICRU Report 50. Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.
 58. Erickson B, Wilson JF. Clinical indications for brachytherapy. *J Surg Oncol*. 1997;65:218–227.
 59. International Commission on Radiation Units and Measurements. *Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology*. ICRU Report 38. Bethesda, MD: International Commission on Radiation Units and Measurements; 1985.

60. Swift P, Purser P, Roberts L, et al. Pulsed low dose rate brachytherapy for pelvic malignancies. *Int J Radiat Oncol Biol Phys.* 1997;37(4):811–817.
61. Lee L, Das I, Higgins S, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part III: Low-dose-rate and pulsed-dose-rate brachytherapy. *Brachytherapy.* 2012;11:53–57.
62. Henschke UK, Hilaris BS, Mahan GD. Afterloading in interstitial and intracavitary radiation therapy. *Am J Roentgenol.* 1963;90:386–395.
63. Nath R, Anderson L, Luxton G, et al. Dosimetry of interstitial brachytherapy sources: recommendations of AAPM Radiation Therapy Committee Task Group No.43. *Med Phys.* 1995;22:209–234.
64. Vahrson H, Glaser FH. History of HDR afterloading in brachytherapy. *Strahlenther Onkol.* 1988;82(suppl):2–6.
65. Abbe R. The use of radium in malignant disease. *Lancet.* 1913;2:524–527.
66. Heyman J. The so-called Stockholm method and the results of treatment of uterine cancer at the Radiumhemmet. *Acta Radiol.* 1935;16:129–147.
67. Lenz M. Radiotherapy of cancer of the cervix at the Radium Institute, Paris, France. *Am J Roentgenol Rad Ther Nucl Med.* 1927;17:335–342.
68. Tod MC, Meredith WJ. A dosage system for use in the treatment of cancer of the uterine cervix. *Br J Radiol.* 1938;11:809–824.
69. Tod MC. The optimum dosage in the treatment of carcinoma of the uterine cervix by radiation. *Br J Radiol.* 1941;14:23–29.
70. Tod MC. Optimum dosage in the treatment of cancer of the cervix by radiation. *Acta Radiol.* 1947;28:565–575.
71. Tod M, Meredith WJ. Treatment of cancer of the cervix uteri—a revised “Manchester method.” *Br J Radiol.* 1953;26:252–257.
72. Fletcher GH, Shalek RJ, Wall JA, et al. A physical approach to the design of applicators in radium therapy of cancer of the cervix uteri. *Am J Roentgenol.* 1952;68:935–949.
73. Fletcher GH. Cervical radium applicators with screening the direction of bladder and rectum. *Radiology.* 1953;60:77–84.
74. Adams GD, Meurk ML. The use of a computer to calculate isodose information surrounding distributed gynaecological radium sources. *Phys Med Biol.* 1964;9:533–540.
75. Fletcher GH, Brown TC, Rutledge FN. Clinical significance of rectal and bladder dose measurements in radium therapy of cancer of the uterine cervix. *Am J Roentgenol Rad Ther Nucl Med.* 1958;79:421–450.
76. Fletcher GH, Wall JA, Bloedorn FG, et al. Direct measurements and isodose calculations in radium therapy of carcinoma of the cervix. *Radiology.* 1953;61:885–902.
77. Fletcher GH, Rutledge FN, Chau PM. Policies of treatment in cancer of the cervix uteri. *Am J Roentgenol.* 1962;87:6–21.
78. Fletcher GH. Cancer of the uterine cervix: Jane-way lecture, 1970. *Am J Roentgenol Rad Ther Nucl Med.* 1971;3:225–242.
79. Delclos L, Fletcher GH, Sampiere V, et al. Can the Fletcher gamma ray colpostat system be extrapolated to other systems? *Cancer.* 1978;41:970–979.
80. Haas JS, Dean RD, Mansfield CM. Dosimetric comparison of the Fletcher family of gynecologic colpostats 1950–1980. *Int J Radiat Oncol Biol Phys.* 1985;11:1317–1321.
81. Batley F, Constable WC. The use of the Manchester system for treatment of cancer of the uterine cervix with modern after-loading radium applicators. *Am J Roentgenol Rad Ther Nucl Med.* 1967;18:396–400.
82. Fletcher, Gilbert H., eds. *Textbook of Radiotherapy.* 3rd ed. Philadelphia, PA: Lea & Febiger; 1980:720–772.
83. Katz A, Eifel P. Quantification of intracavitary brachytherapy parameters and correlation with outcome in patients with carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1417–1425.
84. Eifel PJ, Morris M, Wharton JT, et al. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1994;29:9–16.
85. Logsdon M, Eifel P. FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. *Int J Radiat Oncol Biol Phys.* 1999;43(4):763–775.
86. Potish RA, Gerbi BJ. Cervical cancer: intracavitary dose specification and prescription. *Radiology.* 1987;165:555–560.
87. Potish RA. The effect of applicator geometry on dose specification in cervical cancer. *Int J Radiat Oncol Biol Phys.* 1990;18:1513–1520.
88. Nag S, Chao C, Erickson B, et al. The American Brachytherapy Society recommendations for low dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2002;52(1):33–48.
89. Nag S, Erickson B, Thomadsen B, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2000;48(1):201–211.
90. Lewis GC, Raaventos A, Half J. Space dose relationships for points A and B in the radium therapy of cancer of the uterine cervix. *Am J Roentgenol Rad Ther Nucl Med.* 1960;83:432–446.
91. Gebara W, Weeks K, Jones E, et al. Carcinoma of the uterine cervix: a 3D-CT analysis of dose to the internal, external and common iliac nodes in tandem and ovoid applications. *Radiother Oncol.* 2000;56:43–48.
92. Potish RA, Gerbi BJ. Role of point A in the era of computerized dosimetry. *Radiology.* 1986;158:827–831.
93. Potish RA. Cervix cancer. In: Levitt SH, Khan FM, Potish RA, eds. *Technological Basis of Radiation Therapy.* Philadelphia, PA: Lea & Febiger; 1992:289–299.
94. Cunningham DE, Stryker JA, Velkley DE, et al. Intracavitary dosimetry: a comparison of mg-hr prescription to doses at points A and B in cervical cancer. *Int J Radiat Oncol Biol Phys.* 1981;7:121–123.
95. Potish RA, Deibel FC, Khan FM. The relationship between milligram-hours and dose to point A in carcinoma of the cervix. *Radiology.* 1982;145:479–483.
96. Durrance FY, Fletcher GH. Computer calculation of dose contribution to regional lymphatics from gynecologic radium insertions. *Radiology.* 1968;91:140–147.
97. Krishnan L, Cytacki EP, Wolf CD, et al. Dosimetric analysis in brachytherapy of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 1990;18:965–970.
98. Adams RM, Peterson M, Collins VP, et al. Clinically useful calculations of the dose distribution from multiple radiation sources. *Radiology.* 1965;85:361–364.
99. Maruyama Y, Van Nagell JR, Wrede DE, et al. Approaches to optimization of dose in radiation therapy of cervix carcinoma. *Radiology.* 1976;120:389–398.
100. Hilaris BS, Nori D, Anderson LL. Brachytherapy in cancer of the cervix. In: Hilaris BS, Nori D, Anderson LL, eds. *Atlas of Brachytherapy.* New York, NY: Macmillan Publishing Co.; 1988; 244–256.
101. Mohan R, Ding IY, Toraskar J, et al. Computation of radiation dose distributions for shielded cervical applicators. *Int J Radiat Oncol Biol Phys.* 1985;11:823–830.
102. Decker W, Erickson B, Albano K, et al. Comparison of traditional low dose rate to optimized and nonoptimized high dose rate tandem and ovoid dosimetry. *Int J Radiat Oncol Biol Phys.* 2001;50(2):561–567.
103. Stueckelschweiger GF, Arian-Schad KS, Poier E, et al. Bladder and rectal dose of gynecologic high-dose-rate implants: comparison of orthogonal radiographic measurements with in vivo and CT-assisted measurements. *Radiology.* 1991;181:889–894.
104. Potter R, Knocke T, Fellner C, et al. Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993–1997) compared to the preceding period in the context of ICRU 38 recommendations. *Cancer Radiother.* 2000;4:159–172.
105. Mai J, Rownd J, Erickson B. CT-guided high dose rate prescription for cervical carcinoma: the importance of uterine wall thickness. *Brachytherapy.* 2002;1:27–35.
106. Kapp KS, Stueckelschweiger GF, Kapp DS, et al. Dosimetry of intracavitary placements for uterine and cervical carcinoma: results of orthogonal film, TLD, and CT-assisted techniques. *Radiother Oncol.* 1992;24:137–146.
107. Viswanathan A, Beriwal S, DeLosSantos J, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy. *Brachytherapy.* 2012;11:47–52.
108. Dimopoulos J, Schard G, Berger D, et al. Systematic evaluation of MRI findings in different stages of treatment of cervical cancer: potential of MRI on delineation of target, pathoanatomic structures, and organs at risk. *Int J Radiat Oncol Biol Phys.* 2006;64(5):1380–1388.
109. Dimopoulos JCA, Petrow P, Tanderup K, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. *Radiother Oncol* 2012. Jan 30. [Epub ahead of print].
110. Kirisits C, Potter R, Lang S, et al. Dose and volume parameters for MRI-based treatment planning in intracavitary brachytherapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2005;62(3):901–911.
111. Viswanathan A, Cormack R, Holloway C, et al. Magnetic resonance-guided interstitial therapy for vaginal recurrence of endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2006;66(1):91–99.
112. Haie-Meder C, Potter R, Van Limbergen E, et al. Recommendations for Gynecological (GYN) GEC-ESTRO Working Group (II): concepts and terms in 3D image-based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol.* 2005;74:235–245.
113. Potter R, Haie-Meder C, Van Limbergen E, et al. Recommendations for Gynecological (GYN) GEC ESTRO Working Group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy 3D volume parameters and aspects of 3D image-based anatomy, radiation physics radiobiology. *Radiother Oncol.* 2006;78:67–77.

114. Potter R, Dimopoulos J, Georg P, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol.* 2007;83:148–155.
115. Potter R, Georg P, Dimopoulos JCA, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol.* 2011;100(1):116–123.
116. Perez CA, Breaux S, Madoc-Jones H, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix I. Analysis of tumor recurrence. *Cancer.* 1983;51:1393–1402.
117. Coia L, Won M, Lanciano R, et al. The patterns of care outcome study for cancer of the uterine cervix. *Cancer.* 1990;66:2451–2456.
118. Lanciano RM, Won M, Coia LR, et al. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 Patterns of Care Studies. *Int J Radiat Oncol Biol Phys.* 1991;20:667–676.
119. Montana GS, Martz KL, Hanks GE. Patterns and sites of failure in cervix cancer treated in the USA in 1978. *Int J Radiat Oncol Biol Phys.* 1991;20:87–93.
120. Hanks GE, Herring DF, Kramer S. Patterns of care outcome studies results of the National Practice in Cancer of the Cervix. *Cancer.* 1983; 51:959–967.
121. Lanciano R, Martz K, Coia L, et al. Tumor and treatment factors improving outcome in stage IIIB cervix cancer. *Int J Radiat Oncol Biol Phys.* 1991; 20(1):95–100.
122. Barraclough L, Swindell R, Livsey J, et al. External beam boost for cancer of the cervix uteri when intracavitary therapy cannot be performed. *Int J Radiat Oncol Biol Phys.* 2008; 71(3):772–778.
123. Chen CC, Lin JC, Jan JS, et al. Definitive intensity-modulated radiation therapy with concurrent chemotherapy for patients with locally advanced cervical cancer. *Gyn Oncol.* 2011;122:9–13.
124. Alektiar K. Point. Can intensity-modulated radiation therapy replace brachytherapy in the management of cervical cancer? *Brachytherapy.* 2002;1:191–192.
125. Mundt A. Counterpoint. Can intensity-modulated radiation therapy replace brachytherapy in the management of cervical cancer? *Brachytherapy.* 2002;1:192–194.
126. Perez CA, Kuske R, Glasgow GP. Review of brachytherapy techniques for gynecologic tumors. *Endocuriether Hyperthermia Oncol.* 1985;1:153–175.
127. Delclos L, Fletcher GH, Moore EB, et al. Minicollposts, dome cylinders, other additions and improvements of the Fletcher-Suit afterloadable system: indications and limitations of their use. *Int J Radiat Oncol Biol Phys.* 1980;6:1195–1206.
128. Henschke UK. Afterloading applicator for radiation therapy of carcinoma of the uterus. *Radiology.* 1960;74:834.
129. Kagan AR, DiSaia PJ, Wollin M, et al. The narrow vagina, the antecedent for irradiation injury. *Gynecol Oncol.* 1976;4:291–298.
130. Crook JM, Esche BA, Chaplain G, et al. Dose-volume analysis and the prevention of radiation sequelae in cervical cancer. *Radiother Oncol.* 1987;8:321–332.
131. Cunningham DE, Stryker JA, Velkley DE, et al. Routine clinical estimation of rectal, rectosigmoidal, and bladder doses from intracavitary brachytherapy in the treatment of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 1981;7:653–660.
132. Villasanta U. Complications of radiotherapy for carcinoma of the uterine cervix. *Am J Obstet Gynecol.* 1972;6:717–726.
133. Barillot I, Horiot J, Maingon P, et al. Impact on treatment outcome and late effects of customized treatment planning in cervix carcinomas: baseline results to compare new strategies. *Int J Radiat Oncol Biol Phys.* 2000;48(1):189–200.
134. Hamberger AD, Unal A, Gershenson DM, et al. Analysis of the severe complications of irradiation of carcinoma of the cervix: whole pelvis irradiation and intracavitary radium. *Int J Radiat Oncol Biol Phys.* 1983;9:367–371.
135. Strockbine MF, Hancock JE, Fletcher GH. Complications in 831 patients with squamous cell carcinoma of the intact uterine cervix treated with 3,000 rads or more whole pelvis irradiation. *Am J Roentgenol.* 1970;108:293–304.
136. Unal A, Hamberger AD, Seski JC, et al. An analysis of the severe complications of irradiation of carcinoma of the uterine cervix: treatment with intracavitary radium and parametrial irradiation. *Int J Radiat Oncol Biol Phys.* 1981;7:999–1004.
137. Paris KJ, Spanos WJ, Day TG, et al. Incidence of complications with mini vaginal culpostats in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1991;21:911–917.
138. Pourquier H, Dubois JB, Delard R. Exclusive use of radiotherapy in cancer of the cervix prevention of late pelvic complications. *Cervix.* 1990;8:61–74.
139. Corn BW, Hanlon AL, Pajak TF, et al. Technically accurate intracavitary insertions improve pelvic control and survival among patients with locally advanced carcinoma of the uterine cervix. *Gynecol Oncol.* 1994;53:294–300.
140. Viswanathan AN, Moughan J, Small Jr W, et al. The quality of cervical cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in Radiation Therapy Oncology Group Prospective Trials 0116 and 0128. *Int J Gyn Cancer.* 2012;22(1):123–131.
141. Perez CA, Breaux S, Bedwinek JM, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix. II. Analysis of complications. *Cancer.* 1984;54:235–246.
142. Erickson B, Gillin M. Interstitial implantation of gynecologic malignancies. *J Surg Oncol.* 1997;66:285–295.
143. Viswanathan A, Creutzberg C, Craighead P, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Inter-group (GCIG). *Int J Radiat Oncol Biol Phys.* 2012;82(1):250–255.
144. Viswanathan AN, Erickson BE, Rownd J. Image-based approaches to interstitial brachytherapy. In: Viswanathan AN, Kirisits C, Erickson BE, et al. eds. *Gynecologic Radiation Therapy. Novel Approaches to Image-Guidance and Management.* New York, NY: Springer; 2011:247–259.
145. Beriwal S, Demanes DJ, Erickson B, et al. American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer. *Brachytherapy.* 2012;11:68–75.
146. Gupta A, Vicini F, Frazier A, et al. Iridium-192 transperineal interstitial brachytherapy for locally advanced or recurrent gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 1999; 43(5):1055–1060.
147. Martinez A, Cox RS, Edmundson GK. A multiple site perineal applicator (MUPIT) for treatment of prostatic, anorectal, and gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 1984; 10:297–305.
148. Inoue T, Inoue T, Tanaka E, et al. High dose rate fractionated interstitial brachytherapy as the sole treatment for recurrent carcinoma of the uterus. *J Brachyther Int.* 1999;15:161–167.
149. Syed AMN, Puthawala AA, Neblett D, et al. Transperineal interstitial-intracavitary “Syed-Neblett” applicator in the treatment of carcinoma of the uterine cervix. *Endocuriether Hyperthermia Oncol.* 1986;2:1–13.
150. Syed A, Puthawala A, Abdelaziz N, et al. Long-term results of low-dose-rate interstitial-intracavitary brachytherapy in the treatment of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2002;54(1):67–78.
151. Demanes D, Rodriguez R, Bendre D, et al. High dose rate transperineal interstitial brachytherapy for cervical cancer: high pelvic control and low complication rates. *Int J Radiat Oncol Biol Phys.* 1999;45(1):105–112.
152. Beriwal S, Bhatnagar A, Heron D, et al. High dose rate interstitial brachytherapy for gynecologic malignancies. *Brachytherapy.* 2006;5:218–222.
153. Beriwal S, Rwigyema JC, Higgins E, et al. Three-dimensional image-based high-dose-rate interstitial brachytherapy for vaginal cancer. *Brachytherapy.* 2012;11:176–180.
154. Viswanathan AN, Cormack R, Rawal B, et al. Increasing brachytherapy dose predicts survival for interstitial and tandem-based radiation for stage IIIB cervical cancer. *Int J Gyn Cancer.* 2009;19(8):1402–1406.
155. Nomden C, deLeeuw A, Moerland M, et al. Clinical use of the Utrecht applicator for combined intracavitary/interstitial brachytherapy treatment in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(4):1424–1430.
156. Jurgentliemk-Schulz I, Tersteeg R, Roesink J, et al. MRI-guided treatment-planning optimisation in intracavitary or combined intracavitary/interstitial PDR brachytherapy using tandem ovoid applicators in locally advanced cervical cancer. *Radiother Oncol.* 2009;93:322–330.
157. Dimopoulos J, Kirisits C, Petric P, et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: clinical feasibility and preliminary results. *Int J Radiat Oncol Biol Phys.* 2006;66(1):83–90.
158. Erickson B, Albano K, Gillin M. CT-guided interstitial implantation of gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 1996; 36(3):699–709.
159. Orton C. High and low dose rate brachytherapy for cervical carcinoma. *Acta Oncol.* 1998; 37(2):117–125.
160. Stewart A, Viswanathan A. Current controversies in high-dose-rate versus low-dose-rate brachytherapy for cervical cancer. *Cancer.* 2006;107(5):908–915.
161. Sarkaria JN, Peteret DG, Stitt JA, et al. A comparison of the efficacy and complication rates of low dose-rate versus high dose-rate brachytherapy in the treatment of uterine cervical carcinoma. *Int J Radiat Oncol Biol Phys.* 1994;30:75–82.
162. Stitt JA, Fowler JF, Thomadsen BR, et al. High dose rate intracavitary brachytherapy for carcinoma of the cervix: the Madison system: I. Clinical and radiobiological considerations. *Int J Radiat Oncol Biol Phys.* 1992;24:335–348.
163. Thomadsen BR, Shahabi S, Stitt JA, et al. High dose rate intracavitary brachytherapy for carcinoma of the cervix: the Madison system: II. Procedural and physical considerations. *Int J Radiat Oncol Biol Phys.* 1992;24:349–357.

164. Houdek PV, Schwade JG, Abitbol AA, et al. Optimization of high dose-rate cervix brachytherapy: Part I: Dose distribution. *Int J Radiat Oncol Biol Phys.* 1991;21:1621–1625.
165. Delaloye JF, Coucke PA, Pampallona S, et al. Effect of total treatment time on event-free survival in carcinoma of the cervix. *Gynecol Oncol.* 1996;60:42–48.
166. Himmelmann A, Holmberg E, Oden A, et al. Intracavitary irradiation of carcinoma of the cervix stage IB and IIA. *Acta Radiol Oncol.* 1985;24:139–144.
167. Brenner DJ, Huang Y, Hall EJ. Fractionated high dose-rate versus low dose-rate regimens for intracavitary brachytherapy of the cervix: equivalent regimens for combined brachytherapy and external irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:1415–1423.
168. Brenner D. HDR brachytherapy for carcinoma of the cervix: fractionation considerations. *Int J Radiat Oncol Biol Phys.* 1991;22:221–222.
169. Orton CG. Biologic treatment planning. In: Martinez AA, Orton CG, Mould RF, eds. *Brachytherapy HDR and LDR.* Columbia, MD: Nucletron; 1990:205–215.
170. Orton CG. Application of the linear quadratic model to radiotherapy for gynaecological cancers. *Selectron Brachytherapy J.* 1991;2(suppl.):15–18.
171. Abitbol AA, Houdek P, Schwade JG, et al. Ring applicator with rectal retractor: applicability to high dose rate brachytherapy for cervical cancer. *Selectron Brachytherapy J.* 1990;4:6869.
172. Wollin M, Kagan AR, Olch A, et al. Comparison of the ring applicator and the Fletcher applicator for HDR gynaecological brachytherapy. *Selectron Brachytherapy J.* 1991;2(suppl. 2):25–27.
173. Erickson B, Jones R, Rownd J, et al. Is the tandem and ring applicator a suitable alternative to the high dose rate Selectron tandem and ovoid applicator? *J Brachytherapy Int.* 2000;16:31–144.
174. Brooks S, Bownes P, Lowe G, et al. Cervical brachytherapy utilizing ring applicator: comparison of standard and conformal loading. *Int J Radiat Oncol Biol Phys.* 2005;63(3):934–939.
175. Mai J, Erickson B, Rownd J, et al. Comparison of four different dose specification methods for high dose rate intracavitary radiation for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys.* 2001;51(4):1131–1141.
176. Kim R, Caranto J, Pareek P, et al. Dynamics of pear-shaped dimensions and volume of intracavitary brachytherapy in cancer of the cervix: a desirable pear shape in the era of three-dimensional treatment planning. *Int J Radiat Oncol Biol Phys.* 1997;37(5):1193–1199.
177. Cetingoz R, Ataman O, Tuncel N, et al. Optimization in high dose rate brachytherapy for utero-vaginal applications. *Radiother Oncol.* 2001;58:31–36.
178. Anker C, Cachoeira C, Boucher K, et al. Does the entire uterus need to be treated in cancer of the cervix? Role of adaptive brachytherapy. *Int J Radiat Oncol Biol Phys.* 2010;76(3):704–712.
179. Hoskin PJ, Cook M, Bouscale D, et al. Changes in applicator position with fractionated high dose rate gynaecological brachytherapy. *Radiother Oncol.* 1996;40:59–62.
180. Grigsby PW, Georgiou A, Williamson JF, et al. Anatomic variation of gynecologic brachytherapy prescription points. *Int J Radiat Oncol Biol Phys.* 1993;27:725–729.
181. Kim RY, Meyer JT, Plott WE, et al. Major geometric variations between multiple high-dose-rate applications of brachytherapy in cancer of the cervix: frequency and types of variation. *Radiology.* 1995;195:419–422.
182. Christensen G, Carlson B, Chao C, et al. Image-based dose planning of intracavitary brachytherapy: registration of serial-imaging studies using deformable anatomic templates. *Int J Radiat Oncol Biol Phys.* 2001;51(1):227–243.
183. Kim R, Meyer J, Spencer S, et al. Major geometric variation between intracavitary applications in carcinoma of the cervix: high dose rate vs. low dose rate. *Int J Radiat Oncol Biol Phys.* 1996;35(5):1035–1038.
184. Kim R, Meyer J, Plott W, et al. Major geometric variation between multiple high dose rate applications of brachytherapy in cancer of the cervix: frequency and types of variation. *Radiology.* 1995;195:419–422.
185. Elhanafy O, Das R, Paliwal B, et al. Anatomic variation of prescription points and treatment volume with fractionated high-dose-rate gynecologic brachytherapy. *J Appl Clin Med Phys.* 2002;3(1):1–5.
186. Jones N, Rankin J, Gaffney D. Is simulation necessary for each high-dose-rate tandem and ovoid insertion in carcinoma of the cervix? *Brachytherapy.* 2004;3:120–124.
187. Pham H, Chen Y, Roubey E, et al. Changes in high-dose-rate tandem and ovoid applicator position during treatment in an unfixed brachytherapy system. *Radiology.* 1998;206:525–531.
188. Fu KK, Phillips TL. High-dose-rate versus low-dose-rate intracavitary brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 1990;19:791–796.
189. Orton CG. HDR: forget not “time” and “distance.” *Int J Radiat Oncol Biol Phys.* 1991;20:1131–1132.
190. Orton CG, Seyedsadr M, Somnay A. Comparison of high and low dose rate remote afterloading for cervix cancer and the importance of fractionation. *Int J Radiat Oncol Biol Phys.* 1991;21:1425–1434.
191. Petereit D, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: Is there an optimal fractionation schedule? *Int J Radiat Oncol Biol Phys.* 1999;43(2):359–366.
192. Nag S, Gupta N. A simple method of obtaining equivalent doses for use in HDR brachytherapy. *Int J Radiat Oncol Biol Phys.* 2000;46(2):507–513.
193. Forrest J, Ackerman I, Barbera L. Patient outcome study of concurrent chemoradiation, external beam radiotherapy, and high-dose rate brachytherapy in locally advanced carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2010;20(6):1074–1078.
194. Erickson B, Eifel P, Moughan J, et al. Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996–1999): a Patterns of Care study. *Int J Radiat Oncol Biol Phys.* 2005;63(4):1083–1092.
195. Chen SW, Liang JA, Yang SN, et al. The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. *Radiother Oncol.* 2003;67:69–76.
196. Ferrigno R, Nishimoto IN, Dos Santos Novaes PER, et al. Comparison of low and high dose rate brachytherapy in the treatment of uterine cervix cancer. Retrospective analysis of two sequential series. *Int J Radiat Oncol Biol Phys.* 2005;62(4):1108–1116.
197. Small W, Erickson B, Kwakwa F. American Brachytherapy Society survey regarding practice patterns of post-operative irradiation for endometrial cancer: current status of vaginal brachytherapy. *Int J Radiat Oncol Biol Phys.* 2005;63(5):1502–1507.
198. Small Jr W, Beriwal S, Demanes D, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy.* 2012;11:58–67.
199. Kim R, Pareek K, Duan J, et al. Postoperative intravaginal brachytherapy for endometrial cancer: dosimetric analysis of vaginal colpostats and cylinder applicators. *Brachytherapy.* 2002;1:138–144.
200. Dobbie BW. Vaginal recurrences in carcinoma of the body of the uterus and their prevention. *J Obstet Gynaecol Brit Emp.* 1953;60:702–705.
201. Greven KM, Randall M, Fanning J, et al. Patterns of failure in patients with stage I, grade 3 carcinoma of the endometrium. *Int J Radiat Oncol Biol Phys.* 1990;19:529–534.
202. Price JJ, Hahn GA, Rominger CJ. Vaginal involvement in endometrial carcinoma. *Am J Obstet Gynecol.* 1965;91(8):1060–1065.
203. Grigsby PW, Perez CA, Kuten A, et al. Clinical stage I endometrial cancer: results of adjuvant irradiation and patterns of failure. *Int J Radiat Oncol Biol Phys.* 1991;21(2):379–385.
204. Gore E, Gillin M, Albano K, et al. Comparison of high dose rate and low dose rate dose distributions for vaginal cancers. *Int J Radiat Oncol Biol Phys.* 1995;31(1):165–170.
205. Li Z, Liu C, Palta J. Optimized dose distribution of a high dose rate vaginal cylinder. *Int J Radiat Oncol Biol Phys.* 1998;41(1):239–244.
206. Li S, Aref I, Walker E, et al. Effects of prescription depth, cylinder size, treatment length, tip space, and curved end on doses in high-dose-rate vaginal brachytherapy. *Int J Radiat Oncol Biol Phys.* 2007;67(4):1268–1277.
207. Holloway C, Macklin E, Cormack R, et al. Should the organs at risk be contoured in vaginal cuff brachytherapy? *Brachytherapy.* 2011;10:313–317.
208. Russo J, Armeson K, Richardson S. Comparison of 2D and 3D imaging and treatment planning for postoperative vaginal apex high-dose rate brachytherapy for endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2012;83(1):e75–80.
209. Choo J, Scudiere J, Bitterman P, et al. Vaginal lymphatic channel location and its implication for intracavitary brachytherapy radiation treatment. *Brachytherapy.* 2005;4:236–240.
210. Jhingran A, Burke T, Eifel P. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. *Int J Radiat Oncol Biol Phys.* 2003;56(5):1366–1372.
211. Alektiar K, McKee A, Venkatraman E, et al. Intravaginal high dose rate brachytherapy for stage IB (FIGO Grade 1, 2) endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2002;53(3):707–713.
212. Chadha M. Gynecologic brachytherapy. II: Intravaginal brachytherapy for carcinoma of the endometrium. *Semin Radiat Oncol.* 2002;12(1):53–61.
213. Alektiar K, Venkatraman E, Chi D, et al. Intravaginal brachytherapy alone for intermediate risk endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2005;62(1):111–117.
214. Chada M, Nanavati PJ, Liu P, et al. Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. *Gynecol Oncol.* 1999;75:103–107.
215. Greven MKM, D’Agostino RB Jr, Lanciano RM, et al. Is there a role for a brachytherapy vaginal cuff boost in the adjuvant management of patients with uterine-confined endometrial cancer? *Int J Radiat Oncol Biol Phys.* 1998;42(1):101–104.
216. Randall ME, Wilder J, Greven K, et al. Role of intracavitary cuff boost after adjuvant external

- irradiation in early endometrial carcinoma. *Int J Radiat Oncol Biol Phys.* 1990;19:49–54.
217. Naizi T, Souhami L, Portlance L, et al. Long-term results of high-dose-rate brachytherapy in the primary treatment of medically inoperable stage I–II endometrial carcinoma. *Int J Radiat Oncol Biol Phys.* 2005;63(4):1108–1113.
 218. Taghian A, Pernot M, Hoffstetter S, et al. Radiation therapy alone for medically inoperable patients with adenocarcinoma of the endometrium. *Int J Radiat Oncol Biol Phys.* 1988;15(4):1135–1140.
 219. Knocke T, Kucera H, Weidinger B, et al. Primary treatment of endometrial carcinoma with high-dose-rate brachytherapy: results of 12 years of experience with 280 patients. *Int J Radiat Oncol Biol Phys.* 1997;37(2):359–365.
 220. Disaia PJ, Syed AMN, Puthawala AA. Malignant neoplasia of the upper vagina. *Endocrine-ther Hypertherm Oncol.* 1994;10:83–86.
 221. Puthawala AA, Syed AMN, Fleming PA, et al. Reirradiation with interstitial implant for recurrent pelvic malignancies. *Cancer.* 1982;50:2810–2814.
 222. Monk BJ, Walker JL, Tewari K, et al. Open interstitial brachytherapy for the treatment of local-regional recurrences of uterine corpus and cervix cancer after primary surgery. *Gynecol Oncol.* 1994;52:222–228.
 223. Perez C, Brady L, eds. *Principles and Practice of Radiation Oncology.* 2nd ed. Philadelphia, PA: Lippincott Co.; 1992:1143–1202.
 224. Rotman M, Aziz H, Eifel P. Irradiation of pelvic and para-aortic nodes in carcinoma of the cervix. *Semin Radiat Oncol.* 1994;4(1):23–29.
 225. Hendriksen E. The lymphatic spread of carcinoma of the cervix and of the body of the uterus. A study of 420 necropsies. *Am J Obstet Gynecol.* 1949;58(5):924–942.
 226. Chao C, Williamson J, Grigsby P, et al. Uterosacral space involvement in locally advanced carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1998;40(2):397–403.
 227. Netter F. *The CIBA Collection of Medical Illustrations, Vol 2. Reproductive System.* Summitt, NJ: CIBA Pharmaceutical; 1988.
 228. Park J, Charnsangavej C, Yoshimitsu K, et al. Pathways of nodal metastasis from pelvic tumors: CT demonstration. *RadioGraphics.* 1994;14(6):1309–1321.
 229. Bonin S, Lanciano R, Corn B, et al. Bony landmarks are not an adequate substitute for lymphangiography in defining pelvic lymph node location for the treatment of cervical cancer with radiotherapy. *Int J Radiat Oncol Biol Phys.* 1996;34(1):167–172.
 230. Chun M, Timmerman R, Mayer R, et al. Radiation therapy of external iliac lymph nodes with lateral pelvic portals: identification of patients at risk for inadequate regional coverage. *Radiology.* 1995;194:147–150.
 231. Pendlebury S, Cahill S, Crandon A, et al. Role of bipedal lymphangiogram in radiation treatment planning for cervical cancer. *Int J Radiat Oncol Biol Phys.* 1993;27(4):959–962.
 232. Kim R, McGinnis S, Spencer S, et al. Conventional four-field pelvic radiotherapy technique without CT treatment planning in cancer of the cervix: potential geographic miss. *Radiother Oncol.* 1994;30:140–145.
 233. Kim R, McGinnis S, Spencer S, et al. Conventional four-field pelvic radiotherapy technique without computed tomography treatment planning in cancer of the cervix: potential geographic miss and its impact on pelvic control. *Int J Radiat Oncol Biol Phys.* 1995;31(1):109–112.
 234. Mayr N, Tali E, Yuh W, et al. Cervical cancer: application of MR imaging in radiation therapy. *Radiology.* 1993;189:601–608.
 235. Russell A, Walter J, Anderson M, et al. Sagittal magnetic resonance imaging in the design of lateral radiation treatment portals for patients with locally advanced squamous cancer of the cervix. *Int J Radiat Oncol Biol Phys.* 1992;23(2):449–455.
 236. Thomas L, Chacon B, Kind M, et al. Magnetic resonance imaging in the treatment planning of radiation therapy in carcinoma of the cervix treated with the four-field pelvic technique. *Int J Radiat Oncol Biol Phys.* 1997;37(4):827–832.
 237. Zunino S, Rosato O, Lucino S, et al. Anatomic study of the pelvis in carcinoma of the uterine cervix as related to the box technique. *Int J Radiat Oncol Biol Phys.* 1999;44(1):53–59.
 238. McAlpine J, Schlaerth JB, Lim P, et al. Radiation fields in gynecologic oncology: correlation of soft tissue (surgical) to radiologic landmarks. *Gynecol Oncol.* 2004;92:25–30.
 239. Greer B, Koh W, Stelzer K, et al. Expanded pelvic radiotherapy fields for treatment of local-regionally advanced carcinoma of the cervix: outcome and complications. *Am J Obstet Gynecol.* 1996;174(4):1141–1150.
 240. Greer B, Koh WJ, Figue D, et al. Gynecologic radiotherapy fields defined by intraoperative measurements. *Gynecol Oncol.* 1990;38:421–424.
 241. Finlay M, Ackerman I, Tirona R, et al. Use of CT simulation for treatment of cervical cancer to assess the adequacy of lymph node coverage of conventional pelvic fields based on bony landmarks. *Int J Radiat Oncol Biol Phys.* 2006;64(1):205–209.
 242. Gerstner N, Wachter S, Knocke T, et al. The benefit of beam's eye view based 3D treatment planning for cervical cancer. *Radiother Oncol.* 1999;51:71–78.
 243. Russell A. Contemporary radiation treatment planning for patients with cancer of the uterine cervix. *Semin Oncol.* 1994;21(1):30–41.
 244. Terry L, Piver S, Hanks G. The value of lymphangiography in malignant disease of the uterine cervix. *Radiology.* 1972;103:175–177.
 245. Grigsby P, Siegel B, Dehdashti F, et al. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol.* 2001;19(17):3745–3749.
 246. Rose P, Adler L, Rodriguez M, et al. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol.* 1999;17(1):41–45.
 247. Lin W, Hung Y, Yeh L, et al. Usefulness of ¹⁸F-fluorodeoxyglucose positron emission tomography to detect para-aortic lymph nodal metastasis in advanced cervical cancer with negative computed tomography findings. *Gynecol Oncol.* 2003;89:73–76.
 248. Tsai CS, Chang TC, Lai CH, et al. Preliminary report of using FDG-PET to detect extrapelvic lesions in cervical cancer patients with enlarged pelvic lymph nodes on MRI/CT. *Int J Radiat Oncol Biol Phys.* 2004;58(5):1506–1512.
 249. Wolfson A, Abdel-Wahab M, Markoe A, et al. A quantitative assessment of standard vs. customized midline shield construction for invasive cervical carcinoma. *Int J Radiat Oncol Biol Phys.* 1997;37(1):237–242.
 250. Perez CA, Camel HM, Kuske RR, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix: a 20-year experience. *Gynecol Oncol.* 1986;23:127–140.
 251. Walz B, Perez C, Feldman A, et al. Individualized compensating filter and dose optimization in pelvic irradiation. *Radiology.* 1973;107:611–614.
 252. Han I, Malviya V, Chuba P, et al. Multifractionated high dose rate brachytherapy with concomitant daily teletherapy for cervical cancer. *Gynecol Oncol.* 1996;63:71–77.
 253. Ling C, Smith A, Hanlon A, et al. Treatment planning for carcinoma of the cervix: a Patterns of Care Study report. *Int J Radiat Oncol Biol Phys.* 1998;34(1):13–19.
 254. Lindegaard J, Tanderup K. Counterpoint: time to retire the parametrial boost. *Brachytherapy.* 2012;11:80–83.
 255. Good J, Lalonde S, Blake P. Point: parametrial irradiation in locally advanced cervix cancer can be achieved effectively with a variety of external beam techniques. *Brachytherapy.* 2012;11:77–79.
 256. Fenkell L, Assenolt M, Nielsen S, et al. Parametrial boost using midline shielding results in an unpredictable dose to tumor and organs at risk in combined external beam radiotherapy and brachytherapy for locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys.* 2011;79(5):1572–1579.
 257. Eifel PJ, Levenback C, Wharton JT, et al. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1995;32:1289–1300.
 258. Huang E, Lin H, Hsu H, et al. High external parametrial dose can increase the probability of radiation proctitis in patients with uterine cervix cancer. *Gynecol Oncol.* 2000;79:406–410.
 259. Huang EY, Wang CJ, Hsu HC, et al. Dosimetric factors predicting severe radiation-induced bowel complications in patients with cervical cancer: combined effect of external parametrial dose and cumulative rectal dose. *Gynecol Oncol.* 2004;95:101–108.
 260. Kuipers TJ. Stereo x-ray photogrammetry applied for prevention of sigmoid-colon damage caused by radiation from intrauterine sources. *Int J Radiat Oncol Biol Phys.* 1982;8:1011–1017.
 261. Bahena J, Martinez A, Yan D, et al. Spatial reproducibility of the ring and tandem high dose rate cervix applicator. *Int J Radiat Oncol Biol Phys.* 1998;41(1):13–19.
 262. Perez CA, Fox S, Lockett MA, et al. Impact of dose in outcome of irradiation alone in carcinoma of the uterine cervix: analysis of two different methods. *Int J Radiat Oncol Biol Phys.* 1991;21:885–898.
 263. Perez C, Grigsby P, Chao C, et al. Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. *Int J Radiat Oncol Biol Phys.* 1998;41(2):307–317.
 264. Perez C, Grigsby P, Lockett M, et al. Radiation therapy morbidity in carcinoma of the uterine cervix: dosimetric and clinical correlation. *Int J Radiat Oncol Biol Phys.* 1999;44(4):855–866.
 265. Grigsby P, Singh A, Siegel B, et al. Lymph node control in cervical cancer. *Int J Radiat Oncol Biol Phys.* 2004;59(3):706–712.
 266. Houvenaegel G, Lelievre L, Rigouard A, et al. Residual pelvic lymph node involvement after concomitant chemoradiation for locally advanced cervical cancer. *Gynecol Oncol.* 2006;102:74–79.
 267. Johnsson JE. Recurrences and metastases in carcinoma of the uterine body correlated to the size and localization of the primary tumor. *Acta Obstet Gynecol Scand.* 1979;58:405–408.
 268. Creasman WT, Boronow RC, Morrow CP, et al. Adenocarcinoma of the endometrium: Its metastatic lymph node potential. *Gynecol Oncol.* 1976;4:239–243.
 269. Creasman WT, Morrow P, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. *Cancer.* 1987;60:2035–2041.

270. Boronow RC, Morrow CP, Creasman WT, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. *Obstet Gynecol.* 1984;63(6):825–832.
271. Morrow PC, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1991;40:55–65.
272. DiSaia PJ, Creasman WT, Boronow RC, et al. Risk factors and recurrent patterns in stage I endometrial cancer. *Am J Obstet Gynecol.* 1985;151:1009–1015.
273. Greven KM, Corn BW, Case D, et al. Which prognostic factors influence the outcome of patients with surgically staged endometrial cancer treated with adjuvant radiation? *Int J Radiat Oncol Biol Phys.* 1997;39(2):413–418.
274. Morrow CP, Di Saia J, Townsend DE. The role of postoperative irradiation in the management of stage I adenocarcinoma of the endometrium. *Am J Roentgenol.* 1976;127:325–329.
275. Gallagher M, Brereton H, Rostock R, et al. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. *Int J Radiat Oncol Biol Phys.* 1986;12(9):1565–1573.
276. Huh S, Lim D, Ahn Y, et al. Effect of customized small bowel displacement system in pelvic irradiation. *Int J Radiat Oncol Biol Phys.* 1998;40(3):623–627.
277. Shanahan T, Mehta M, Bertelrud K, et al. Minimization of small bowel volume within treatment fields utilizing customized “belly boards.” *Int J Radiat Oncol Biol Phys.* 1990;19(2):469–476.
278. Ghosh K, Padilla L, Murray K, et al. Using a belly board device to reduce the small bowel volume within pelvic radiation fields in women with postoperatively treated cervical carcinoma. *Gynecol Oncol.* 2001;83:271–275.
279. Olofsen-van Acht M, van den Berg H, Quint S, et al. Reduction of irradiated small bowel volume and accurate patient positioning by use of a belly board device in pelvic radiotherapy of gynecologic cancer patients. *Radiother Oncol.* 2001;59:87–93.
280. Pinkawa M, Gagel B, Demirel C, et al. Dose-volume histogram for prone and supine patient position in external beam radiotherapy for cervical and endometrial cancer. *Radiother Oncol.* 2003;69:99–105.
281. Weiss E, Eberlein K, Pradier O, et al. The impact of patient positioning on the adequate coverage of the uterus in the primary irradiation of cervical carcinoma: a prospective analysis using magnetic resonance imaging. *Radiother Oncol.* 2002;63:83–87.
282. Buchali A, Koswig S, Dinges S, et al. Impact of the filling status of the bladder and rectum on their integral dose distribution and movement of the uterus in the treatment planning of gynaecological cancer. *Radiother Oncol.* 1999;52:29–34.
283. Martinez A, Weiner S, Podratz K, et al. Improved outcome at 10 years for serous-papillary/clear cell or high-risk endometrial cancer patients treated by adjuvant high-dose-whole abdomino-pelvic irradiation. *Gynecol Oncol.* 2003;90:537–546.
284. Small W, Mayadevan A, Roland P, et al. Whole-abdominal radiation in endometrial carcinoma: an analysis of toxicity, patterns of recurrence, and survival. *Cancer J.* 2000;6(6):394–400.
285. Rotman M, Aziz H, Choi K. Radiation damage of normal tissues in the treatment of gynecologic cancers. *Front Radiat Ther Oncol.* 1989;23:349–366.
286. Rubin P, Casarett G. *Clinical Radiation Pathology.* Vol. 1–2. Philadelphia, PA: WB Saunders Co.; 1968.
287. Emami B, Lyman J, Brown A, et al. Tolerance to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:109–122.
288. Bentzen S, Constine L, Deasy J, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): An introduction to the scientific issues. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S3–S9.
289. Marks L, Yorke E, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S10–S19.
290. Cox J, Ang K, eds. *Radiation Oncology: Rationale, Technique, Results.* 8th ed. St. Louis, MO: Mosby; 2003.
291. Jeter M, Janne P, Brooks S, et al. Gemcitabine-induced radiation recall. *Int J Radiat Oncol Biol Phys.* 2002;53(2):394–400.
292. Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. *Radiother Oncol.* 2001;59:237–245.
293. Grigsby P, Russell A, Bruner D, et al. Late injury of cancer therapy on the female reproductive tract. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1289–1299.
294. Tai P, Hammond A, Van Dyk J, et al. Pelvic fractures following irradiation of endometrial and vaginal cancer—a case series and review of literature. *Radiother Oncol.* 2000;56:23–28.
295. Huh S, Kim B, Kang M, et al. Pelvic insufficiency fracture after pelvic irradiation in uterine cervix cancer. *Gynecol Oncol.* 2002;86:264–268.
296. Grigsby P, Roberts H, Perez C. Femoral head fracture following groin irradiation. *Int J Radiat Oncol Biol Phys.* 1995;32(1):63–67.
297. Lawrence T, Robertson J, Anscher M, et al. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1237–1248.
298. Pan C, Kavanagh B, Dawson L, et al. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S94–S100.
299. Dawson L, Kavanagh B, Paulino A, et al. Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S108–S115.
300. Hintz BL, Kagan AR, Chan P, et al. Radiation tolerance of the vaginal mucosa. *Int J Radiat Oncol Biol Phys.* 1980;6:711–716.
301. Fidarova E, Berger D, Schussler S, et al. Dose volume parameter D_{2cc} does not correlate with vaginal side effects in individual patients with cervical cancer treated within a defined treatment protocol with very high brachytherapy doses. *Radiother Oncol.* 2010;97:76–79.
302. Au S, Grigsby P. The irradiation tolerance dose of the proximal vagina. *Radiother Oncol.* 2003;67:77–85.
303. Williams J, Clarke D, Dennis W, et al. The treatment of pelvic soft tissue radiation necrosis with hyperbaric oxygen. *Am J Obstet Gynecol.* 1992;167(2):412–416.
304. Pasquier D, Hoelscher T, Schmutz J, et al. Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. *Radiother Oncol.* 2004;72:1–13.
305. Okunieff P, Augustine E, Hicks J, et al. Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol.* 2004;22(11):2207–2213.
306. Kavanagh B, Pan C, Dawson L, et al. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S101–S107.
307. Mayer R, Klemen H, Quehenberger F, et al. Hyperbaric oxygen—an effective tool to treat radiation morbidity in prostate cancer. *Radiother Oncol.* 2001;61:151–156.
308. Carl U, Peusch-Dreyer D, Frieling T, et al. Treatment of radiation proctitis with hyperbaric oxygen: what is the optimal number of HBO treatments? *Strahlenther Onkol.* 1998;174(9):482–483.
309. Woo TCS, Joseph D, Oxer H, et al. Hyperbaric oxygen treatment for radiation proctitis. *Int J Radiat Oncol Biol Phys.* 1997;38(3):619–622.
310. Michalski J, Gay H, Jackson A, et al. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S123–S129.
311. Marks L, Carroll P, Dugan T, et al. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1257–1280.
312. Viswanathan A, Yorke E, Marks L, et al. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S116–S122.
313. Bevers RFM, Bakker D, Kurth KH. Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. *Lancet.* 1995;346:803–804.
314. McIntyre J, Eifel P, Levenback C, et al. Ureteral stricture as a late complication of radiotherapy for stage IB carcinoma of the uterine cervix. *Cancer.* 1995;75(3):836–843.
315. Roeske J, Mundt A, Halpern H, et al. Late rectal sequelae following definitive radiation therapy for carcinoma of the uterine cervix: a dosimetric analysis. *Int J Radiat Oncol Biol Phys.* 1997;37(2):351–358.
316. Stryker J, Bartholomew M, Velkley D, et al. Bladder and rectal complications following radiotherapy for cervix cancer. *Gynecol Oncol.* 1988;29:1–11.
317. Kapp K, Stueckschweiger G, Kapp D, et al. Carcinoma of the cervix: analysis of complications after primary external beam radiation and Ir-192 HDR brachytherapy. *Radiother Oncol.* 1997;42:143–153.
318. Wang C, Leung S, Chen H, et al. High-dose rate intracavitary brachytherapy (HDR-IC) in treatment of cervical carcinoma: 5-year results and implication of increased low-grade rectal complication on initiation of an HDR-IC fractionation scheme. *Int J Radiat Oncol Biol Phys.* 1997;38(2):391–398.
319. Ito H, Kutuki S, Nishiguchi I, et al. Radiotherapy for cervical cancer with high-dose rate brachytherapy correlation between tumor size, dose and failure. *Radiother Oncol.* 1994;31:240–247.
320. Ogino I, Kitamura T, Okamoto N, et al. Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. *Int J Radiat Oncol Biol Phys.* 1995;31:725–734.
321. Chen MS, Lin FJ, Hong CH, et al. High-dose-rate afterloading technique in the radiation treatment of uterine cervical cancer: 399 cases and 9 years experience in Taiwan. *Int J Radiat Oncol Biol Phys.* 1991;20:915–919.
322. Fowler JF. The radiobiology of brachytherapy. In: Martinez AA, Orton CG, Mould RF, eds. *Brachytherapy HDR and LDR.* Columbia, MD: Nucletron; 1990:121–137.
323. Sakata KI, Nagakura H, Oouchi A, et al. High-dose-rate intracavitary brachytherapy: results of analyses of late rectal complications. *Int J Radiat Oncol Biol Phys.* 2002;54(5):1369–1376.
324. Cheng JCH, Peng LC, Chen YH, et al. Unique role of proximal rectal dose in late rectal

- complications for patients with cervical cancer undergoing high-dose-rate intracavitary brachytherapy. *Int J Radiat Oncol Biol Phys.* 2003;57(4):1010–1018.
325. Takeshi K, Katsuyuki K, Yoshiaki T, et al. Definitive radiotherapy combined with high dose rate brachytherapy for stage III carcinoma of the uterine cervix: retrospective analysis of prognostic factors concerning patient characteristics and treatment parameters. *Int J Radiat Oncol Biol Phys.* 1998;41(2):319–327.
 326. Teshima T, Chatani M, Hata K, et al. Rectal complication after remote afterloading intracavitary therapy for carcinoma of the uterine cervix. *Strahlentherapie.* 1985;161:343–347.
 327. Teshima T, Chatani M, Hata K, et al. High-dose rate intracavitary therapy for carcinoma of the uterine cervix: II. Risk factors for rectal complication. *Int J Radiat Oncol Biol Phys.* 1988;14:281–286.
 328. Sood B, Garg M, Avadhani J, et al. Predictive value of linear-quadratic model in the treatment of cervical cancer using high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2002;54(5):1377–1387.
 329. Chen S, Liang J, Yang S, et al. The prediction of late rectal complications following the treatment of uterine cervical cancer by high dose rate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2000;47(4):955–961.
 330. Chen SW, Liang JA, Yeh LS, et al. Comparative study of reference points by dosimetric analyses for late complications after uniform external radiotherapy and high-dose-rate brachytherapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2004;60(2):663–671.
 331. Toita T, Kakinohana Y, Ogawa K, et al. Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys.* 2003;56(5):1344–1353.
 332. Lee SW, Suh CO, Chung EJ, et al. Dose optimization of fractionated external radiation and high-dose-rate intracavitary brachytherapy for FIGO stage IB uterine cervical carcinoma. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1338–1344.
 333. Van Lancker M, Storme G. Prediction of severe late complications in fractionated, high dose-rate brachytherapy in gynecologic applications. *Int J Radiat Oncol Biol Phys.* 1991;20:1125–1129.
 334. Georg P, Potter R, Georg D, et al. Dose effect relationship for late side effects of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. *Int J Radiat Oncol Biol Phys.* 2012;82(2):653–657.
 335. Georg P, Lang S, Dimopoulos J, et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys.* 2011;79(2):356–362.
 336. Koom W, Sohn D, Kim J-Y, et al. Computed tomography-based high-dose-rate intracavitary brachytherapy for uterine cervical cancer: preliminary demonstration of correlation between dose-volume parameters and rectal mucosal changes observed by flexible sigmoidoscopy. *Int J Radiat Oncol Biol Phys.* 2007;68(5):1446–1454.
 337. Georg P, Kirisits C, Goldner G, et al. Correlation of dose-volume parameters, endoscopic and clinical rectal side effects in cervix cancer patients treated with definitive radiotherapy including MRI-based brachytherapy. *Radiother Oncol.* 2009;91:173–180.

MICHAEL A. BOOKMAN

HISTORICAL OVERVIEW OF CANCER CHEMOTHERAPY

We are in the midst of an important transition from conventional cytotoxic agents to new strategies that incorporate molecular-targeted therapeutics. Even with these changes in our treatment paradigm, several conventional cytotoxic agents maintain a central role in the care of women with gynecologic cancers. In that context, a brief review of drug development provides a framework to understand the evolving balance between toxicity, efficacy, and design of treatment regimens.

The first report of a drug-mediated tumor response was noted over 125 years ago using Fowler's solution (arsenic trioxide in potassium bicarbonate) in patients with Hodgkin's disease and leukemia (1). Arsenic compounds had been used for various medicinal purposes for over 2,000 years, and it was not surprising that they were tested in patients with cancer. Cyclic hematologic toxicity was observed following arsenic administration in normal individuals and patients with leukemia (2), establishing a close association between tumor response and host toxicity that still exists today. Cumulative dose-limiting toxicity (arsenic poisoning) was also described following expanded utilization of arsenic in chronic myelogenous leukemia (3), coinciding with a transition toward radiation therapy for the management of leukemia and lymphoma around 1940.

The term *chemotherapy* has been attributed to Paul Ehrlich, a Nobel laureate physician and bacteriologist, who developed *in vivo* rodent models of infection, including the introduction in 1910 of Salvarsan, an organic arsenical originally used to cure syphilis and still used in the management of trypanosomiasis. His early *in vivo* modeling also encouraged the development of inbred transplantable rodent tumors, thereby establishing a paradigm that has been widely adopted for screening new antitumor agents.

Although the topical vesicant properties of sulfur mustard received much attention during World War I, multiple systemic effects, including leukopenia, bone marrow aplasia, and mucosal ulceration, emerged with further study and would ultimately have greater importance. Cancer chemotherapy, in the traditional sense, began with the demonstration that nitrogen mustard had reproducible activity against transplanted lymphoma in mice, prompting clinical trials as early as 1942 (4). However, owing to World War II, much of the research remained classified until 1946. Following the demonstration by Farber in 1948 that aminopterin, an antifolate, could induce temporary remission in childhood leukemia (5), antimetabolites became the next major category of agents to be developed, and were ultimately associated with cures in women with choriocarcinoma (6). Research during the 1940s also included the Nobel Prize-winning observations of Huggins and others (7) regarding the antitumor effect of estrogens in prostatic cancer.

Conventional Cytotoxic Agents

Between 1945 and 1965, many important chemotherapeutic agents, such as actinomycin D, cyclophosphamide, 5-fluorouracil, Vinca alkaloids, and progestogens, were developed and demonstrated to have antitumor activity in clinical trials. Between 1965 and 1975, the pace of new drug discovery and development continued. During this period, cisplatin was shown to have activity in testicular and ovarian tumors, and doxorubicin, bleomycin, etoposide, and tamoxifen entered our clinical arsenal. This was followed by the identification of analogs, such as carboplatin, idarubicin, and vinorelbine, with antitumor activity similar to the parent compound but with a reduction in nonhematologic toxicity. The 1990s and beyond have brought important new agents into clinical practice, including the taxanes (paclitaxel and docetaxel), nontaxane microtubule-binding agents (epothilones), camptothecins (topotecan and irinotecan), nucleoside analogs (gemcitabine and capecitabine), alternative organoplatinums (oxaliplatin, satraplatin), an inhibitor of the proteasome complex (bortezomib), and an agent that binds to the minor groove of DNA, distinct from alkylating agents (trabectedin).

Attention has also been directed at alternative formulations of standard agents, including liposomal or polymer-based encapsulation, protein conjugation, nanoparticles, or lipid solubilization, to modify drug disposition, tumor targeting, and the potential for host toxicity. In addition, conventional agents have been utilized for regional (intraperitoneal) administration, prolonged intravenous infusion, continuous oral administration, high-dose therapy with hematopoietic progenitor cell support, and weekly low-dose therapy, each with the goal of improving the therapeutic ratio, but with a variable impact on host toxicity and clinical outcomes.

With the availability of multiple agents, each with a different molecular target, mechanism of action, pattern of resistance, and spectrum of host toxicity, we have also seen frequent utilization of multidrug combinations, particularly as primary therapy for advanced disease. The use of adjuvant therapy, including concurrent chemoradiation for early-stage disease, has been greatly expanded in selected clinical situations, with the result that a larger proportion of patients are exposed to chemotherapy at an earlier point in the natural history of their disease. Based on a combination of intrinsic and acquired factors, the majority of advanced tumors eventually demonstrate broad resistance to conventional cytotoxic chemotherapy, and there has been renewed interest in novel biologic and immunologic approaches with non-cross-resistant mechanisms. In addition, with improved understanding of the mechanisms associated with drug resistance, newer agents have been developed that may partially reverse resistant phenotypes through blockade of specific pathways, inhibition of DNA repair, or promotion of cellular apoptosis.

Molecular-Targeted Agents

Exploration of the biologic mechanisms associated with tumor invasion, metastasis, and angiogenesis has led to the development of inhibitors directed against metalloproteinases, adhesion molecules, and growth factors (including ligands and receptors). As basic research in tumor biology uncovers specific molecular targets, small molecules have been developed that modulate key pathways associated with tumorigenesis. These include blockade of gene products associated with specific activating (driver) mutations or genetic translocations, alterations in epigenetic factors (such as promoter methylation or histone modification), inhibition of protein tyrosine kinases associated with specific growth-factor receptors and downstream components of signal transduction, blockade of cyclin-dependent kinases and components of the mitotic apparatus associated with cell cycle progression, interference with posttranslational protein modifications (including proteasome function and catabolism), and modification of the host immune response.

In general, these novel targeted agents exhibit toxicities that are distinct from conventional cytotoxic chemotherapy, often sparing proliferative compartments, such as bone marrow and mucosal epithelium. However, there is still the potential for serious toxicity, including drug interactions, alterations in hepatic or renal function, bleeding, thrombosis, pneumonitis, leukoencephalitis, and autoimmunity.

A Contemporary Challenge: Drug Shortages

Trends in drug development within the academic community and pharmaceutical industry have dramatically changed over the last 10 years, and we are now seeing an abundance of new molecular-targeted agents, with only a limited investment in conventional cytotoxics. Many of our most widely utilized standard chemotherapeutic agents have exceeded the period of patent protection and are now produced and distributed as generic compounds. With reductions in insurance reimbursement rates and the rising expense associated with manufacturing and quality control, the profitability of generic medications and the number of generic manufacturing facilities have declined. This has contributed to intermittent and chronic shortages of a number of compounds, including cisplatin, paclitaxel, 5-fluorouracil, leucovorin, bleomycin, polyethylene-glycosylated liposomal doxorubicin, antiemetics, and steroids. Consequences include greater costs to obtain drugs through alternate sources, omission of specific drugs from standard treatment regimens, and closure or delay of important clinical trials. Solutions to this international problem are complex, and it is likely that important shortages will manifest for a number of years to come. Information on current drug shortages can be obtained from the U.S. Food and Drug Administration (FDA) and the American Society of Health-System Pharmacists (ASHSP):

<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>

<http://www.ashp.org/DrugShortages/Current>

TUMOR BIOLOGY IN RELATION TO CHEMOTHERAPY

Tumor Growth and Cellular Kinetics

Many of the principles of modern chemotherapy are derived from knowledge of the growth characteristics of normal and tumor tissues. Each tissue has an innate capacity for growth that is regulated by internal and external factors. The growth

characteristics of tumors differ from normal tissues, and the exploitation of these differences has provided the historical basis for utilization of radiation and chemotherapy. The cellular kinetics of normal tissues also explains many of the toxicities associated with chemotherapy. All normal tissues, particularly during fetal development and variably during adult life, possess the capacity for cellular division and growth.

The *static* population includes well-differentiated cells that arise from pluripotent fetal stem cells and rarely undergo cell division during adult life. Typical of this group are striated muscle, neurons, and nephrons, with oocytes representing a specialized subcategory. Damage to these cells can have long-term consequences and has prompted interest in stem cell biology.

The *expanding* population of normal tissues retains the capacity to grow, but in their adult state, they are normally quiescent. Under stress, especially after injury, a proliferative burst is followed by return to quiescence. Typical of this pattern of growth are the components of liver parenchymal tissue, including hepatocytes, bile duct epithelium, and vascular endothelium.

The *renewing* cell population is in a continuous proliferative state with ongoing cell division balanced by cell loss and terminal differentiation. Typical renewing populations include the bone marrow, epidermis, gastrointestinal epithelium, and spermatocytes.

The patterns of normal cell growth partially explain some of the toxic effects of cytotoxic therapy and why some tissues are commonly spared (8,9). Renewing cell populations with constant turnover are most sensitive to acute injury from conventional chemotherapy or irradiation. This is reflected by the frequent occurrence of dose-limiting bone marrow suppression, mucositis, and azoospermia during cytotoxic drug treatment, with relative sparing of nonproliferative compartments, such as brain, muscle, kidney, bone, and oocytes. However, even nondividing tissues can experience late chronic effects related to DNA damage.

Dysregulated growth of cancer cells occurs because of altered growth-factor signaling and/or disruption of checkpoint mechanisms that exist in normal cells. Despite a capacity for continuous growth, the actual process of cancer cell division is not more rapid than division in normal cells.

Programmed cell death, or apoptosis, has emerged as a major mechanism for regulating growth and development of tissues. Furthermore, certain oncogenes, like *c-myc* and *bcl-2*, and tumor-suppressor genes (antioncogenes), including *Rb* and *TP53*, are central to the regulation of apoptosis. Expression of these genes can alter the sensitivity of cancer cells to treatment with chemotherapy and radiation. For instance, overexpression of functional *bcl-2* and nonfunctional *p53* genes can render tumor cells resistant to a number of chemotherapeutic agents (10), suggesting that efforts to restore apoptotic signaling may improve chemosensitivity.

Emerging data have also described stem-like behavior in subpopulations of ovarian cancer cells, including dormant cells with a low mitotic index that exclude cytotoxic drugs from their cytoplasm and demonstrate increased resistance to chemotherapy (11,12). These stem-like cells are generally enriched during the repopulation that occurs following primary chemotherapy, and targeting of these distinct cell populations has become an important area of research.

Gompertzian Tumor Growth

During initial cell divisions, tumor growth seems to follow an exponential pattern. As the tumor grows larger, the rate of growth slows. This pattern of exponential growth with exponential growth retardation is known as gompertzian growth (Fig. 13.1). As the tumor mass increases, the time required to double the tumor volume also increases. The kinetic explanation for this apparent paradox is illustrated in Figure 13.2, which compares the number of cells in the tumor mass with the number of doublings (13). In accordance with gompertzian kinetics,

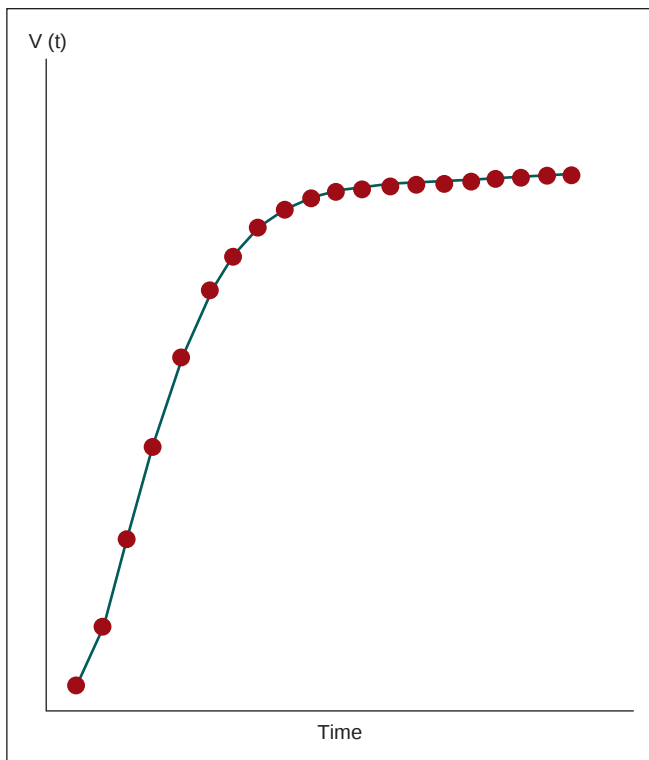


FIGURE 13.1. Hypothetical gompertzian tumor growth curve. Exponential tumor growth with exponential growth retardation. The vertical axis is tumor volume, and the horizontal axis is time.

exponential growth is not strictly maintained throughout the entire growth history. For example, if a skilled radiologist recognized a 0.5-cm tumor on a chest radiograph, or if a clinician palpated a 1-cm tumor mass, we might assume that the tumor had been detected quite early. In reality, the tumor has already undergone at least 30 doublings prior to detection, and this does not include any adjustment for ongoing cell loss.

Limited information exists regarding the actual doubling times of human tumors *in vivo* (14,15), as summarized in Table 13.1. For this historical analysis, tumors were relatively circumscribed and serially measured by radiographic imaging, often as pulmonary metastases. It is clear that embryonal tumors, lymphomas, and mesenchymal tumors have shorter doubling times than adenocarcinomas or squamous cell carcinomas. In addition, metastases generally have faster doubling times than their corresponding primary lesions.

The model also suggests other conclusions of clinical relevance. First, metastatic spread may occur well before obvious evidence of the primary lesion. Second, at later stages of tumor growth, a small number of doublings can produce a marked change in tumor size, with an increased potential for adverse clinical consequences. For instance, a 1-cm mass (at least 30 prior doublings) becomes a 4-cm mass after just 2 more doublings.

Host-Tumor Interactions

Ultimately, dysregulated growth exceeds local resources, and the tumor becomes dependent on the manipulation of host angiogenic pathways for delivery of oxygen, access to nutrients, and removal of waste products. Tumors generally grow without induction of host lymphatics and are characterized by increased interstitial pressures as a consequence of disordered capillary proliferation with leaky vessels and accumulation of extracellular fluid. Together, these factors result in regional hypoxia, acidosis, and necrosis that can limit the effective delivery of chemotherapy and

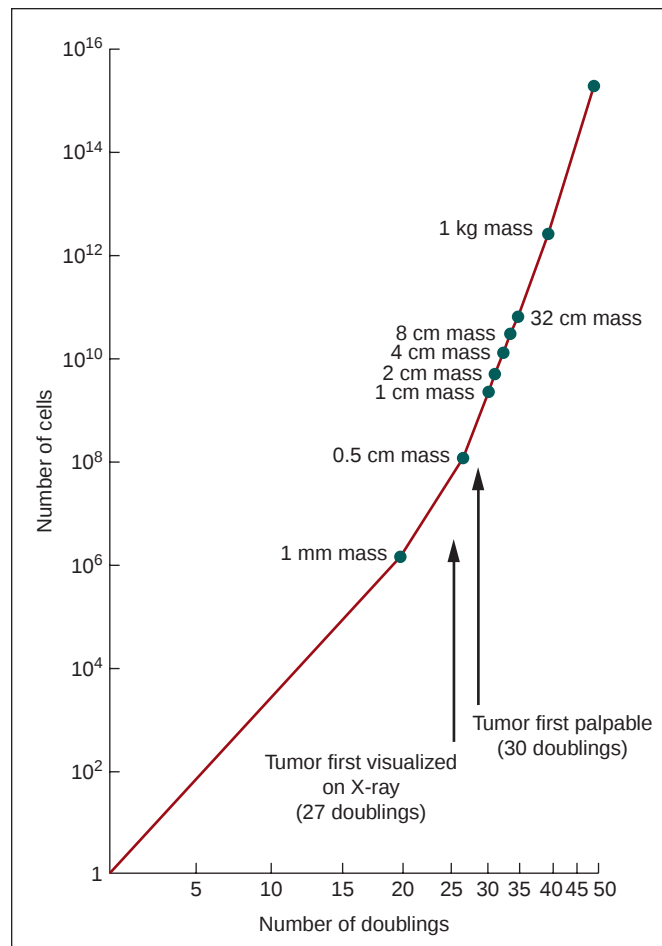


FIGURE 13.2. Theoretical tumor doubling curve assumes exponential tumor growth. The vertical axis is the number of cells, and the horizontal axis is the number of doublings.

may protect viable tumor cells that are more distant from functional capillaries. One of the potential benefits observed with anti-angiogenic therapy has been normalization of tumor vessels with reduced interstitial pressures and improved drug delivery (16).

Cell Cycle Kinetics

The kinetic behavior of individual tumor cells is also important in understanding tumor growth. Figure 13.3 is a schematic view

Table 13.1 Doubling Times of Human Tumors

Tumor Histology	Patients (n)	Doubling Time (Mean $\pm$ 2 SD, Days)
Embryonal tumors (lung metastases)	76	27 $\pm$ 5
Lymphomas	51	29 $\pm$ 6
Malignant mesenchymal tumors	87	41 $\pm$ 7
Squamous-cell carcinomas (lung metastases)	51	58 $\pm$ 9
Squamous-cell carcinomas (primary tumors)	97	82 $\pm$ 14
Adenocarcinomas (lung metastases)	4	83 $\pm$ 12
Adenocarcinomas (primary tumors)	34	166 $\pm$ 48

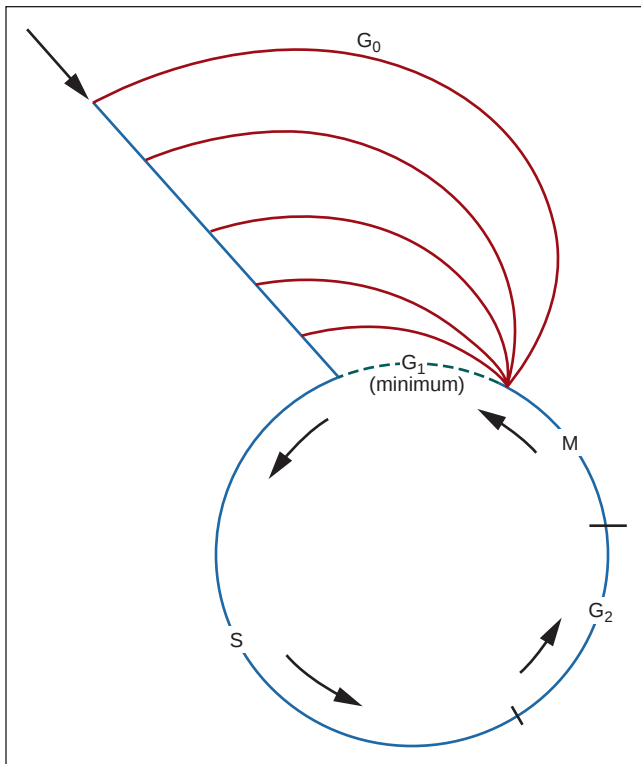


FIGURE 13.3. Phases of the cell cycle, beginning with M (mitosis) and proceeding through G₁ (postmitotic phase), S (DNA synthetic phase), and G₂ (premitotic phase). As G₁ becomes progressively longer, it is known as G₀.

of the cell cycle. Cells can remain in a noncycling postmitotic compartment (G₀) for extended periods of time, but retain the ability to reenter active cycling when triggered by growth factors or other local signals. The point of entry, or first gap phase (G₁), can be of variable length and associated with diverse cellular activities, including protein and RNA synthesis, DNA repair, and cell growth. After passing the first checkpoint in G₁, the cell enters the DNA synthetic phase (S), during which a complete copy of the cellular DNA is created through replication. The second gap phase (G₂) provides another opportunity for checkpoint control before entering active mitosis (M), during which the nuclear membrane disappears and the chromosomes condense (prophase) and align (metaphase) in conjunction with the appearance of the mitotic apparatus, consisting of microtubules, centrioles, and the kinetochore. Mitotic alignment is associated with one final checkpoint prior to actual separation (anaphase), followed by dissolution of the mitotic apparatus (telophase) and creation of daughter cells through cytokinesis. The postmitotic period (G₁) is variable, and cells can further differentiate, enter a noncycling state (G₀), or initiate another cycle.

Cell cycle events have important implications for the patient, tumor, and cancer therapist. Most chemotherapeutic agents disrupt DNA, RNA, or protein synthesis. Rapidly proliferating cells (i.e., short G₁) are most sensitive to chemotherapy, whereas cells that slowly proliferate (i.e., G₀ or long G₁) are generally less sensitive. Nondividing cells, such as the differentiated elements of a mature teratoma, may occupy space and contribute to tumor bulk and symptoms, but are relatively insensitive to chemotherapy.

Cell cycle times may be estimated by performing labeled mitotic curves *in vivo* or *in vitro*, and appear to be relatively similar for many solid tumors, with cycle times ranging from 10 to 31 hours (17). Compared with the tremendous variation in human tumor doubling times, this is a relatively narrow range, suggesting that the primary reason for variations in clinical tumor growth cannot be ascribed to variations in the cell cycle.

Growth fraction and programmed cell death also influence the overall tumor growth rate and response to therapy. The growth fraction is the proportion of tumor cells that are actively cycling. Often, these proliferating cells are located proximal to small blood vessels. Growth fractions in human tumors are quite variable, ranging from 25% to 95%. Although it may seem paradoxical, cell loss is usually very high in human tumors, ranging from 70% to more than 95%, and small changes in cell loss could produce major changes in apparent tumor growth (18).

Log Cell Kill

In principle, the rational use of chemotherapy relies on basic concepts of cellular kinetics, but the translation from preclinical models to solid tumors has been challenging. In animals, the curability of transplanted tumors is inversely proportional to the tumor cell number and size, and timing of treatment initiation. In part, this is the result of important tumor-host interactions, such as the time required to establish a blood supply. However, this is also an illustration of first-order cell-kill kinetics, whereby a constant fraction of exposed cells is killed, rather than a constant number. Using first-order kinetics, a single treatment for a tumor weighing 1 g (approximately 10⁹ cells) might yield 90% cell kill and would decrease the tumor population by only one log, leaving 10⁸ viable cells. Without further treatment, the tumor would grow back at a constant rate, with only a modest delay in lethality. Only when the log cell kill is very large (>99%) and repetitive can chemotherapy be curative or capable of reducing residual disease to less than 10⁴ cells. Certain cancers, such as choriocarcinoma, can be cured with a single application of a single drug. However, majority of cancers are intrinsically less sensitive and require multiagent chemotherapy over multiple cycles to achieve clinical benefit. Distribution of treatment over multiple cycles allows for host recovery while still achieving the cumulative cell kill required for tumor regression and cure.

Cell Cycle Specificity

Chemotherapeutic agents have complex mechanisms of action and can affect tumor cells through multiple pathways. Nevertheless, certain anticancer drugs are known to be proliferation-dependent and cell cycle-specific. Other drugs are cycle nonspecific, and are capable of killing in all phases of the cell cycle, generally without dependence on the proliferative rate. Examples of cycle-nonspecific drugs include alkylating agents, particularly nitrogen mustard, which are effective against a variety of solid tumors, including those with low growth fractions. Cell cycle-specific agents depend on the proliferative fraction of the tumor and phase of the cell cycle. A typical example is hydroxyurea, which inhibits ribonucleotide reductase. Not surprisingly, cell cycle-specific drugs tend to be more effective against tumors with a high proliferative rate and growth fractions. The interaction of specific cytotoxic agents with the cell cycle is summarized in Table 13.2.

PHARMACOLOGIC PRINCIPLES OF CHEMOTHERAPY

General pharmacologic principles should be considered by the physician in selecting individual drugs and managing their administration according to standards of dose and schedule. Many factors may influence the effectiveness and/or toxicity of chemotherapy, including absorption, distribution, metabolism, and excretion, as well as clinical complications, such as renal impairment, malnutrition, or drug-drug interactions.

Table 13.2 Relationship of Chemotherapy Agents to Intracellular Targets and Cell-Cycle Progression

Classification	Cell-Cycle Specificity	Cellular Targets and Mechanisms	Examples
Inhibition of DNA synthesis and repair	G ₁ , S	Inhibition of nucleotide synthesis and metabolism. Inhibition of thymidylate synthase, thymidylate phosphorylase, dihydrofolate reductase, ribonucleotide reductase	Antifolates (methotrexate, pemetrexed), nucleoside analogues (6-mercaptopurine, 5-fluorouracil, cytarabine, fludarabine, gemcitabine), hydroxyurea
	S	Stabilization of DNA-topoisomerase II cleavable complex, DNA intercalation, +/- free radical formation	Anthracyclines (doxorubicin, daunomycin, idarubicin, epirubicin), anthracenediones (mitoxantrone), epipodophyllotoxins (etoposide), actinomycin D
	S	Stabilization of DNA-topoisomerase I cleavable complex	Camptothecins (topotecan, irinotecan)
Alkylating agents and related compounds	G ₁ , G ₂ , S	Direct DNA damage, DNA adduct formation, free radical production, strand breakage	Radiation, platinum compounds (cisplatin, carboplatin, oxaliplatin), bleomycin, mitomycin C, nitrogen mustard, nitrosoureas, ecteinascidin
Antimicrotubule reagents	M	Inhibition of tubulin polymerization	Vinca alkaloids (vinristine, vinblastine, vinorelbine), colchicine
		Promotion of tubulin polymerization	Taxanes (paclitaxel, docetaxel), epothilones
		Kinesin spindle proteins	Investigational agents
Cell cycle agents	G ₁ , S, G ₂ , M	Mitotic checkpoint control, cyclin-dependent kinases (CDK), aurora kinases	Flavopiridol, investigational agents
Signal transduction modulators	G ₀ , G ₁ , S, G ₂	Growth factor sequestration, receptor blockade	Trastuzumab, cetuximab, pertuzumab, aflibercept, bevacizumab
		Inhibition of tyrosine kinase-mediated signal transduction	Erlotinib, gefitinib, dasatinib, imatinib, sorafenib, sunitinib, lapatinib
		Modulation of protein kinase C	Bryostatin, enzastaurin
		Inhibition of hormonal pathways	Tamoxifen, raloxifene, anastrozole, letrozole, fulvestrant, megestrol, mifepristone, flutamide, leuprolide
Gene regulation	NA	Gene regulation by inhibition of promoter methylation, DNA methyltransferase, or histone deacetylase	Azacitidine, suberoylanilide hydroxamic acid (vorinostat, belinostat)
Protein modifications	NA	Posttranslational protein modifications, inhibition of farnesylation	Tipifarnib, bisphosphonates
		Inhibition of the proteasome complex and clearance of ubiquitinated proteins	Bortezomib

Absorption, Distribution, and Transport

Drugs may be given orally, intravenously, intramuscularly, intra-arterially, or intraperitoneally. Selection of the route of administration depends on solubility, requirements for drug activation, local tissue tolerance, feasibility for an individual patient, and optimal tumor drug exposure, which is estimated as the area under the concentration time curve (AUC) for the drug and active metabolites. The ultimate effectiveness of any chemotherapeutic agent depends on optimizing the AUC at critical tumor sites. However, there are no established techniques for noninvasive measurement of active drug concentration at these critical sites, and we are forced to extrapolate tumor drug exposure from preclinical models and plasma concentrations over time. Techniques such as magnetic resonance spectroscopy and positron emission tomography can potentially provide information on drug distribution and tumor metabolism, but they require a substantial investment in technology and specialized reagents.

The increasing utilization of oral chemotherapy and development of oral molecular-targeted agents has renewed interest in bioavailability in the setting of meals and other factors that can modulate local intestinal transport. In most cases, initial dose and schedule guidelines from FDA-approved package inserts reflect data from large phase 3 trials, rather than smaller studies that might examine dietary or drug interactions. For example, the bioavailability of one tyrosine kinase inhibitor could be

increased over threefold in the setting of a high-fat meal (19), but the package insert recommends taking the drug on an empty stomach. With the high cost of chronic medication, it is apparent that there could also be substantial economic implications to these pharmacokinetic observations (20).

Some natural compounds, such as those found in grapefruit juice, can inhibit the cytochrome P450 isozyme CYP3A4 within the intestinal mucosa (21), as well as the drug efflux pump p-glycoprotein. Drugs that are substrates for either of these compounds can be more efficiently absorbed after ingestion of grapefruit juice, due to reduced local metabolism, leading to increased serum levels that may have clinical consequences, including cyclosporine, erythromycin, calcium channel blockers, and benzodiazepines.

The extent of drug binding to serum proteins, as well as physical properties, such as lipid solubility, diffusion, or molecular weight, may have an impact on tumor drug exposure. In addition, some areas of the body, particularly the brain, are actively protected from drug exposure and can serve as pharmacologic tumor sanctuaries, where small numbers of sequestered cancer cells may survive otherwise curative systemic therapy. Larger solid tumors eventually disrupt the blood-brain barrier, restoring access to conventional chemotherapy. In this manner, even drugs that are normally excluded from the central nervous system, such as carboplatin, can achieve dramatic reductions in metastatic disease (22).

In addition to achieving local delivery, most drugs must be internalized within tumor cells to achieve cytotoxicity. Internalization can be accomplished by passive diffusion, active transport, pinocytosis, or receptor-mediated endocytosis. Molecular targeting has also been utilized to enhance the delivery of conventional cytotoxic agents to tumors, based on expression of tumor-associated antigens, or the presence of specific receptors.

Many chemotherapeutic agents are lipophilic and highly protein bound in plasma, particularly to albumin. Commonly used agents with greater than 95% protein binding include cisplatin, paclitaxel, docetaxel, etoposide, and the active metabolite of irinotecan (SN-38). Agents with less protein binding include doxorubicin (75%), topotecan (35%), gemcitabine (10%), carboplatin (<5%), and ifosfamide (<5%). It is generally the unbound “free” drug that mediates toxicity, and any condition associated with variability in protein binding can have an impact on cumulative drug exposure. For example, the toxicity of chemotherapy is frequently accentuated in patients with poor nutritional status, which is associated with reduced protein levels and other metabolic changes (23). Docetaxel offers an interesting example for potential interactions, due to extensive binding to albumin, lipoproteins, and α -acidic glycoprotein (AAG), which has been correlated with changes in drug clearance, prompting further evaluation of optimized dosing (24).

Intraperitoneal Chemotherapy

Although most chemotherapy is administered by the systemic route, there are unique situations in which the regional use of chemotherapy has been studied, with intraperitoneal administration a specific example. If primary tumors or their metastases are anatomically confined to specific organs or particular regions of the body, or if unique pharmacokinetic circumstances exist that favor regional clearance, there is a theoretical rationale for regional chemotherapy. For example, intraarterial drug administration has been studied in cervical cancer, localized recurrence of rectal carcinoma, and head and neck cancer. Local complications are potentially serious, including arterial thrombosis, wound slough, lymphedema, and osteonecrosis caused by the shared arterial blood supply between the tumor and neighboring normal tissues. While high response rates can be achieved in selected patients, larger randomized trials are needed to evaluate overall risks and long-term outcomes.

Intracavitary chemotherapy has been used for tumors confined to the peritoneum, pleura, or pericardium. The rationale for this approach is based on the fact that clearance from a body cavity is delayed compared to the systemic circulation, achieving more prolonged exposure to higher regional concentrations of active agents. This technique has been most extensively studied in ovarian cancer, with evaluation of many agents, including 5-fluorouracil, doxorubicin, cisplatin, carboplatin, cytarabine, melphalan, etoposide, and paclitaxel (25,26). Phase 1–2 studies have uniformly demonstrated a pharmacologic advantage favoring the intraperitoneal compartment but have not documented enhanced drug delivery to actual sites of disease. Of key importance, penetration of peritoneal tumor nodules by passive diffusion is limited by fibrotic adhesions, tumor encapsulation, and high interstitial pressures, as a consequence of intratumoral capillary leak without functional lymphatic drainage. In addition, both cisplatin and carboplatin are rapidly cleared from the peritoneal compartment and recirculate through the blood, limiting the window for direct tumor penetration, exposing the host to systemic toxicity, and raising questions about the clinical importance of the local pharmacokinetic advantage. Based on these observations, it has been postulated that the major role for intracavitary therapy would be in patients with minimal residual disease.

Cisplatin has received the greatest attention for intraperitoneal delivery in ovarian cancer, including the management of

small-volume residual disease at the time of second-look laparotomy (27,28) and primary treatment of small-volume residual disease following initial cytoreductive surgery (29). In view of the risk of systemic nonhematologic toxicity from intraperitoneal cisplatin, there has been renewed interest in the substitution of intraperitoneal carboplatin, which differs in terms of reduced protein binding and increased overall time required for *in situ* activation (via aquation), with the possibility that clinical outcomes could be different between the 2 agents, and this is currently under investigation in a phase 3 randomized trial.

In contrast to cisplatin, paclitaxel is poorly absorbed from the peritoneal compartment, suggesting that patients might benefit from combined intravenous and intraperitoneal administration to optimize tumor drug exposure. As a single agent, intraperitoneal paclitaxel demonstrated a 61% pathology-confirmed complete response rate among 28 assessable patients with initial microscopic disease (30). However, only 1 of 31 patients (3%) with greater than microscopic disease achieved a complete response, emphasizing the limitations of drug access and penetration by diffusion from the peritoneal space.

Intraperitoneal therapy could also have an impact on the tumor-host relationship through alterations in local cytokine production, angiogenic response, or immunoregulation. Hopefully, future studies will evaluate some of these biologic parameters to assist with optimization of therapy. In this regard, it is also possible that intraperitoneal therapy could have clinical benefit regardless of the extent of disease, and current randomized trials have enrolled a subset of patients with suboptimal residual disease following primary cytoreductive surgery.

Biotransformation

Some agents, such as cyclophosphamide, ifosfamide, and capecitabine, are administered as true prodrugs and must undergo irreversible metabolism to the active form, most commonly in the liver, but also in tumor or other host tissues. For many of these agents, intraperitoneal or intraarterial administration would be ineffective, as it would achieve high local concentrations of the native compound, but without an opportunity for bioconversion. Other agents are in reversible equilibrium with reactive intermediates, such as irinotecan and SN-38 (7-ethyl-10-hydroxycamptothecin), with dependencies on local pH and presence of specific enzymes, such as carboxylesterase. Cisplatin and carboplatin both require activation through irreversible aquation to a reactive intermediary before they can initiate DNA adduct formation. Although the final reactive compounds are identical, the rate of aquation and adduct formation is much slower with carboplatin (31), but can be accelerated in the presence of activating nucleophiles, such as glutathione (32), even though the same nucleophiles can partially block cisplatin adduct formation at higher concentrations.

Renal Excretion and Physiologic Age

Drug inactivation, elimination, or excretion can dramatically influence cumulative exposure, which significantly affects antitumor activity and host toxicity. Inactivation and excretion of chemotherapeutic agents occurs primarily through the liver, kidneys, and body tissues, with lesser elimination through the stool. While any impairment of normal liver or kidney function can disturb drug metabolism and excretion, the most common problem encountered in the setting of gynecologic cancer is acute or chronic renal insufficiency due to tumor-mediated obstruction, drug-induced toxicity, advanced age, or preexisting comorbidities.

The use of combination chemotherapy in the elderly patient can pose a number of challenges related to bone marrow reserve and vital organ function (33). Although the risk of hematologic

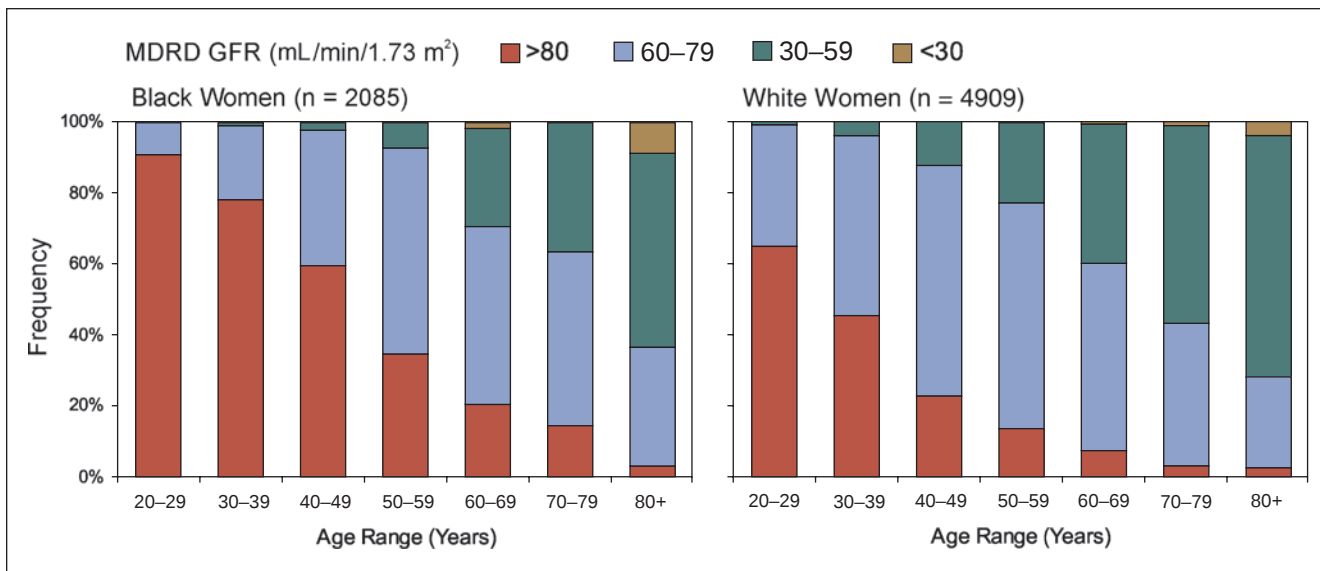


FIGURE 13.4. Distribution of renal function in nondiabetic adults. Weighted distribution of predicted GFR (mL/min/1.73 m²) based on the MDRD formula from the Third National Health and Nutrition Examination Survey (NHANES III).

Source: From Clase CM, Garg AX, Kiberd BA. Prevalence of low glomerular filtration rate in nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol*. 2002;13:1338–1349, with permission.

toxicity is generally increased, overall benefits from active chemotherapy regimens can still be demonstrated, as illustrated by the analysis of data from several breast cancer trials (34). Studies in ovarian cancer have indicated that age is an adverse prognostic factor, but there are insufficient data to determine how the benefits of treatment change with age. In part, this is related to the underutilization of chemotherapy in elderly patients (35) and reduced enrollment of elderly patients on clinical trials (36). From that perspective, it is important to define tolerable and effective treatment regimens that can be safely administered in elderly patients, incorporating supportive care, geriatric assessment, and adjustments for age-related changes in vital organ function (37).

In surveying the general nondiabetic female population, the incidence of moderate renal insufficiency dramatically increases with age, which is of particular relevance to the care of women with gynecologic cancer (38). For example, in the 60 to 69 year age group, over one-third of women have an estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² (Fig. 13.4). In addition, serum creatinine levels can be inappropriately low in women with gynecologic cancer, as a consequence of reduced muscle mass, malnutrition, post-operative recovery, or third-space fluid accumulation. In those settings, any of the standard formulae will overestimate GFR, with potential clinical consequences. Clearly, universal caution in dosing drugs with high renal clearance, especially carboplatin, is required.

Several methods are available to estimate GFR and classify the extent of renal injury based on age, sex, serum creatinine, and other factors (39–41). In general, serum creatinine is the dominant factor, and it remains unclear whether minor differences between formulae might have meaningful and/or consistent clinical consequences with regard to drug dosing. In most cases, it is sufficient to estimate GFR rather than obtain a precise measurement. However, all of these formulae are based on stable normalized biologic parameters and are less useful in the setting of dynamic changes following acute renal injury, or other nonrenal fluctuations in serum creatinine.

While urine collection for estimation of creatinine clearance (based on measured creatinine in the urine over a period of time) might appear to provide a better estimate of GFR, it is also subject to clinical variability, due to different rates of creatinine tubular secretion. Utilization of direct techniques to measure actual GFR, such as clearance of ⁵¹Cr-ethylenediamine tetraacetic acid (EDTA)

or inulin, remains the standard for comparison with indirect estimates, but these assays are rarely used in clinical practice due to cost and complexity.

Staging of chronic renal disease has been used to reflect overall severity and guide management decisions, including dose modifications. The most commonly used staging system is from the National Kidney Foundation (42). The formula derived from the Modification of Diet in Renal Disease (MDRD) study has been incorporated in standardized laboratory reports (39). However, the MDRD has not generally been validated for actual drug dosing. As a result, the Cockcroft-Gault (40) and Jelliffe (41) formulae are more commonly used for drug dose calculation (Table 13.3).

The situation has become further complicated by an international effort to recalibrate creatinine standards based on isotope dilution mass spectrometry (IDMS). These new standards have now been adopted by all major vendors and commercial laboratories. The relationship between old (pre-IDMS) and new (IDMS) creatinine values within the same patient is variable, depending on the specific vendor and equipment. In general, IDMS standards will lower the serum creatinine value by approximately 12%. Using the IDMS creatinine value will therefore increase the estimated GFR, and could lead to higher doses of chemotherapy, particularly carboplatin, with an impact on hematologic

Table 13.3 Commonly Utilized Formulae to Estimate Creatinine Clearance

Formula Name	Estimation of Creatinine Clearance (CrCl)
Cockcroft-Gault formula (40)	CrCl (mL/min) = (140 – age) × weight (kg) × (0.85 if female)/serum Cr (mg/dL) × 72
Jelliffe formula (41)	CrCl (mL/min) = [98 – [0.8 × (age – 20)]] × (0.9 if female)/serum Cr (mg/dL)
MDRD formula (39)	GFR (mL/min/1.73 m ²) = 170 × [serum Cr (mg/dL)] ^{–0.999} × (age) ^{–0.176} × (0.762 if female) × (1.180 if African American) × [SUN (mg/dL)] ^{–0.170} × [Alb (g/dL)] ^{+0.318}

Alb, serum albumin concentration; Cr, creatinine; GFR, glomerular filtration rate; MDRD formula, the Modification of Diet in Renal Disease study equation; SUN, serum urea nitrogen concentration.

toxicity (43). These changes prompted a review by the FDA, the National Cancer Institute (NCI), and the national cooperative groups, followed by distribution of safe initial dose recommendations in 2010 for patients enrolled in clinical trials, as modified below, incorporating recommendations from GOG (44):

- Safe initial dosing of carboplatin is based on using the Calvert formula with measured GFR, although estimated GFR is routinely employed in clinical practice.

$$\text{Carboplatin Total Dose (mg)} = \text{Target AUC (mg} \cdot \text{min/mL)} \cdot [\text{GFR} + 25] (\text{mL/min})$$

- Estimated GFR should be determined using a standard formula. The Gynecologic Oncology Group (GOG) currently recommends using the Cockcroft-Gault equation, although this formula was developed and validated for drug dosing using pre-IDMS creatinine values.

$$\text{Creatinine Clearance (mL / min)}$$

$$= \frac{[140 - \text{Age (years)}] \cdot \text{Weight (kg)} \cdot 0.85 (\text{for women})}{72 \cdot \text{Serum Creatinine (mg / dL)}}$$

- Actual body weight should be used for estimated GFR (Cockcroft–Gault) for patients with a body mass index (BMI) < 25. For obese patients (BMI > 25), GOG recommends using an adjusted weight.

$$\text{Adjusted Weight (kg)} = (\text{Actual Weight} - \text{Ideal Weight}) \cdot 0.40 + \text{Ideal Weight}$$

$$\text{Ideal Weight (kg)} = ([\text{Height in cm}/2.54] - 60) \cdot 2.3 + 45.5$$

- Due to abnormally low serum creatinine values, the estimated GFR can be nonphysiologic (falsely elevated) and should not exceed a maximum value of 125 mL/min. In addition, serum creatinine values for estimation of GFR should not be lower than a minimum value of 0.6 mg/dL (NCI) or 0.7 mg/dL (GOG). Using a maximum GFR of 125, the Calvert formula yields a maximum carboplatin dose of 900 mg at AUC = 6, or 750 mg at AUC = 5, or 600 mg at AUC = 4.

- After determination of a safe starting dose, subsequent modifications are based primarily on hematologic toxicity, or, in the event of a change in renal function, recalculation.

Specific guidelines exist for modifying drug doses for patients with renal impairment (45), with special attention to a growing list of agents with renal-dominant clearance (Table 13.4). Dosing parameters for patients on dialysis receiving individual drugs, such as cisplatin (46) and carboplatin (47), are also available. However, owing to the rapid introduction of new agents, clinicians are urged to consult updated prescribing information and online database resources.

Metabolism and Pharmacogenomics

Drugs can be metabolized in the liver, in other normal host tissues, or within tumors. Aside from those agents with extensive renal clearance, hepatic metabolism usually predominates. A large number of microsomal and cytoplasmic enzymes contribute to this process, with associated genetic polymorphisms that can account for individual variability in clearance, efficacy, resistance, and the risk of hepatic or nonhepatic toxicity. Techniques for screening and identification of pharmacogenomic elements are expanding, with potential implications for individualized drug selection, dosing, prediction of efficacy, and risk of toxicity.

Phase I reactions are characterized by attachment of polar groups to lipophilic compounds to facilitate water solubility, primarily through the cytochrome P450 superfamily of mixed function oxidases (CYP). Over 50 individual proteins have been

Table 13.4 Modifications in the Setting of Renal and Hepatic Dysfunction

Agents that Should Be Considered for Modification in the Presence of Moderate Renal Dysfunction	Agents that Generally Do Not Require Modification in the Presence of Moderate Renal Dysfunction	Agents that Should Be Considered for Modification in the Presence of Hepatic Dysfunction
Actinomycin D	Anastrozole	Docetaxel
Bleomycin	Bevacizumab	Doxorubicin
Capecitabine	Cabazitaxel	Epirubicin
Carboplatin	Cetuximab	Mitoxantrone
Cisplatin ^a	Docetaxel	NAB-paclitaxel
Cyclophosphamide	Doxorubicin	Paclitaxel
Etoposide	Epirubicin	PEG-liposomal doxorubicin
Hydroxyurea	Erlotinib	Vinblastine
Ifosfamide	Fluorouracil	Vincristine
Melphalan	Gefitinib	Vinorelbine
Methotrexate	Gemcitabine	
Pemetrexed	Irinotecan	
Topotecan	Letrozole	
	Leucovorin	
	Leuprorelin	
	Megestrol	
	Mitomycin	
	NAB-paclitaxel	
	Oxaliplatin	
	Paclitaxel	
	PEG-liposomal doxorubicin	
	Tamoxifen	
	Temozolomide	
	Trastuzumab	
	Vinblastine	
	Vincristine	
	Vinorelbine	

^aCan be administered at full doses in anephric patients receiving hemodialysis.

grouped into 18 families, with 3 families (CYP1, CYP2, and CYP3) that have evolved to handle the majority of exogenous agents. In particular, CYP3A4 catalyzes the biotransformation of more than half of our commonly used drugs (48), setting the stage for numerous drug-drug interactions.

Phase II reactions further increase water solubility by conjugation to a large polar entity, such as glucuronic acid, sulfate, acetate, glycine, glutathione, or a methyl group. These reactions result in the formation of nontoxic substances that can be excreted in the bile or urine. The predominant enzymes include UDP-glucuronyl transferases (UGT1 and UGT2), sulfotransferases, and glutathione S-transferases.

Phase III reactions directly promote biliary excretion mediated by transporter proteins, which are members of the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily.

With awareness of polymorphisms in key enzymes, it has been possible to identify individuals with a dramatic increased risk of toxicity. For example, dihydropyrimidine dehydrogenase (DPD) controls the rate-limiting step in fluoropyrimidine metabolism, and approximately 10 variant DPD alleles occur with sufficient frequency to merit consideration of screening, as patients can be at risk for life-threatening mucosal injury and bone marrow suppression after receiving a single standard dose of 5-fluorouracil. While methods are available for screening, the potential reduction in risk needs to be balanced against the costs of a widespread screening program (49). Fluorouracil, or the pro-drug capecitabine, is not used in the primary treatment of gynecologic cancers, with the exception of some chemoradiation strategies and occasional palliative management of recurrent disease.

Uridine diphospho-glucuronosyl-transferase 1A1 (UGT1A1) is responsible for glucuronidation of bilirubin and a number of drug metabolites, most notably SN-38, the major active metabolite of irinotecan. As such, patients with a deficiency in UGT1A1 are at increased risk for life-threatening diarrhea and bone marrow suppression after receiving irinotecan and potentially other camptothecin derivatives with SN-38 metabolites (50). The UGT1A1*28 promoter mutation has been studied most extensively. However, mutations in the coding region can also occur, particularly in Asian populations, and may predict for efficacy in addition to toxicity (51). Gilbert's syndrome is associated with a mild unconjugated hyperbilirubinemia and reduced activity of UGT1A1 that is also associated with an increased risk of toxicity in both homozygous and heterozygous patients (52).

The ABC family of drug efflux proteins is also involved in biliary transport of camptothecins. Polymorphisms of ABCB1, also known as p-glycoprotein or multidrug resistance protein 1 (MDR-1) as well as ABCC2, also known as canalicular multi-specific organic anion transporter (cMOAT) or MRP2, appear to have an impact on the clinical efficacy and toxicity (neutropenia and diarrhea) associated with irinotecan therapy in Asian patients (53).

Dose modifications should be considered for patients with liver disease (54), particularly for paclitaxel, docetaxel, nanoparticle albumin-bound paclitaxel (55), doxorubicin, and the Vinca alkaloids (vincristine, vinblastine, and vinorelbine), which are primarily metabolized in the liver and/or excreted in the bile. Excessive toxicity may occur with doses that would ordinarily be acceptable, and guidelines for treating patients with impaired liver function should be consulted. However, variability in nonhepatic clearance, compensatory host adaptations, and interactions with other drugs, make these recommendations less reliable than those provided for patients with renal dysfunction. For example, dose reduction of etoposide in the setting of biliary obstruction remains controversial and may not be required (56).

Drug Interactions

During routine care, patients may receive a variety of drugs, including antiemetics, antihistamines (H_1 and H_2), steroids, nonsteroidal anti-inflammatory agents, anticoagulants, narcotics, and anti-infective agents. In addition, older patients are frequently receiving medication to manage underlying comorbidities, such as diabetes, hypertension, and elevated cholesterol. In view of the number and diversity of medications in common use, it is somewhat surprising that most interactions with cytotoxic chemotherapy appear to be of little consequence. However, prospective studies of chemotherapy administration in noncancer volunteers are impractical, and many potential interactions have not been fully explored. In fact, patients are likely to be excluded from enrollment on clinical trials on the basis of concomitant medications, rather than prospectively collecting valuable data to document safety or the need for treatment modifications. In clinical

practice, the occurrence of excessive hematologic and/or nonhematologic toxicity in an individual patient is usually attributed directly to the chemotherapy and managed with treatment modifications, rather than ascribed to a potential drug interaction.

When they occur, interactions can be critical, and some of the more important drug interactions are listed in Table 13.5. Particular attention should be placed on drugs that could alter renal function, such as aminoglycoside antibiotics, nonsteroidal anti-inflammatory agents, and diuretics, in patients with reduced fluid intake. Typical of *in vivo* interactions relevant in gynecologic cancer chemotherapy are the displacement of methotrexate from its transport protein by aspirin or sulfonamides, suppression of pseudocholinesterase by alkylating agents with increased apnea duration during succinylcholine-assisted general anesthesia, impairment of doxorubicin clearance by preadministration of paclitaxel, and impairment of paclitaxel clearance by preadministration of cisplatin.

Increased attention has been focused on drug metabolism and potential interactions with CYP isozymes, particularly CYP3A4, which has been linked to the metabolism of nearly half of all pharmaceutical agents (48). These interactions are guided by several common principles. Drugs that are *substrates* for the same isozyme may competitively inhibit metabolism, but these interactions are usually not of clinical consequence. Drugs that *directly inhibit* CYP isozymes without being a substrate for that isozyme are more likely to have clinical consequences. In this regard, itraconazole, ketoconazole, and fluconazole can inhibit CYP3A4 at low concentrations, and erythromycin can inhibit CYP3A4 via covalent binding and inactivation. Other drugs act as *inducers* of CYP isozymes by increasing gene expression or protein levels, such as glucocorticoids, barbiturates, and rifampin, which can increase the net activity of CYP3A4, resulting in decreased concentrations of susceptible compounds. In addition, many drugs that interact with CYP3A4 are natural products and may also interact with ABC family drug efflux pumps, including MDR-1. Among the anticancer agents that are substrates for CYP3A4 are cyclophosphamide, ifosfamide, docetaxel, etoposide, paclitaxel (also CYP2C8), docetaxel, vincristine, vinblastine, tamoxifen, and gefitinib (57). CYP2C9 and CYP2D6 are inhibited by imatinib, and doxorubicin can inhibit CYP2D6. Cyclosporine and verapamil can increase concentrations of doxorubicin and etoposide, probably through blockade of the P170 drug efflux pump (Table 13.6).

Owing to the diversity and rapid adoption of new compounds, information regarding drug interactions is best obtained from online databases, such as the Medical Letter (<http://www.medicalletter.com>), Micromedex (<http://www.micromedex.com>), the Drug Interaction Database from the University of Washington (<http://www.druginteractioninfo.org>), Medscape (<http://reference.medscape.com/drug-interactionchecker>), the package insert, or directly from the manufacturer.

DRUG RESISTANCE AND TUMOR CELL HETEROGENEITY

The curative potential of chemotherapy is limited by the emergence of drug resistance, which can be either intrinsic or acquired, and may involve one drug or multiple agents (pleiotropic resistance). Of interest, tumors with intrinsic or primary drug resistance to natural products often arise from duct cells or cells lining excretory organs (58). These cells, which normally detoxify, transport, and excrete a wide variety of toxic compounds, may retain these normal functions after transformation, manifesting as chemoresistance.

Intrinsic drug resistance is inferred based on clonal survival of tumor populations after initial chemotherapy exposure. Solid tumors are thought to consist of a mixture of clonal variants

Table 13.5 Physiologic and Pharmacologic Interactions in Cancer Chemotherapy

Physiologic Condition	Causation	Impact and Examples
Renal insufficiency	Obstruction, chronic kidney disease, hypovolemia, hypotension, nonsteroidals, nephrotoxins (aminoglycosides, cisplatin)	Decreased clearance of methotrexate, carboplatin, and other agents
Hepatobiliary dysfunction	Biliary obstruction, hepatitis, cirrhosis	Decreased clearance of doxorubicin, mitoxantrone, vincristine, vinblastine, etoposide, paclitaxel, docetaxel
	Gilbert's syndrome, impaired glucuronidation and polymorphisms (UGTA1A)	Increased exposure to SN-38 (from irinotecan)
	Decreased microsomal activity	Impaired activation of cyclophosphamide and ifosfamide
Reduced protein binding	Carrier displacement (sulfonamide, salicylates, phenytoin) Reduced carrier proteins (malnutrition)	Increased toxicity, higher free drug levels (methotrexate) Increased toxicity, higher free drug levels (cisplatin, paclitaxel, docetaxel, etoposide, SN-38)
Altered intestinal absorption	Oral antibiotics (neomycin)	Decreased absorption of methotrexate
	High-fat meal	Increased bioavailability of lapatinib Decreased bioavailability of capecitabine
	Grapefruit juice (intestinal CYP3A4 inhibition)	Increased bioavailability (cyclosporine, erythromycin, benzodiazepines)
Decreased metabolism	Caused by allopurinol Dihydropyrimidine dehydrogenase (DPD) deficiency	Delayed clearance of 6-mercaptopurine Lethal toxicity from 5-fluorouracil
Cholinesterase inhibition	Caused by cyclophosphamide	Decreased clearance of succinylcholine
Monoamine oxidase inhibition	Caused by procarbazine	Neurotoxicity and seizures (tricyclic antidepressants and phenothiazines)
MDR-1 competition	Associated with natural products and other substrates, including verapamil, cyclosporine, tamoxifen	Decreased efflux and increased toxicity from natural products (doxorubicin, vincristine, paclitaxel, docetaxel)
CYP2C9 Inhibition	Caused by capecitabine	Increased AUC of warfarin
CYP3A4 Induction	Caused by glucocorticoids, barbiturates, rifampin	Increased activation of cyclophosphamide
Inhibition	Caused by ketoconazole, itraconazole, fluconazole, erythromycin	Decreased metabolism of substrates (potentially significant)
Substrate competition	Caused by cyclophosphamide, ifosfamide, paclitaxel, docetaxel, etoposide, vincristine, vinblastine, tamoxifen, gefitinib	Decreased metabolism of other substrates (usually not clinically significant)

with different pre-existing mutations and patterns of resistance. Following repetitive cycles of chemotherapy, a process of clonal selection can occur, enriching for resistant populations, even while there could be a reduction in clinical tumor volume associated with elimination of more sensitive tumor elements.

Acquired resistance develops from cumulative somatic mutations, regulation of gene expression (including epigenetic processes), or other phenotypic alterations, over a period of time. From a clinical perspective, the end result of this process is indistinguishable from acquired resistance. However, acquired resistance is more likely to have a reversible component that could influence the timing and selection of subsequent chemotherapy. The most well-documented specific example is amplification of the dihydrofolate reductase (*DHFR*) gene, which is associated with acquired resistance to methotrexate (59). *DHFR* gene amplification is not generally observed prior to methotrexate exposure and can be reversed in the absence of drug exposure.

From the perspective of gynecologic oncology, there are 2 major patterns of drug resistance that emerge with continued treatment. The first is broad-based multidrug, or pleiotropic, drug resistance that has been associated with overexpression of *MDR 1* (P 170 glycoprotein) and/or other membrane-associated transport proteins (60,61). This multidrug resistance phenotype has maximal impact on natural products and their analogs, including the anthracyclines, Vinca alkaloids, and taxanes. The second is

resistance to alkylating agents, especially platinum compounds, mediated through a completely different set of cellular mechanisms, including reduced cellular uptake due to loss of membrane transport proteins, increased detoxification of reactive intermediates by glutathione production, increased damage tolerance due to defective detection and/or apoptotic signaling, and expanded capacity for DNA repair (62).

Multidrug Resistance

After exposure to a potential *MDR 1* substrate, tumor cells will develop cross resistance to a variety of structurally and functionally unrelated agents derived from natural products. This pleiotropic resistance is associated with increased drug efflux and a net lowering of intracellular drug concentration. Although relatively uncommon in newly diagnosed ovarian cancer (63,64), with increased utilization of natural products, including taxanes, etoposide, and liposomal doxorubicin, this pattern of resistance generally emerges over a period of time.

Other chemotherapeutic agents, including nucleoside analogues, are not substrates for *MDR 1* and remain unaffected by increased expression. In some resistant cell lines, a “collateral sensitivity” to gemcitabine has been observed, characterized by increased uptake and phosphorylation, which could be reversed

Table 13.6 Specific Mechanisms of Tumor Drug Resistance

Resistance Mechanism	Examples	Specific Cellular Target or Effects
<i>Impaired activation</i>	5-Fluorouracil	Reduced levels of thymidylate synthase, thymidylate phosphorylase, or dihydropyrimidine dehydrogenase
	Methotrexate	Reduced intracellular polyglutamation
	Doxorubicin	Low P450 enzymes
	Cyclophosphamide, ifosfamide	Decreased microsomal transformation
	Gemcitabine	Decreased deoxycytidine kinase
<i>Increased drug efflux</i>	Natural products	Increased <i>MDR 1</i> (P 170)
	Topotecan, mitoxantrone	Increased <i>BCRP</i> (ABCG2)
<i>Increased drug inactivation</i>	Alkylating agents, platinum	Elevated glutathione and other cellular thiols
<i>Accelerated DNA repair</i>	Alkylating agents, platinum, radiation	Induction of DNA repair enzymes
<i>Increased damage tolerance</i>	Alkylating agents, platinum, radiation	Loss of DNA mismatch repair
<i>Transport defects</i>	Melphalan	Reduced carrier-mediated uptake
	Gemcitabine	Decreased nucleoside transporter
	Platinum	Decreased copper transporter-1
<i>Target alterations</i>	Methotrexate	<i>DHFR</i> gene amplification
	Paclitaxel, docetaxel	Increased tubulin- $\beta 3$ isoforms or mutations
	Hydroxyurea, gemcitabine	Decreased ribonucleotide reductase
	Glucocorticoids	Decreased receptor binding
	Camptothecins	Decreased topoisomerase-I
	Anthracyclines, etoposide	Decreased topoisomerase-II

by verapamil, an inhibitor of *MDR 1* (65). This has not yet been validated in the clinical setting.

Other energy-dependent transporter proteins have been identified in resistant cell lines that may not overexpress *MDR 1*. These include the multidrug resistance-associated protein (MRP), which is representative of a family of cMOAT proteins (66). Similar to *MDR 1*, these proteins include multiple transmembrane domains but appear to have more broad tissue distribution and greater association with intracellular membrane-bound compartments. Another member of the family with relevance to gynecologic cancer is the breast cancer resistance protein (BCRP) or ABC protein G2 (ABCG2) that dimerizes to form a membrane-associated energy-dependent drug efflux pump responsible for atypical multidrug resistance following exposure to mitoxantrone or camptothecins, including topotecan. Overexpression of BCRP has been documented in ovarian cancer cells resistant to topotecan (67).

Platinum Resistance and DNA Repair

Although a number of DNA alkylating agents and radiation are used in the treatment of gynecologic cancer, platinum derivatives are the most important compounds in clinical practice. The dramatic success of platinum-based therapy is nearly overshadowed by the emergence of platinum resistance, and this observation has stimulated a substantial body of research over the last 35 years.

As a highly polar compound, cisplatin enters cells relatively slowly, and uptake can be influenced by local cation concentrations, pH, and the presence of reducing agents, prompting a search for membrane transporter proteins that could supplement passive diffusion. The major transporter involved in copper homeostasis, copper transporter-1 (CTR1), has now been shown to have a substantial role in cisplatin influx (68). Downregulation of CTR1 expression can reduce cisplatin uptake, leading to one mechanism of resistance. Targeted methods to safely and selectively increase platinum uptake in tumors are not yet available. However, it has been observed that ovarian cancer cell lines can rapidly downregulate membrane CTR1 after cisplatin exposure, followed by proteasomal-mediated degradation (69), suggesting that sequence and schedule of drug administration could have an impact on platinum uptake. JM-118, or cis-ammine-dichloro-cyclohexylamine-platinum (II), retains activity in tumor cells that have lost CTR1 (70). In that context, it is interesting to note that satraplatin (JM-216), an orally active carboplatin analogue that undergoes biotransformation to JM-118, has demonstrated promising activity in the treatment of prostate cancer (71).

Human ovarian cell lines resistant to alkylating agents, cisplatin, and irradiation contain elevated levels of cellular glutathione (GSH). Using resistant cell lines, it has been possible to demonstrate a restoration of drug sensitivity by exposure to the synthetic amino acid buthionine sulfoximine (BSO), which inhibits gamma-glutamylcysteine synthetase, causing GSH depletion (72). The exact mechanism by which GSH and other thiol compounds modulate cytotoxicity is unknown, although they can interfere with the formation of DNA-platinum adducts (73). There is also evidence of increased drug metabolism through GSH-linked transferases, which can vary for specific platinum compounds (74), and which may also contribute to cisplatin-mediated nephrotoxicity (75). Although clinical trials of BSO with melphalan have documented an 80% to greater than 90% reduction in tumor-associated GSH levels (76,77), this approach has not yet been demonstrated to improve the outcomes of platinum-based therapy.

In view of the prominent role of thiols in mediating a subset of platinum resistance, a sterically hindered platinum complex, picoplatin (JM473, ZD0473), was developed with the expectation that it would favor interacting with DNA rather than glutathione or metallothioneins (78). A phase 2 trial in recurrent ovarian cancer documented response rates of 8.4% in platinum-resistant disease and 32.4% in platinum-sensitive disease, similar to expectations with cisplatin or carboplatin (79). Of interest, there was no documented peripheral neuropathy or nephrotoxicity even in this group of patients with prior platinum therapy, implicating thiol reactions in the generation of these nonhematologic toxicities.

Enhanced capacity for DNA damage tolerance and repair can play a role in drug resistance to alkylating agents and cisplatin. Human ovarian cancer cell lines resistant to melphalan demonstrate increased ability to repair DNA, and this phenotype can be reversed by aphidicolin, a potent inhibitor of α and β DNA polymerase (80). Increased damage tolerance is another mechanism that contributes to resistance and is perhaps best illustrated by the mismatch repair system. Errors in DNA replication following platinum adduct formation can be detected by the postreplicative DNA mismatch repair system, which contains several well-characterized genes, including *MLH1* and *MSH2*.

Of note, cellular attempts to repair platinum alkylation by this mechanism are not successful, as the repair is directed at the nascent daughter DNA strand rather than the platinated parental strand. Eventually, abortive attempts at repair are associated with apoptotic cell death. Thus, loss of mismatch repair can actually promote cell survival by ignoring DNA damage in noncritical areas of the genome and has emerged as another mechanism of drug resistance.

Loss of *MLH1* or other mismatch repair genes is not uncommon in ovarian cancer and appears to increase after exposure to carboplatin or cisplatin (81). In addition, functional loss of *MLH1* activity in patients with ovarian cancer can also occur through hypermethylation-mediated silencing of the *MLH1* gene following exposure to platinum and has been correlated with poor survival (82). Preclinical models with platinum-resistant cell lines have shown improved treatment outcomes following exposure to 2'-deoxy-5-azacytidine (decitabine), which blocks DNA methylation, unmasking expression of *MLH1* (83). However, this can also result in increased hematologic toxicity, and novel strategies will be required to enhance the overall therapeutic benefit.

Oxaliplatin is one of several diaminocyclohexane (DACH) platinum derivatives that forms platinum adducts that differ in three-dimensional structure from the more established diamine compounds, such as cisplatin and carboplatin (84). As a consequence of these structural differences, oxaliplatin adducts are not detected by the mismatch repair system (85), and there was hope that oxaliplatin would retain clinical activity in patients with platinum-resistant tumors. However, in phase 2 studies, the response rate among ovarian cancer patients with less than a 6-month platinum-free interval was less than 7% (86,87).

Nucleotide excision repair (NER) is the primary mechanism to remove platinum-DNA adducts from genomic DNA. Excision repair cross-complementing 1 (*ERCC1*) is a critical gene on the NER pathway. Platinum resistance has been linked to *ERCC1* mRNA levels in tumors, including ovarian cancer (88). In lung cancer, immunohistochemical evaluation of *ERCC1* levels was also predictive for survival following cisplatin-based adjuvant therapy, with improved survival in patients with *ERCC1*-negative tumors (89). However, *ERCC1* may also have prognostic significance independent of chemotherapy, as patients assigned to observation with *ERCC1*-positive tumors had better survival compared to those with *ERCC1*-negative tumors (90). Randomized trials to prospectively assign chemotherapy for lung cancer based on *ERCC1* status have suggested that higher response rates can be achieved, but without a difference in progression-free or overall survival (91). The role of *ERCC1* as a prognostic or selective factor in women with ovarian cancer seems less clear (92).

The association between ovarian cancer risk and mutations in *BRCA1* and *BRCA2* sparked interest in DNA repair after it became apparent that patients with *BRCA1/2*-associated tumors had improved outcomes compared with patients with high-grade serous tumors without loss of *BRCA1/2* (93). These patients have tumors that are also more likely to respond to multiple lines of therapy with agents that target DNA, such as cisplatin, carboplatin, and doxorubicin, and this can be explained by the association of *BRCA1/2* with high-fidelity DNA repair pathways.

DNA repair can be targeted with inhibitors of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP), particularly in tumors with loss of *BRCA1/2* or other evidence of homologous recombination deficiency (HRD). The importance of these pathways is illustrated by the finding that tumors can develop a secondary mutation that partially restores *BRCA* function following exposure to PARP inhibitors, essentially reversing the drug sensitivity phenotype.

There are at least 2 distinct strategies for incorporation of PARP inhibitors in cancer chemotherapy. First, concurrent combinations of PARP inhibitors with platinum-based chemotherapy will increase platinum-mediated cytotoxicity, regardless of defects in homologous recombination repair. However, this

is not tumor specific, and has been associated with increased hematologic toxicity, requiring adjustments in dose and schedule to safely administer multiple cycles of chemotherapy. Second, PARP inhibitors can be administered as a single agent following completion of primary therapy, creating a synthetic lethal paradigm for tumors with HRD. In this regard, it is important to note that these defects are not simply limited to inherited mutations of *BRCA1* or *BRCA2*, but include somatic (intra-tumoral) mutations, methylation status, and mutations in other genes associated with DNA repair, exceeding 50% overall incidence in patients with high-grade serous or endometrioid histology, as reflected in data from The Cancer Genome Atlas project (94).

Clearly, in spite of considerable wide-ranging research, platinum resistance remains a major challenge in the treatment of gynecologic cancers, particularly high-grade serous ovarian cancer.

Taxane Resistance

In view of the prominent role of taxanes in the primary treatment of gynecologic cancers, a number of laboratories have explored pathways associated with taxane resistance. Overexpression of the drug efflux protein MDR-1 has been consistently associated with resistance to paclitaxel in cell lines in retrospective analysis of clinical outcomes (95). However, prospective clinical trials using an inhibitor of MDR-1 with paclitaxel, or with a combination of paclitaxel and carboplatin, failed to improve clinical outcomes (96,97).

Mutations in the β -tubulin subunit have been associated with paclitaxel resistance in preclinical models, but this does not appear to be a common clinical mechanism (98,99). Alteration in the proportion of tubulin- $\beta 3$ isoforms has been implicated in resistance to paclitaxel, while retaining sensitivity to nontaxane antitubulin agents, such as the epothilones (100). Expression of tubulin- $\beta 3$ has also been linked to cell survival pathways, with a potential impact on clinical outcomes (101).

Neither of these molecular mechanisms adequately explains the clinical behavior associated with paclitaxel therapy in women with ovarian cancer. For example, patients can still respond to paclitaxel on a weekly schedule after progressing within 6 months of receiving three-weekly paclitaxel as a component of primary therapy (102). Preclinical studies are examining a number of diverse pathways, including angiogenesis, cytokine networks, and microtubule-associated proteins (MAPs).

Other Mechanisms of Agent-Specific Resistance

A number of specific alterations have been identified in the setting of individual drugs (Table 13.6). For example, *DHFR* gene amplification was demonstrated in a patient with methotrexate-resistant ovarian cancer who had localized *DHFR* gene copies on an abnormally staining region of chromosome 4q (103). Methotrexate resistance has also been associated with defects in polyglutamation, limiting intracellular methotrexate accumulation (104). The action of nucleoside analogs, such as gemcitabine (2,2-difluorodeoxycytidine), is dependent on active membrane transport for uptake, which is followed by double phosphorylation and potential incorporation in DNA. This complex process offers several opportunities for development of resistance, such as decreased activity of specific nucleoside transport proteins or reduced phosphorylation by depletion of deoxycytidine kinase (105). In addition, the main enzymatic target of phosphorylated gemcitabine, the M2 subunit of ribonucleotide reductase, can undergo gene amplification in resistant cell lines (106) similar to the primary mechanism of resistance to hydroxyurea, an inhibitor of ribonucleotide reductase. Of interest, sensitivity to gemcitabine can actually be increased severalfold by prior exposure

to flavopiridol, an inhibitor of cyclin-dependent kinase activity, which has been shown to accelerate catabolism of the M2 subunit protein through the proteasome complex (107). Increased levels of target gene expression or protein, including thymidylate synthase, thymidylate phosphorylase, and dihydropyrimidine dehydrogenase, have also been associated with resistance to 5-fluorouracil in colon cancer, and have been correlated with clinical outcomes following 5-fluorouracil treatment (108,109). Even a superficial analysis of these specific examples would suggest potential strategies for screening of tumor tissue to guide the selection of optimal chemotherapy regimens, providing a basis for the application of tissue, gene, and protein arrays.

Tumor Profiling

Solid tumors have traditionally been considered to be a homogeneous collection of clonally derived cells with similar features, but it is now clear that tumors are composed of subpopulations with diverse biologic characteristics. Through genetic instability and epigenetic processes, such as gene promoter methylation and histone modifications, these subpopulations may exhibit different properties, with an impact on chemotherapy response. In addition, there can be variability in the potential for metastatic spread among cells that appear to be similar at a morphologic and genetic level (110). Recognition of tumor heterogeneity has altered our understanding of tumor behavior, with broad implications for multiagent and multimodality treatment programs.

Following the development of model systems for screening new anticancer compounds, it is not surprising that attention was focused on the process of screening actual human tumor cells for sensitivity and resistance to chemotherapy agents (111). A variety of methods have been developed utilizing clonogenic survival, ^3H -thymidine incorporation, vital dye exclusion, treatment of transplanted tumor xenografts, and colorimetric analysis of adenosine triphosphate levels. Although there is relatively good correlation between high-level resistance to individual agents demonstrated *in vitro* and lack of a clinical response *in vivo*, it is more difficult to predict sensitivity to specific agents, or to guide the utilization of drug combinations (112), reflecting tumor cell heterogeneity, assay complexity, and inability to evaluate the tumor-host relationship, including the impact of angiogenesis, cytokines, and immune response. A nonrandomized trial in recurrent ovarian cancer suggested good correlation between *ex vivo* assay sensitivity and clinical response (113), but this may be no better than selecting reasonable agents based on routine clinical factors, especially in the setting of recurrent disease. Importantly, there is a lack of prospective randomized data to validate these approaches, as well as concern for the cost and complexities associated with obtaining and shipping fresh tumor tissue.

With the rapid development of gene expression and proteomic arrays, mutational analysis, RNA sequencing, whole genome scanning, and whole genome sequencing, these questions have been carried to a new level of sophistication, as illustrated by The Cancer Genome Atlas project (94). In addition, as drug development has shifted toward molecular-targeted agents, there has been a request from FDA to incorporate predictive or selective biomarkers in regulatory filing, even though the cellular pathways and regulatory networks are not always well understood. Finally, large population-based molecular data repositories are under development, with the potential to rapidly identify targets, select patients, and evaluate new drugs without randomized trials, raising a number of interesting questions.

Dose Intensity and Density

The dose and frequency of drug administration can contribute to the overall effectiveness of a treatment regimen, as well as the

spectrum and severity of host toxicity. Dose intensity is a standardized measure of the amount of drug administered over time, most commonly expressed as mg/m^2 per week.

Preclinical studies demonstrate a sigmoidal relationship between dose and tumor response. This is characterized by a *lag phase* and a lower-limit *threshold* for observing benefit; a *linear phase*, where increases in dose are matched by improved efficacy; and a *plateau*, where toxicity continues to increase but there is no incremental improvement in response. In highly responsive tumors (e.g., choriocarcinoma, dysgerminoma), the entire dose-response curve is shifted to the left, with the result that standard chemotherapy doses are already situated near the upper plateau, and further dose increases are unlikely to achieve any improvement in clinical outcomes. In resistant tumors (e.g., previously treated cervical cancer), the curve is shifted to the right, and is also flattened, reducing the maximal potential benefit and increasing the risk of toxicity. For heterogeneous tumors with sensitive and resistant populations, such as epithelial ovarian cancer, it is unlikely that increased dose intensity would achieve long-term clinical benefit. However, lower-than-standard doses are potentially suboptimal, and arbitrary dose reductions or delays for nonphysiologic factors should be avoided. True dose-intense regimens have not been demonstrated to improve long-term clinical outcomes in women with gynecologic cancer, with the possible exception of recurrent germ cell tumors.

The dose intensity hypothesis has been extensively evaluated in the setting of advanced ovarian cancer, beginning with a series of retrospective reports (114). However, within practical dose ranges that can be achieved in the clinical setting, prospective randomized trials have not demonstrated significant improvements in either disease-free or overall survival (115). While frontline studies focused on platinum dose intensity, the question of paclitaxel dose intensity was also addressed in the setting of recurrent disease, again without evidence of improved outcomes.

Dose intensity is limited by acute (single-cycle) and cumulative (multicycle) nonhematologic and hematologic toxicity. Although multiple cycles of high-dose carboplatin and paclitaxel (with or without topotecan or gemcitabine) can be safely administered with hematopoietic progenitor and growth factor support, it is more difficult to overcome serious nonhematologic toxicities. Thus far, there is no evidence that a two- to three-fold increase in carboplatin dose intensity and cumulative dose delivery is associated with a substantial improvement in clinical outcomes (116–118), and it is unlikely that this approach will be further evaluated.

In contrast, there is renewed interest in “dose-dense” therapy, in which a series of 2 or 3 individual single agents are sequentially administered at maximal tolerated doses using short cycle intervals. This approach has been favorably evaluated in the adjuvant therapy of breast cancer (119), although it has not been clearly established if the clinical benefit is secondary to dose density or weekly scheduling of specific components. In ovarian cancer, the Japanese Gynecologic Oncology Group (JGOG) has conducted a phase 3 trial using standard scheduling of carboplatin together with weekly dose-dense scheduling of paclitaxel, with improved progression-free and overall survival (120), and other groups are working to validate and extend these observations. Overall hematologic toxicity was increased with dose-dense therapy, and it remains unclear if the therapeutic advantage is more dependent on optimal scheduling of paclitaxel, or the cumulative dose delivered. Short cycle intervals may offer a safer approach for intensification by reinforcing normal biologic rhythms that can accelerate repair and minimize host toxicity. For other drugs without known schedule dependence (such as cisplatin or carboplatin), weekly divided doses may not have a therapeutic advantage, and could possibly be less effective, due to lower peak serum concentrations.

GENERAL PRINCIPLES OF CHEMOTHERAPY

Treatment Objectives

Although certain general principles guide the clinician in choosing the appropriate classes of drugs or combinations, the decision to use these agents *at all* must be considered carefully. The critical factors involved in formulating a recommendation are reviewed in Table 13.7.

Natural History

Antineoplastic agents should be used only in patients whose malignancy has been established with pathologic confirmation, and with thoughtful consideration of the expected natural history, based on the primary tumor site, extent of disease, and rate of progression. Individual factors that could have an impact on tolerance for therapy must be evaluated in the context of treatment goals, including physiologic age (as reflected by vital organ function), general health, performance status, nutritional status, desire for treatment, and the presence of underlying illness. Prior history, including any previous cancer treatment and residual functional impairment, as well as patterns of recurrence, should also be considered. Finally, the emotional, social, and financial concerns of the patient and family must be respected (Table 13.7). Recommendations and goals should be presented to the patient and family in conjunction with a reasonable analysis of potential risks and benefits, which contributes to the process of informed consent and which should be followed by sharing of written information for future reference.

Clinical Assessment

Chemotherapy should not be instituted unless the physician is prepared to monitor tumor response (if applicable) carefully while managing expected and unexpected toxicities. If proper facilities are not readily available and the decision is made to begin therapy, the patient should be referred to a physician or facility that can provide integrated care.

Table 13.7 Important Considerations before Using Antineoplastic Drugs

Natural history of the malignancy

- Biopsy proof of malignancy
- Identification of primary site
- Rate of progression or grade
- Stage of disease, patterns of spread

Patient characteristics

- Physiologic age, nutritional status, performance status
- Vital organ function; bone marrow reserve
- Comorbid conditions
- Extent of previous treatment

Supportive care

- Adequate facilities to evaluate, monitor, and treat potential drug toxicities
- Emotional, social, and financial status; support from family
- Collaboration with referring physician

Treatment goals

- Parameters to monitor objective response to treatment
- Potential benefits
 - Curative intent
 - Improved or sustained quality of life
 - Control of disease
 - Palliation of symptoms

In view of the potential for serious toxicity, it is desirable to have some objective means of measuring tumor response by physical examination, radiographic imaging, and/or analysis of serum tumor markers. However, it is not uncommon to administer multiple cycles of adjuvant or postoperative chemotherapy without any direct means of documenting tumor response. In these circumstances, the physician should be alert for any clinical evidence of tumor recurrence or progression during treatment. In patients with evaluable disease, continued administration of chemotherapy requires verification of ongoing benefit.

Expectations

The likelihood of achieving long-term benefit influences the choice of treatment and the acceptance of potential toxicity. Primary tumors (and recurrence after surgical resection or radiation without prior chemotherapy) can generally be grouped according to the likelihood of achieving a durable response. However, chemotherapy is also being utilized more frequently in the setting of early-stage disease, including postoperative adjuvant therapy of ovarian cancer, concurrent chemoradiation in cervical cancer, and postoperative treatment (with or without sequential radiation) in endometrial cancer. While the use of chemotherapy in each of these scenarios is supported by data from phase 3 clinical trials, it is also apparent that research findings are often extended to populations with lower risk, and more patients are being exposed to platinum-based therapy at earlier points in their natural history, with an increased risk of treatment-resistant disease at the time of recurrence.

Most importantly, there is a group of tumors for which primary chemotherapy has been curative in the majority of patients, including choriocarcinoma and ovarian germ cell tumors. These patients should be treated aggressively with curative intent. Toxicity in this setting is acceptable, assuming that it is reversible, as the probability of long-term survival is high.

A second group, including advanced epithelial ovarian carcinoma, has high response rates to primary therapy (exceeding 75%), with prolongation of disease-free and median overall survival, but with only a modest improvement in overall mortality. Patients with these tumors usually benefit from therapy in terms of extended survival or quality-adjusted survival, and they should receive primary treatment at full doses unless contraindicated.

A third group of cancers, including advanced (or recurrent) endometrial cancer, cervical cancer, and uterine mixed Müllerian tumors, have intermediate or lower response rates to primary chemotherapy, with shorter duration of remission and limited improvement in overall survival. Treatment with an initial course of therapy is reasonable, with careful monitoring of toxicity and response.

Other tumors, including uterine leiomyosarcoma, are more resistant to primary therapy, achieving a low frequency of objective response without prolongation of survival. In this setting, the use of chemotherapy should be restricted and particular emphasis placed on including these patients in well-structured clinical trials to evaluate innovative treatments.

In patients with recurrent or progressive disease (PD) after prior chemotherapy, the expectations of response are reduced due to the emergence of drug resistance and the impact of prior therapy and/or disease on performance status and vital organ function. As such, treatment goals are usually palliative, with attention to quality of life and control of symptoms. In this population, the frequency of stable disease (SD) usually exceeds the objective response rate. With appropriate chemotherapy regimens that avoid cumulative toxicity, patients without further disease progression may remain on therapy for prolonged periods of time with an acceptable quality of life. Most patients are best managed with single-agent chemotherapy with regular assessment of ongoing response and management of toxicity. However, patients with epithelial ovarian cancer and a

prolonged treatment-free interval generally receive a platinum-based combination.

The decision to embark on antineoplastic drug therapy is obviously complex. Optimal patient care demands careful review of the multiple factors affecting therapy to maximize any opportunity for improving survival and quality of life.

Choice of Specific Chemotherapeutic Regimens

After the decision to use chemotherapy has been made, the appropriate regimen must be selected. The physician is aided in this task by the results of randomized trials and evolving standards of care, including published practice guidelines. However, not every patient can receive “standard” therapy because of idiosyncratic reactions, vital organ dysfunction, prior treatment, or other factors. Practical individualized decisions are facilitated by the logical grouping of chemotherapeutic agents in several classes with similar pharmacologic properties, mechanisms of action, and spectrum of toxicity. The most important classes are the platinum-based alkylating agents, nonplatinum alkylating agents, antimetabolites, antitumor antibiotics, antimicrotubule agents, nucleoside analogs, hormones, and newer molecular targeted therapies.

A number of combination regimens have been evaluated in the management of gynecologic cancer, and some have been widely adopted as “standard of care” for primary management of advanced-stage or recurrent disease. Phase 3 trials have demonstrated the superiority of specific regimens, such as paclitaxel with either cisplatin (121) or carboplatin (122) in ovarian cancer; a triplet combination of paclitaxel, cisplatin, and doxorubicin with granulocyte colony-stimulating factor (G-CSF) in endometrial cancer (123); cisplatin with either paclitaxel (124) or topotecan in cervical cancer (125); and ifosfamide with paclitaxel in uterine mixed Müllerian tumors (126).

However, none of the standard combinations for advanced ovarian, endometrial, or cervical cancer has been directly compared to sequential therapy with the best active single agents, and the superiority of combination therapy has not been fully established. In the setting of ovarian cancer, phase 3 trials have suggested that sequential therapy with platinum followed by paclitaxel may offer similar long-term outcomes to a combination of platinum and paclitaxel (127,128). Although the initial frequency of tumor response is often increased with combination therapy, long-term outcomes such as overall survival and symptom-adjusted quality of life can be similar for patients who receive optimal sequential therapy with single agents. This is primarily related to the advanced stage of disease at the time of initial treatment with systemic chemotherapy and the lack of curative therapy for the majority of patients. As such, if individual patient circumstances contraindicate the use of a standard combination regimen, it remains a reasonable option to begin therapy with one of the active single agents. In addition to their application as primary therapy for advanced disease, combinations can also be employed as adjuvant therapy for patients with early-stage disease at increased risk for recurrence and for patients with late recurrence after good response to initial therapy.

Adjuvant chemotherapy refers to the initial use of systemic chemotherapy after surgery and/or radiation therapy has been performed with curative intent and there is no evidence of residual disease. Adjuvant chemotherapy is considered if the subsequent risk for recurrence after initial definitive therapy is relatively high (generally greater than 20%), but it is not routinely recommended when the risk of recurrence is less than 10%. In the adjuvant therapy of epithelial ovarian cancer, long-term results from randomized trials have documented a reduction in the risk of recurrence after platinum-based chemotherapy (129,130). However, in carefully staged patients (to exclude occult advanced-stage disease),

it has been difficult to establish an advantage in overall survival. Phase 3 studies in endometrial cancer (131) and uterine mixed Müllerian tumors (132) have documented improved survival with the use of adjuvant combination chemotherapy compared to whole abdomen radiation in selected patients with high-risk disease, increasing the overall proportion of patients who receive adjuvant therapy.

Concurrent chemotherapy with radiation (chemoradiation) refers to the use of chemotherapy to sensitize the tumor to the effects of radiation delivered with curative intent. This has been most extensively studied in the primary management of locally advanced cervical cancer, where platinum-based chemoradiation has been proven to be superior to radiation alone (133). In general, the duration of chemotherapy coincides with the duration of external beam radiation. Although the preferred weekly dose of cisplatin might appear to be low, these regimens generally exceed the overall dose intensity of cisplatin when used to treat advanced disease, and patients require monitoring to avoid cumulative toxicity and treatment interruptions.

Neoadjuvant chemotherapy generally refers to the use of chemotherapy in the management of locally advanced disease in situations where it would be difficult or impractical to perform immediate surgery or radiation. Following a response to initial chemotherapy, there is an expectation that morbidity associated with the overall treatment program can be minimized in conjunction with a reduction in radiation treatment volume or extent of surgery. This approach is most often considered in advanced cervical cancer, where high initial response rates to neoadjuvant therapy have been observed. However, the long-term benefit of this approach has not been established. Neoadjuvant therapy is also a consideration in advanced ovarian cancer, particularly in patients with large-volume ascites, pleural effusions, diffuse small-volume disease, or comorbidities that might increase surgical risk (134). In this setting, it has been difficult to conduct randomized neoadjuvant trials owing to impaired performance status, the desire to establish a definitive tissue diagnosis, and the bias toward initial cytoreductive surgery.

Monitoring of Tumor Response

Generally accepted criteria for evaluation of responses are necessary to facilitate treatment decisions and comparisons among different regimens. Several standards have been used, including those developed by the World Health Organization (WHO). However, in 2000, an international working group including the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute of Canada (NCIC), and the National Cancer Institute (NCI) of the United States developed, validated, and published new Response Evaluation Criteria in Solid Tumors (RECIST 1.0), which were widely adopted within clinical trials and updated as RECIST 1.1 in 2009 (135).

RECIST is based on the prospective designation of measurable lesions, ≥ 10 mm in one dimension (longest axis) on computed tomographic (CT) imaging, and at between 1 and 5 “target lesions” that can be reproducibly measured to determine tumor response, as well as “nontarget lesions” that are used to corroborate response. Lymph nodes represent a special category, as normal anatomic structures, and must be ≥ 15 mm on the short axis to qualify as a measurable or target lesion. Helical CT and magnetic resonance imaging (MRI) are the preferred techniques to monitor tumor response, and the same technique that is used for initial assessment should be used for subsequent measurements. With the expanding use of positron emission tomography (PET) and merged PET-CT imaging, it is important to note that PET data are not included in RECIST, but the CT component of a PET-CT study can be used for RECIST if the CT is of sufficient diagnostic quality. The use of physical examination is restricted to cutaneous lesions or superficial adenopathy that

can be directly measured with calipers. The omission of findings on bimanual pelvic examination poses a particular challenge for monitoring regional disease in patients with gynecologic tumors, and most of these findings would be categorized as nontarget lesions, unless confirmed on radiographic imaging. An overview of RECIST determinations is provided in Table 13.8.

The summary response designation within RECIST integrates the findings from target and nontarget lesions, as well as serum tumor markers (if applicable). Serum tumor markers are not sufficient to declare response but, if initially elevated, must normalize to designate a complete response. International criteria to declare disease progression on the basis of a serial elevation in CA-125 have been widely adopted (136,137), but there is incomplete agreement on criteria to define a partial response during treatment (138). Changes in CA-125, alone, without other evidence of disease, are not recognized within the RECIST paradigm and

Table 13.8	Evaluation of Overall Disease Response (Recist 1.1)
Complete Response (CR) ^a	Disappearance of all <i>target</i> ^b and <i>nontarget</i> lesions, absence of new lesions, and normalization of tumor marker levels (if appropriate). Pathologic lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (PR)	Disappearance of all <i>target</i> lesions, without progression of <i>nontarget</i> lesions, without appearance of new lesions, and with persistence of abnormal tumor marker levels. Or At least a 30% decrease in the sum LD of <i>target</i> lesions (taking as reference the baseline sum LD) without progression of <i>nontarget</i> lesions or appearance of new lesions.
Progressive Disease (PD)	At least a 20% increase in the sum LD of <i>target</i> lesions, taking as reference the smallest sum LD recorded since the start of treatment, or the appearance of one or more new lesions, or progression of any <i>nontarget</i> lesion. The sum LD must demonstrate an increase ≥5 mm.
Stable Disease (SD) ^c	Neither sufficient shrinkage of <i>target</i> lesions to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the start of treatment. No appearance of new lesions (<i>target</i> or <i>nontarget</i>).

Note: Measurable lesions can be accurately measured in at least one dimension with longest diameter (LD) ≥20 mm using conventional radiography, or ≥10 mm with spiral CT scan, or ≥10 mm with calipers on physical exam. Lymph nodes must be ≥15 mm along the short axis to be considered pathologic or measurable. *Nonmeasurable lesions* consist of all other lesions, including small lesions (longest diameter <20 mm with conventional imaging techniques or <10 mm with spiral CT scan), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis, cystic lesions, and abdominal masses that are not confirmed or followed by imaging techniques.

^aTo be assigned PR or CR, changes in tumor measurements must be confirmed by repeat assessments no less than 4 weeks after the criteria for response are first met. The duration of overall response is measured from the time that criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

^bTarget lesions include measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representing all involved organs, selected on the basis of size (lesions with the longest diameter) and suitability for accurate repeated measurements.

Nontarget lesions include all other lesions (or sites of disease) to be identified and recorded at baseline. Serial measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. ^cIn the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol. SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

are not validated for seeking regulatory approval of new treatments. Overall, RECIST is more detailed and specific than previous response criteria, and is also more demanding of the clinical team and radiologist, particularly if there are a large number of target and nontarget lesions.

Complete Response (CR) refers to the complete disappearance of all objective evidence of tumor, including normalization of tumor markers, and a resolution of all signs and symptoms referable to the tumor. Complete regressions of cancer are generally those associated with a prolongation of survival.

Partial Response (PR) refers to at least a 30% decrease in the sum of the longest diameter of all measurable lesions (shortest diameter for lymph nodes). Usually, this would be accompanied by some degree of subjective improvement and the absence of any new lesions during treatment. Partial remissions are generally accompanied by improved well-being for a period of time but are not expected to improve overall survival. A variety of terms have been used to designate lesser responses (e.g., minor response, objective regression), but these are rarely associated with any significant clinical benefit.

Progressive Disease (PD) is defined as a 20% or greater increase in the sum of the longest diameter of all measurable lesions (shortest diameter for lymph nodes) or the appearance of new lesions. Note that measurements refer to the shortest value in prior measurements, not necessarily the measurements obtained prior to initiating treatment.

Stable Disease (SD) is the term applied to patients without measurable tumor response or progression fitting one of the prior criteria. Disease stabilization is an acceptable goal in the setting of palliative therapy for recurrent disease provided that symptoms have not progressed and the patient can tolerate continued therapy.

Changes in the volume of ascites or pleural fluid are not usually considered in the measurement of response, as a number of factors unrelated to cancer can influence third-space fluid accumulation, such as nutritional status, renal function, and treatment-related toxicity. However, appearance of a new fluid collection with cytologic verification would represent PD. Similarly, the appearance of new symptoms, such as a partial small bowel obstruction, does not always indicate progression of disease but could be related to prior surgery, irradiation, chemotherapy, or infection. In general, it is preferable to base decisions regarding treatment on objective measures of response, as described, rather than subjective findings or symptoms. Overall monitoring of small-volume intraperitoneal, diaphragmatic, or intrapleural disease is not adequately addressed within RECIST, and practical modifications have been proposed for patients with mesothelioma (139).

MANAGEMENT OF CHEMOTOXICITIES

Dose Selection, Toxicity Assessment, and Supportive Care

Chemotherapeutic regimens are universally toxic, with a narrow margin of safety, and it is generally necessary to adjust individual doses in accordance with patient tolerance. Initial dosing is derived from body surface area, weight, renal function, and hepatic function. However, there are a number of other factors that could further influence tolerance, including nutritional status, performance status, extent of disease, exposure to prior therapy, third-space fluid accumulations, metabolic polymorphisms, and uncharacterized drug interactions. Current dose algorithms generally fail to address these factors, although emerging pharmacodynamic and pharmacogenomic research has improved individualized dosing in selected cases.

Optimal dosing in obese patients has been questioned, as the distribution and metabolism of drugs within adipose tissue could vary from other compartments. Obesity is also a risk factor for cancer development and is common in the setting of endometrial cancer. In addition obesity is associated with a number of other comorbidities or metabolic conditions that could alter drug kinetics or the risk of toxicity. For these reasons, and in view of toxicity observed within previously radiated endometrial cancer patients, GOG has previously capped the body surface area (BSA) used for initial drug dosing to a value of 2.0 m². However, actual data to reinforce this decision are limited (140), and a recent guidelines panel recommended that obese patients should receive full weight-based dosing without arbitrary reductions or caps (141).

Consistent and standardized monitoring of host toxicity will help to avoid life-threatening events and assist in the implementation of dose adjustments. The Cancer Therapy Evaluation Program (CTEP) of the NCI has developed a detailed and comprehensive set of guidelines for the description and grading of acute and chronic organ-specific toxicity in collaboration with the FDA, international cooperative groups, and the pharmaceutical industry. Most clinical research protocols have incorporated these criteria, which are also applicable to the grading of toxicity for standard chemotherapy regimens outside of a clinical trial. The current version of the Common Terminology Criteria for Adverse Events (CTCAE) is available in electronic format from CTEP (<http://ctep.cancer.gov/protocolDevelopment/>). Basic hematologic parameters from CTCAE version 4 have been summarized in Table 13.9.

An unintended consequence of our current regulatory environment is that most new medications receive single-agent FDA approval at a dose and schedule that is close to the maximally tolerated dose (MTD), increasing the likelihood of host toxicity, particularly when administered over multiple cycles. The association between dose and toxicity is usually dramatic at levels close to the MTD. As such, a modest reduction in dose or an adjustment in schedule can have a substantial impact on acute and cumulative toxicities. The impact of these minor modifications on efficacy is generally unknown, but unlikely to be as dramatic as the impact on toxicity, and many clinicians frequently make modifications in the starting dose and/or schedule of single agents

or combinations, essentially deviating from FDA-approved indications. As these modifications become integrated with clinical practice, limited supporting data emerge, usually from nonrandomized trials, but the primary FDA-approved dose and schedule is rarely changed. Many agents in common use today, including polyethylene glycol (PEG)-liposomal doxorubicin, topotecan, paclitaxel, docetaxel, and gemcitabine, are frequently modified in accord with emerging clinical experience, but without changes in the FDA-approved regimen. It is thus important for the clinician to be aware of emerging data, as well as data from pivotal trials that were used to support original FDA registration.

In view of the narrow safety margin for chemotherapy, it is important that all orders be reviewed by a nurse and pharmacist with oncology experience. Height, weight, calculation of body surface area, ideal weight adjustments (if appropriate), pertinent laboratory values, and methods of dose calculation should be clearly indicated and verifiable. Templated orders encourage systematic review and can reduce the risk of error. In addition, it is preferable to have defined dose levels to account for expected treatment modifications rather than relying on percentage-based modifications. For example, it is not always obvious if a percentage refers to the degree of dose reduction or the amount of drug to be administered, which becomes compounded over multiple cycles, with the potential for more than one modification. One convenient method of structured dose modification is illustrated in Table 13.10. With this approach, modifications for the subsequent course of therapy are implemented according to the

Table 13.9 CTCAE Grading of Myelosuppression

Adverse Event Terminology	Grade			
	1	2	3	4
White Blood Cell Decreased (per mm ³)	LLN to 3,000	<3,000 to 2,000	<2,000 to 1,000	<1,000
Neutrophil Count Decreased (per mm ³)	LLN to 1,500	<1,500 to 1,000	<1,000 to 500	<500
Anemia (Hemoglobin) (g/dL)	LLN to 10.0	<10.0 to 8.0	<8.0; transfusion indicated	Life-threatening consequences, urgent intervention indicated
Platelet Count Decreased (per mm ³)	LLN to 75,000	<75,000 to 50,000	<50,000 to 25,000	<25,000

LLN, lower limit normal (institutional).

Source: CTCAE, Common Terminology Criteria for Adverse Events, version 4.03, Cancer Therapy Evaluation Program, National Cancer Institute. <http://ctep.cancer.gov/protocolDevelopment/> (Published June 14, 2010).

Table 13.10 Representative Drug Dose Modifications for Hematologic Toxicity

Category (Timing)	Parameters	CTCAE Grade	Dose or Schedule Modifications
Granulocytes (day of therapy)	>1,500/mm ³	0, 1	Full doses of all drugs.
	<1,500/mm ³	2, 3, 4	Delay until recovered. If delay >7 days, reduce doses by one level or add G-CSF. If delay >14 days, reduce doses by one level and add G-CSF.
Platelets (day of therapy)	WNL	0	Full doses of all drugs.
	< LLN to 75,000/mm ³	1	Delay until recovered.
	<75,000/mm ³	2, 3, 4	Delay until recovered. If delay >7 days, reduce doses by one level.
Granulocytes (cycle nadir)	>1,000/mm ³	0, 1, 2	Full doses of all drugs.
	<500/mm ³ for ≥7 days	4	Reduce doses by one level. If already reduced, add G-CSF for future cycles.
	<1,000/mm ³ with fever	3, 4	Add G-CSF for current episode, reduce doses by one level for future cycles. If already reduced, add G-CSF for future cycles.
Platelets (cycle nadir)	≥50,000/mm ³	3	Full doses of all drugs.
	<50,000/mm ³ with bleed	3, 4	Reduce doses by one level.
	<25,000/mm ³	4	Reduce doses by one level.

CTCAE, Common Terminology Criteria for Adverse Events; G-CSF, granulocyte colony-stimulating factor; LLN, lower limit normal; WNL, within normal limits. Dose reductions for individual drugs within a combination regimen should be based on the likelihood that a particular drug contributes to the observed hematologic toxicity.

degree (grade), duration, and timing of toxicity experienced during the preceding course. Although treatment can be delayed on a week-by-week basis to allow for recovery, delays of greater than 2 weeks should be avoided through dose modification and utilization of hematopoietic growth factors. With expanded utilization of combination regimens, it is also helpful to know the patterns of toxicity associated with individual drugs, as it might be appropriate to modify one component rather than an entire regimen.

Bone Marrow Toxicity

Bone marrow toxicity is the most common dose-limiting side effect associated with cytotoxic drugs, and neutropenia is the most common manifestation of bone marrow toxicity, occurring 7 to 14 days after initial drug treatment and persisting for 3 to 10 days. CTCAE grading criteria are summarized in Table 13.9. For purposes of dose modification, the absolute neutrophil count (ANC) is preferred over total white blood count, as this more accurately reflects dose tolerance and risk of infection, which parallels the duration of grade 4 neutropenia ($ANC \leq 500/mm^3$). Dose-limiting thrombocytopenia is less common than neutropenia, but has become more frequent with wider utilization of carboplatin and carboplatin-based combinations. A systematic approach to management of hematologic toxicity can help to reduce the risk of error and facilitate overall compliance with a treatment regimen (Table 13.10).

Radiation, alkylating agents (e.g., melphalan, carboplatin), and other DNA-damaging agents (e.g., nitrosoureas, mitomycin C), can have cumulative long-term effects on bone marrow reserve. Most other agents, including the taxanes and topotecan, show no evidence of cumulative toxicity and can be administered for multiple cycles without dose modification.

In view of the frequent occurrence of neutropenia and the risk of infectious complications, utilization of G-CSF, including filgrastim or the longer-acting PEG-filgrastim, has increased. Although these agents promote more rapid granulocyte recovery, thus avoiding potential complications and facilitating the maintenance of dose intensity, their use has not been shown to improve long-term survival for patients with gynecologic cancer, compared to conservative management with dose reduction and cycle delay. In addition, G-CSF is not effective in the management of thrombocytopenia and may actually increase the degree of thrombocytopenia by diversion of immature marrow elements, a particular problem after multiple cycles of carboplatin. Recombinant megakaryocyte growth factor is an option to maintain platelet counts (142). However, current treatment programs are not associated with a high frequency of complicated grade 4 thrombocytopenia, and the value of aggressive support would appear to be limited.

Moderate degrees of anemia are quite common in cancer patients receiving chemotherapy, which may contribute to chronic fatigue. With increased recognition of blood-borne viral pathogens and limited supplies of banked blood, frequent transfusions are not practical or recommended, and many patients will adapt to chronic anemia with minimal symptoms. The availability of recombinant erythropoiesis-stimulating agents (ESA), including erythropoietin (epoetin alfa) and darbepoietin, has provided a generally safe and effective alternative for the management of anemia associated with chemotherapy (143) and should be considered on a case-by-case basis, although financial costs at the recommended dose and schedule can be greater than the intermittent use of blood products (144). Emerging data with regard to the potential risks associated with ESA, including cardiovascular events, thrombosis, and reduced tumor-related survival in placebo-controlled, randomized trials (145), have prompted the FDA to reevaluate the role for ESAs in routine practice and to implement specific Risk Evaluation and Mitigation Strategies (REMS) that require physician training, registration, and

auditing (146,147). A Medicare National Coverage Determination also limited reimbursement to patients with confirmed hemoglobin of >10 g/dL (148). Patients with anemia should undergo evaluation of iron stores, with appropriate use of iron replacement, prior to initiation of ESA.

Gastrointestinal Toxicity

Most anticancer agents are associated with some degree of nausea, vomiting, and anorexia. There are 3 major categories of nausea and vomiting: *anticipatory*, occurring prior to actual administration of chemotherapy; *acute onset*, beginning within 1 hour of chemotherapy administration and persisting for less than 24 hours; and *delayed*, beginning more than 1 day after chemotherapy administration and persisting for several days. Prophylactic management of these adverse effects improves patient acceptance and facilitates completion of therapy with full doses on schedule.

The antiemetic regimen is tailored to the emetogenic potential of the treatment, which reflects the incorporation of specific drugs, as well as the dose and schedule of drug administration. Mild nausea and vomiting can often be managed effectively with H_1 antihistamines (diphenhydramine), phenothiazines (prochlorperazine or thiethylperazine), butyrophenones (haloperidol), steroids (dexamethasone or methylprednisolone), benzamides (metoclopramide), or benzodiazepines (lorazepam). These are likely to be sufficient with drugs such as bleomycin, docetaxel, paclitaxel, Vinca alkaloids, 5-fluorouracil, methotrexate, mitomycin C, gemcitabine, PEG-liposomal doxorubicin, and topotecan.

For drugs with more severe emetogenic potential, including cisplatin, carboplatin, cyclophosphamide, or dactinomycin, a more aggressive prophylactic regimen is required. In general, these patients should receive a 5-hydroxytryptamine (5-HT₃) receptor antagonist, such as ondansetron or granisetron, prior to chemotherapy and repeated at 8- to 12-hour intervals. Both compounds are also available in an oral formulation, which has been helpful in the management of delayed and/or chronic nausea after chemotherapy or nausea associated with multiday oral chemotherapy regimens. Longer-acting 5-HT₃ antagonists have also become available, including palonosetron and dolasetron, which require only a single intravenous or oral dose prior to chemotherapy. As a group, the 5-HT₃ antagonists have been quite effective in controlling severe emesis, with few side effects, but are more expensive than prochlorperazine (149). Chronic nausea and vomiting can be a particular problem after several cycles of cisplatin and occasionally carboplatin (150). The mechanism is poorly understood, and symptoms can be difficult to control with currently available medications, prompting the use of extended steroid administration, cannabinoids, or repeated dosing with 5-HT₃ receptor antagonists.

Anticipatory nausea and vomiting can become a significant problem during repeated cycles of chemotherapy, as patients associate environmental cues (such as odor, carpeting, or paint colors) with nausea. In addition to behavioral modification, it can sometimes be modulated by pretreatment with antiemetics and amnesic drugs, such as benzodiazepines, administered orally at home prior to arriving at the treatment center. Lorazepam (0.05 mg/kg) can also be given by slow intravenous push 1 hour before therapy, with doses being continued as needed every 4 hours for up to 6 doses (151). Unfortunately, this particular schedule produces significant sedation and can be used only in hospitalized patients or outpatients with independent transportation.

Diarrhea, oral stomatitis, esophagitis, and gastroenteritis are also potential problems. Patients with significant oral or esophagogastric symptoms may have symptoms managed with oral viscous lidocaine (2%), other topical anesthetics, or parenteral narcotics in severe cases. Randomized controlled trials

following 5-fluorouracil-based chemotherapy or radiation have failed to document any clinical improvement with sucralfate, which can bind to ulcerated mucosa (152,153). However, randomized placebo-controlled trials have demonstrated that multiple intravenous doses of recombinant keratinocyte growth factor (palifermin) before and after treatment can reduce the incidence and severity of chemotherapy-induced oral stomatitis associated with bolus 5-fluorouracil (154), high-dose chemotherapy, or concurrent chemoradiation (155,156). In general, dose-limiting mucosal injury is uncommon with platinum-based combinations, taxanes, and other single agents used in the treatment of gynecologic cancer. While many patients might develop some degree of diarrhea in the setting of concurrent pelvic chemoradiation, palifermin has not been specifically evaluated in that setting.

In refractory cases, patients should be screened for secondary infectious complications, such as candidiasis and herpes simplex. Following treatment with irinotecan, noninfectious secretory diarrhea is a well-recognized dose-limiting toxicity associated with local exposure to the active metabolite SN-38 and is generally managed with prophylactic antimotility agents and intravenous hydration, with utilization of octreotide in severe cases. Diarrhea can also result from diffuse mucosal injury following administration of doxorubicin (including PEG-liposomal doxorubicin), 5-fluorouracil, methotrexate, and other agents. In the setting of recent surgery and chemotherapy, patients are also at increased risk for infectious diarrhea, and screening for *Clostridium difficile* is appropriate.

Alopecia

Scalp alopecia is one of the most emotionally taxing side effects of chemotherapy. Aside from long-lasting alopecia that follows cranial irradiation, it is almost always reversible, but it can be a major deterrent to successful chemotherapy. Total scalp alopecia is particularly common with drugs like doxorubicin and paclitaxel, and there is generally some degree of partial alopecia with cisplatin, carboplatin, cyclophosphamide, docetaxel, Vinca alkaloids, and 5-fluorouracil. In a minority of cases, patients treated with paclitaxel will also experience loss of eyelashes, eyebrows, and other body hair, which can be particularly distressing. A variety of physical techniques have been devised to minimize alopecia, including scalp tourniquets and ice caps designed to decrease scalp blood flow. Although partially effective, they are rarely successful with extended chemotherapy.

Skin Toxicity

Skin toxicities that occur during chemotherapy include allergic or hypersensitivity reactions (HSR), skin hyperpigmentation, photosensitivity, radiation recall reactions, nail abnormalities, folliculitis, palmar-plantar erythrodysesthesia (PPE, hand-foot syndrome), and local extravasation necrosis. Many of these are drug specific and self-limited, but occasionally they may be dose limiting.

PPE is a reversible but painful erythema, scaling, swelling, or ulceration involving the hands and feet. This occurs more often with chronic oral or intravenous medications, weekly treatment regimens, and formulations that increase drug circulation time, such as prolonged oral etoposide, weekly and continuous-infusion 5-fluorouracil, capecitabine, and PEG-liposomal doxorubicin, where it has emerged as a major dose-limiting toxicity (157).

Extravasation necrosis is a serious complication seen after tissue infiltration of vesicant drugs such as doxorubicin, dactinomycin, mitomycin C, and vincristine (158). These drugs should always be administered through a freely flowing intravenous line with careful monitoring. Caution is also required during

utilization of central venous ports, as malfunctions in the needle, hub, or tubing can be associated with gradual extravasation that will not be apparent for several hours (159). Small series have reported a limited experience with local infiltration or topical application of steroids, *n*-acetylcysteine, dimethyl sulfoxide (DMSO), and hyaluronidase, with variable results, and recommendations are imprecise. However, single or multiple intravenous doses of dexrazoxane, a topoisomerase II catalytic inhibitor, appear to offer specific protection against injury from anthracyclines, including doxorubicin and daunorubicin (160,161). Skin necrosis from some extravasations may eventually require surgical debridement and skin grafting.

Neurotoxicity

Peripheral neuropathy is the most common neurotoxicity encountered in gynecologic oncology and is a particular risk with administration of cisplatin, paclitaxel, docetaxel, nanoparticle albumin-bound (NAB) paclitaxel, epothilones, Vinca alkaloids, and hexamethylmelamine (162,163). Although less common with carboplatin than cisplatin, neuropathy can still occur, particularly in combination with paclitaxel. Peripheral neuropathy generally begins with symptoms of paresthesia accompanied by loss of vibratory and position sense in longer nerves associated with the feet and hands. It then progresses to functional impairment, with gait unsteadiness and loss of fine motor coordination, such as trouble buttoning clothes and writing. This is closely followed by loss of deep tendon reflexes and eventual development of motor weakness. With paclitaxel and other nonplatinum agents, this is almost always reversible but may require several months posttherapy for substantial improvement. In more severe cases, accompanied by neuronal injury or demyelination, recovery may require active neuronal regeneration over an extended period of time, and symptoms may persist for the lifetime of the patient.

In current clinical practice, neurotoxicity from widely utilized microtubule-stabilizing agents is predominant (164,165). The frequency of moderate to severe toxicity is more common with paclitaxel, compared to docetaxel or epothilones. Risk appears related to peak levels associated with individual doses, as well as cumulative doses over multiple cycles, which is further complicated by alternative schedules and newer drug formulations. For example, although the risk associated with NAB-paclitaxel on the FDA-approved 3-week schedule is at least as high as paclitaxel (166), the risk is reduced with NAB-paclitaxel administered on a weekly schedule, even with higher cumulative doses. In addition, as the primary means of assessment is clinical, reported frequencies vary widely in clinical trials, reflecting variability in documenting history, and subjective and objective findings.

If related to cisplatin, neuropathy can continue to progress after therapy has been discontinued owing to ongoing axonal demyelination and loss, with long-term persistence of symptoms. Cisplatin has also been associated with permanent ototoxicity and, at higher doses, with loss of color vision (167) and autonomic neuropathy. Oxaliplatin can produce a long-term peripheral neuropathy similar to cisplatin (168), but it is also associated with transient acute reactions, including paresthesia and cold-sensitive laryngeal dysesthesia (169), which may reflect blockade of membrane ion channels (170). Infusions of calcium and magnesium have been used to ameliorate acute oxaliplatin reactions (171), but the potential risk of interfering with clinical response has not been resolved.

Although some patients report transient distal paresthesia after a single dose of paclitaxel, the onset of persistent neuropathy is generally more gradual. Neuropathy can become clinically apparent after 2 to 3 courses of therapy, with mild symptoms that resolve between cycles. Careful questioning and examination may reveal subtle findings at an earlier stage, and functional assessments have been developed that demonstrate good concordance

with actual neuropathy (172). Patients with underlying neurologic problems, such as diabetes, alcoholism, or carpal tunnel syndrome, are particularly susceptible, and substitution of docetaxel for paclitaxel can be a useful strategy in some situations. All patients who receive potentially neurotoxic therapy, especially cisplatin and paclitaxel, should be routinely queried regarding proprioception and fine motor tasks and examined for loss of vibratory sense, high-frequency hearing, and deep tendon reflexes.

In view of the frequency of neurotoxicity and the impact on daily life, there has been interest in agents that might prevent nerve damage, encourage recovery, or ameliorate symptoms (173). Amifostine was reported to reduce the frequency and severity of platinum-mediated neuropathy. However, a non-randomized study in patients receiving cisplatin and paclitaxel in combination with amifostine failed to achieve a targeted reduction in the incidence of neuropathy (174). In addition, widespread substitution of carboplatin for cisplatin has reduced, but not eliminated, the overall risk. Small studies with glutamine, vitamin E, and other agents have been inconclusive, and there are no agents that can be recommended for prevention of neuropathy in routine practice. Clinical management of painful paresthesia has been reported with amitriptyline and gabapentin (175), prompting the empiric use of similar agents for relief of symptoms.

Other neurotoxicities include acute and chronic encephalopathies, usually associated with intrathecal chemotherapy, acute cerebellar syndromes, autonomic dysfunction, inappropriate secretion of antidiuretic hormone (SIADH), and cranial nerve paresis. Of particular relevance to the gynecologic cancer population, an acute reversible metabolic encephalopathy has been well-described in association with ifosfamide and attributed to the toxic metabolite chloroacetaldehyde. Of note, this syndrome can potentially be prevented by infusion of methylene blue (176), which may act through inhibition of monoamine oxidase activity with reduced chloroacetaldehyde formation in the liver.

Genitourinary Toxicity

Renal toxicity is a well-recognized side effect of cisplatin, with implication of specific local metabolites, even though only a small fraction of cisplatin is cleared by renal excretion. In contrast, carboplatin undergoes extensive renal clearance with little risk of toxicity. Indeed, with increased substitution of carboplatin for cisplatin, and with a reduction in overall cisplatin dose intensity, there has been a decline in clinical familiarity with cisplatin-mediated nephrotoxicity. However, the expanded utilization of concurrent cisplatin and pelvic radiation for management of early-stage cervical cancer has renewed awareness of this potential problem, particularly as commonly utilized weekly dosing can exceed 100 mg/m² over a 3-week period. Careful attention to hydration status and saline-driven urinary output before, during, and immediately after therapy is required to reduce the risk associated with this serious complication (177).

Another troublesome side effect is hemorrhagic cystitis, which can be seen with cyclophosphamide or ifosfamide, attributed to the metabolite acrolein. With moderate-dose cyclophosphamide, this complication can be prevented by maintaining high urinary output, which reduces overall urothelial exposure to the toxic metabolites. However, patients receiving combination regimens often have reduced oral intake postchemotherapy, and selected patients receiving cyclophosphamide might benefit from supplemental intravenous hydration. The risk of cystitis is essentially 100% with ifosfamide, even with aggressive hydration, but this can be prevented with simultaneous administration of mesna, which binds and neutralizes acrolein in the urine (178).

Hypersensitivity Reactions

Increased utilization of paclitaxel, a natural product with poor solubility, has focused attention on the risk of HSR. For intravenous administration, paclitaxel is formulated in Cremophor-EL, a mixture of polyoxyethylated castor oil and dehydrated alcohol, which has been associated with mast cell degranulation and clinical HSR. Over 80% of reactions occur within minutes during either the first or second cycle of drug administration and can usually be managed with prophylactic medication (corticosteroids, histamine H₁/H₂ blockade) followed by rechallenge beginning at a lower rate of infusion (179,180). Similar reactions have been reported with docetaxel and PEG-liposomal doxorubicin, but with lower frequency in the absence of Cremophor-EL. Emerging data with NAB-paclitaxel indicate a marked reduction in the risk of HSR, further emphasizing the role of formulation, vehicle, and carriers.

With improved survival and an increased utilization of second-line therapy, patients can also experience more traditional allergic reactions to selected chemotherapy agents. Carboplatin, an organoplatinum compound, has emerged as a major source of late allergic reactions. These occur most often during the second cycle of a second course of therapy, suggesting a process of antigen recall and priming of the immune response (181). Patients receiving a second course of carboplatin-based therapy should be closely monitored for early signs of hypersensitivity to avoid more serious reactions. Unlike the situation with paclitaxel, carboplatin reactions are not readily prevented or circumvented with prophylactic medication, although inpatient (182) and outpatient strategies for desensitization have been reported (183) and successfully utilized for responding patients. It is important to note that the desensitization routine does not eliminate the allergic process and must generally be repeated with each cycle of treatment. Of interest, the combination of carboplatin with PEG-liposomal doxorubicin has a much lower incidence of carboplatin allergy, compared to a combination of carboplatin and paclitaxel or single-agent carboplatin, and might be preferred in the management of recurrent disease (184).

Other Significant Toxicities

A comprehensive discussion of all potential toxicities for currently available chemotherapeutic agents is beyond the scope of this chapter, and additional information is available throughout the text. Nevertheless, a variety of other important toxicities are occasionally encountered in regimens commonly used in gynecologic oncology. These include cardiac toxicity from cumulative doxorubicin exposure, radiation recall vasculitis from doxorubicin, pulmonary fibrosis from bleomycin, gonadal dysfunction in premenopausal women from alkylating agents, and secondary acute leukemia from the chronic administration of alkylating agents, particularly melphalan, in ovarian cancer.

DEVELOPMENTAL CHEMOTHERAPY

Background

The identification, evaluation, and regulatory approval of effective drugs for cancer treatment is a long, complicated, and expensive process. Of note, it has been argued that the expanded availability of only 17 existing generic chemotherapeutic agents would substantially improve worldwide mortality from cancer (185). However, most cases of advanced disease remain incurable with current treatments. Promising candidates are identified and prioritized through preclinical screening, utilizing derivatives of previously defined active agents or established drug classes or

new compounds engineered to interact with a specific target. In addition, there continues to be broad screening of natural products isolated from terrestrial and marine sources (186). Some evidence of antitumor activity during screening must be demonstrated before clinical trials are undertaken. Thus far, all useful antitumor agents have demonstrated antitumor activity using *in vitro* or *in vivo* screening systems.

These traditional approaches are being increasingly challenged by the large number of new genes and potential targets identified through molecular biology, genomics, and proteomics. Principles of genomic libraries, solid-phase organic synthesis, and combinatorial chemical library generation have been adopted by the pharmaceutical industry to promote high-throughput screening. As new targets are identified, a large number of related compounds can be created, beginning with lead natural products or known reagents, and then screened for improved target binding and/or inhibition of target function. Substantial bioinformatics resources are required to manage and analyze the large amount of data generated from these processes, but the accumulation of gene expression and proteomic data can facilitate “pre-discovery” modeling of potential targets and reagents prior to making decisions about actual development. To some extent, these processes have evolved in parallel, as it is clear that agents generated from a library or a database will still require some form of biologic validation prior to entering complex and expensive clinical studies.

After antitumor activity has been identified, the new agent must be formulated for human use and produced in sufficient quantities to support clinical trials. This is never a trivial achievement, as was evident from the natural supply limitations and formulation problems encountered in early trials with paclitaxel (187) and the camptothecins (188). Clinical-grade material is then subjected to detailed preclinical toxicology tests in animals. These toxicology trials are done in several animal species and may explore different schedules of drug administration to provide a basis for clinical development. As such, they are time consuming, complex, and expensive.

After all of the steps of preclinical testing are completed, new agents can enter clinical evaluation. As such, clinical trials are the primary means utilized to evaluate new agents in a systematic manner. All physicians and patients are urged to consider participation in clinical trials, which are available for almost all diagnoses and treatment circumstances. Sponsors of clinical trials include the NCI in collaboration with individual institutions and national groups, such as the GOG, as well as the pharmaceutical industry and individual institutions.

Clinical Trials

Detailed rationale and methodology for clinical trials design has been covered in other sections. This material is provided to highlight key concepts related to investigational drug development.

Phase 1 Trials

Phase 1 trials are typically first-in-human studies for new compounds and employ a dose- and/or schedule-escalating design to determine the dose-limiting toxicity (DLT), maximally tolerated dose (MTD), and pharmacokinetic parameters applicable to each regimen. In the most common model, accrual is suspended when more than one DLT event occurs within a dose level (2 of 6 patients), as this would generally exceed predefined limits for the MTD. Modifications of the standard dose-escalation schema have been developed to enroll fewer patients at lower dose levels with greater dose increments between successive dose levels in the absence of toxicity. As the MTD is approached, the dose level increments are reduced and accrual can be expanded. These newer methods aim to minimize the number of patients

treated at very low (nonefficacious and nontoxic) doses, while providing greater precision for estimating the MTD and DLT at higher doses.

With the shift from conventional cytotoxic agents to molecular-targeted agents, the traditional phase 1 paradigm needs to be reexamined. Many agents, such as human monoclonal antibodies, may not demonstrate traditional dose-limiting or dose-related toxicities, and phase 1 studies can reach their highest predetermined dose level without achieving DLT or defining a traditional MTD. In addition, these agents are frequently intended for chronic administration, and cumulative toxicity over multiple cycles is perhaps more relevant than acute toxicity during the first cycle. Finally, with an identified biologic target, it is also important to consider the optimal biologic dose that achieves a desired level of receptor blockade or signal transduction inhibition. With these considerations, it is apparent that a modified phase 1 design utilizing expanded cohorts treated for multiple cycles, with laboratory-based correlates, would provide better data to guide large randomized trials.

Tumor response is not a primary endpoint within a phase 1 trial, which will typically include patients representing a variety of primary tumor types with multiple prior therapies. Some phase 1 studies have included an expanded cohort to confirm safety and targeting, or an embedded phase 2 component to estimate clinical activity. These integrated strategies conserve patient resources while accelerating the overall development process, but with some risk of missing smaller treatment effects.

Phase 1 studies can also serve to evaluate new combinations that build on standardized chemotherapy regimens to establish feasibility and tolerability of the proposed regimen before embarking on larger trials. In certain situations, such as epithelial ovarian cancer, phase 1 trials may enroll newly diagnosed patients without prior therapy, as the experimental combinations generally incorporate other known active agents.

Phase 2 Trials

After the recommended dose and schedule have been defined, the regimen can receive focused evaluation in patients with a specific cancer diagnosis, usually in the setting of measurable disease after 1 (or 2) prior chemotherapy regimens. Phase 2 trials are designed and powered based on a surrogate endpoint that is thought to reflect potential clinical benefit, such as response rate, disease stabilization rate, biochemical (tumor marker) response rate, or the proportion of patients alive and progression-free at a specific time interval. In general, each phase 2 trial tests a single hypothesis, to determine if the new agent or regimen crosses a threshold based on historical data in the same patient population with an appropriate degree of power (type II or β error) and precision (type I or α error). Through this process, new agents are “selected” for further development or rejected. In order to conserve patient resources and minimize the number of patients who might receive ineffective therapy, most phase 2 studies utilize a multi-stage accrual design with early-stopping parameters, as proposed by Gehan (189) and modified by Simon (190).

This strategy was developed to efficiently screen conventional cytotoxic agents, one at a time, without direct comparisons between agents. It has obvious limitations when applied to targeted molecular agents, which may not have the same potential to elicit a measurable tumor response, or may be designed to work in conjunction with conventional therapy. As such, there is a risk that modest but clinically important treatment effects could be missed.

Traditional phase 2 trials utilize a single arm without randomization. However, there are circumstances where randomization is appropriate (191–193). Randomized phase 2 trials allocate patients among 2 or more treatment arms to minimize potential differences in prognostic factors or other variables.

Each arm is then independently tested against the same historical threshold value. Using this approach, one or both arms can be selected for further clinical development. Such randomized trials are generally underpowered for direct comparison of response rate and survival between each arm, owing to the limited number of patients.

In view of the number of new agents that merit evaluation, it would be appealing to have a more efficient paradigm that could incorporate combinations (with a reference arm) and offer the ability to compare and select among agents within the same general class. In practical terms, this has proven difficult, due to the need to involve multiple sponsors with different investigational agents. When early-phase data appear interesting but might not support a fully powered phase 3 trial, there have been randomized designs that incorporate an embedded phase 2 component to confirm disease-specific activity and feasibility prior to enabling full phase 3 accrual.

Phase 3 Trials

If a promising regimen is identified for further testing, it then moves toward a phase 3 randomized trial, in which it is directly compared with an existing standard regimen in a particular clinical setting, as defined by the type of cancer, stage of disease, and prior therapy. The size and duration of the trial depends on the primary endpoint (progression-free survival, overall survival, or quality-adjusted survival), anticipated effect size, and the power and precision of the statistical design. Generally, this is also a collaborative process, which combines scientific, clinical, and regulatory objectives.

Owing to the large number of uniformly staged and treated patients required for a phase 3 trial, such studies are best conducted through a national clinical trials organization with international collaboration. To minimize potential sources of bias, phase 3 trials frequently stratify patients into groups according to key prognostic variables prior to randomization, such as stage or extent of residual disease. This can expand the opportunity for preplanned post hoc analysis and contribute to the overall value of the study. Verification of patient diagnosis, stage of disease, eligibility, treatment delivered, and tumor response can further improve the reliability of reported results. Eligibility criteria and treatment flexibility represent a balance between scientific rigor, real-world clinical objectives, and ability to generalize findings.

The traditional phase 3 endpoint of overall survival has been challenged by an increasing number of available treatment options for management of recurrent disease, and the vast majority of well-planned trials fail to achieve a survival advantage. This has prompted greater consideration of progression-free survival as the preferred primary endpoint, as the timing of progression is not altered by secondary treatments. However, progression-free survival is subject to observer and detection bias, requiring better control over posttreatment monitoring. Regulatory authorities have also questioned if progression-free survival may not always translate into clinical benefit, without some type of adjustment for quality of life or control of disease-related symptoms. In view of these uncertainties, most registration trials include sufficient accrual to evaluate both progression-free and overall survival.

With the push toward targeted therapy and individualized treatments, there has also been increased pressure from regulatory agencies to include companion diagnostics to predict the likelihood of response and to select appropriate patients. However, not all presumptive biomarkers will be validated, and it is sometimes more useful to include a wider variety of patients with tumor specimens that can be studied for multiple markers and pathways. In addition, if the patient population is too narrowly defined, it may be more difficult to randomize patients to a treatment arm that does not include access to a particular drug.

FDA Approval and Postmarketing Studies

Following a successful phase 3 trial or, preferably, a group of related trials, a sponsor can apply to FDA for marketing approval for a specific disease indication. This triggers a detailed review of data by the Oncology Drug Advisory Committee (ODAC), which then issues a recommendation to FDA, followed by formal review and a decision by FDA, which may grant approval or request additional data. In the United States, all commercial marketing requires FDA approval for at least one specific indication. The average time from initial drug discovery to application for an FDA-approved indication is 10 to 12 years, involving considerable expense and effort, as noted above. Supplemental phase 4 or postmarketing studies can be required by FDA as part of the approval process or be performed by the sponsor to evaluate alternative drug formulations or resolve questions regarding dose, schedule, or toxicity. In addition, phase 4 studies may involve substitution of the new agent in combination chemotherapeutic regimens already established for the disease. These studies are not commonly employed in the development of new chemotherapeutic regimens, but can provide confirmatory evidence of safety and efficacy.

Development of Combination Regimens

With some notable exceptions, single agents are not sufficient to achieve prolonged survival or cure. Combinations of conventional cytotoxics can approach maximal cell kill by including drugs with minimal overlap of toxicities, such that antitumor effects can be summed but the toxicities dispersed. Combinations are also more likely to demonstrate activity against heterogeneous tumor populations, and effective combinations would prevent the emergence of drug resistance. However, in practice it may also encourage greater resistance among surviving cell fractions.

No direct evidence currently exists to indicate whether optimal combinations should utilize sequential single agents, doublets, or triplets. Utilization of single agents generally precludes any biologic interaction between the various components of a treatment regimen, but permits administration of each agent at the full active dose. The use of doublets generally permits higher doses of individual drugs, compared to a triplet regimen, but over a smaller number of cycles with each agent. Doublets have the potential advantage of sequentially introducing more than one regimen with a different mechanism of action and/or pattern of resistance, which has been postulated to prevent the emergence of drug resistance.

Development of combination chemotherapy has been guided by several principles (Table 13.11). However, much of the reported experience has been derived from empiric combinations

Table 13.11 Principles of Combination Chemotherapy

Each component should have

- Activity against the target tumor as a single agent
- A different mechanism of action and cellular target
- A biochemical basis for additive or synergistic effects in combination with at least one of the other agents
- No evidence of antagonistic interactions
- Distinct patterns of resistance to discourage the emergence of drug-resistant phenotypes

Optimal dose, schedule, and sequence of drug administration should be determined from preclinical data and early clinical trials to maximize tumor response and minimize host toxicity.

Minimal overlap of nonhematologic toxicity is desirable to safely maintain full therapeutic doses of each component over multiple cycles.

Table 13.12 Representative Agents for Development of Combination Regimens

Agent	Cellular Target	Mechanism of Action	Schedule-Dependent Effects	Patterns of Resistance	Interaction with Platinum
<i>Platinum</i>	DNA	DNA adduct formation	Generally independent of schedule	↑ GSH ↑ DNA repair ↑ Damage tolerance ↓ Accumulation	NA
<i>Paclitaxel</i>	β tubulin	↑ Tubulin aggregation	↑ Heme and mucosal toxicity with prolonged infusion ↑ Efficacy with weekly schedule	↑ MDR 1 (P 170) ↑ Tubulin- β 3 isoforms	↓ Platelet toxicity ↑ Neuropathy
<i>Topotecan</i>	Topoisomerase-I	Stabilize DNA-topoisomerase complex	↑ Efficacy with 5-day exposure Sequence-dependent toxicity	↓ Topoisomerase-I ↑ BCRP (ABCG2)	↑ Heme toxicity
<i>Gemcitabine</i>	Ribonucleotide reductase, DNA, nucleotide pool	↓ DNA synthesis ↓ Nucleotide pools Masked chain termination	Saturated uptake and phosphorylation with rapid infusion	↑ Ribonucleotide reductase	↑ Heme toxicity
<i>PEG-liposomal doxorubicin</i>	Topoisomerase-II	↓ DNA synthesis	Prolonged clearance (PEG formulation)	↑ MDR 1 (P 170)	↑ Heme toxicity

evaluated in conventional phase 1 dose-escalating trials. Bone marrow recovery usually proves to be the dominant factor in cycle timing, and in practice most combinations can be repeated every 3 to 4 weeks. Dose-dense strategies have also been developed using weekly or biweekly schedules.

Several combinations were evaluated in epithelial ovarian cancer, in an effort to improve on the results obtained with a standard combination of carboplatin and paclitaxel (Table 13.12). Each of the selected agents (topotecan, gemcitabine, and PEG-liposomal doxorubicin) had demonstrated independent single-agent activity against recurrent ovarian cancer, and could interfere with repair of platinum-DNA adducts, providing a clinical and scientific rationale for the combinations. However, based on completed phase 3 trials in approximately 12,000 women, none of the combinations achieved an improvement in clinical outcomes, providing additional support for a shift in developmental priorities toward molecular-targeted agents and other novel approaches (194).

Drug Interactions, Scheduling, and Sequence

Drugs should be used in their optimal dose and schedule. However, new combinations have the potential to alter the pharmacokinetics, bioavailability, toxicity, and efficacy of individual components based on substrate-dependent effects, such as a reduction in nucleotide pools or altered metabolism. Therefore, the optimal dose and schedule for individual agents within a combination might differ from their use as single agents.

As an illustration, the impact of sequence variations using cisplatin or carboplatin with either paclitaxel or topotecan has been explored in phase 1 clinical trials. Prior administration of cisplatin can delay subsequent clearance of paclitaxel when administered as a 24-hour infusion (195). The mechanism for this effect is unknown, but it is not attributable to platinum-mediated renal dysfunction. Instead, it has been postulated to occur following cisplatin-mediated inhibition of cytochrome P450 mixed-function oxidases that participate in paclitaxel metabolism. This enzymatic effect is not shared by carboplatin, and prior carboplatin exposure has not been demonstrated to interfere with clearance of paclitaxel. However, most combinations with carboplatin have utilized a shorter (3-hour) paclitaxel infusion, to minimize hematologic toxicity. Earlier preclinical models had demonstrated enhanced cytotoxicity when paclitaxel was administered prior to cisplatin and antagonism by the reverse sequence (196, 197). Thus, the schedule ultimately

adopted in clinical practice (paclitaxel followed by cisplatin) is both less toxic and potentially more efficacious, and this was empirically extended to carboplatin-based combinations. In part, this sequence was based on practical considerations related to the risk of acute paclitaxel HSR, which can require interruption of treatment, and it was more acceptable to administer the carboplatin after it was clear that the patient had already tolerated the paclitaxel.

A different pattern was observed with sequences of platinum and topotecan. Preclinical models have consistently favored the sequence of cisplatin followed by topotecan, which has been postulated to interfere with repair of platinum-mediated DNA damage. In a phase 1 clinical trial, treatment with cisplatin on day 1 was associated with increased bone marrow toxicity, compared with the reverse sequence (198). In this instance, the sequence recommended for further clinical evaluation was also more toxic, and the question of antitumor efficacy remains to be resolved. When combined with carboplatin, the risk of hematologic toxicity was further accentuated, and a similar sequence-dependent relationship was identified (199). Once again, higher doses of topotecan could be safely administered using the reverse sequence of drug administration (with carboplatin on day 3). Topotecan has also been evaluated in sequence with docetaxel (200), showing a reduction in docetaxel clearance associated with increased neutropenia when topotecan was administered prior to docetaxel, emphasizing that each new combination may require independent evaluation.

Even with a single drug, the schedule of administration can have a significant impact on host toxicity and potential efficacy (Table 13.13). Early studies with paclitaxel utilized an arbitrary 24-hour infusion, which was selected to reduce the risk of HSR. Preclinical data suggested that prolonged exposure (96 hours) might have greater efficacy. Owing to increased bone marrow and mucosal toxicity, the MTD was lowered, and the frequency of serious neuropathy was reduced. However, the 96-hour regimen was not demonstrated to have significant activity in patients with recurrent ovarian cancer (201). In addition, the efficacy of a 3-hour infusion was comparable to a 24-hour infusion in a phase 3 trial (202), reinforcing a clinical shift toward the convenient 3-hour schedule, which achieved a higher MTD, primarily due to a marked decrease in bone marrow toxicity, but with an increased incidence of neuropathy. This was followed by phase 1 evaluation of a weekly low-dose 1-hour infusion, which was almost devoid of serious toxicity, including a decreased incidence of alopecia, with maintenance of clinical efficacy (203). Thus, the optimal preclinical regimen (96-hour exposure)

Table 13.13A Impact of Paclitaxel Infusion Duration and Schedule on Toxicity and Efficacy

Paclitaxel Dose and Schedule			Dose-Limiting Toxicities				
Infusion Duration (hr)	Dose Interval (wk)	Single-Agent Unit Dose (mg/m ² /d)	Neutropenia	Mucositis	Alopecia	Neuropathy	Antitumor Efficacy
96	3–4	80–120	+++	++	+++	+	+++
24	3	135	++	0	+++	++	+++
3	3	175	+	0	+++	+++	+++
1	1	60–80	0	0	+	+	+++

was superseded in the clinical setting by an unexpected series of observations from empiric phase 1 trials, yielding decreased toxicity, improved convenience, and the potential for increased efficacy.

With topotecan, a different relationship was defined (Table 13.13b). Initial studies utilized an inconvenient daily infusion for 5 consecutive days, which was based on preclinical data suggesting that prolonged exposure would be more efficacious. This 5-day regimen achieved a 33% response rate in a GOG phase 2 trial in recurrent platinum-sensitive ovarian cancer with expected dose-limiting neutropenia and thrombocytopenia (204). This was followed by the evaluation of a single 24-hour infusion once every 3 weeks, achieving only a 7% response rate in a similar population (205). An attempt to define an intermediate 3-day regimen achieved only a 14% response rate (206).

Topotecan was also evaluated as a prolonged intravenous infusion for 21 days to maximize the duration of exposure (207). Although the study was conducted in a different patient population, the overall response rate (35%) was similar to the 5-day regimen, and once again there was equivalent hematologic toxicity without dose-limiting nonhematologic toxicity. When evaluated as a weekly treatment program, tolerability and acceptance were improved, but the overall efficacy was reduced (208, 209). In this situation, changes in drug schedule, over a wide range, were associated with substantial differences in efficacy, but without any change in the spectrum or severity of host toxicity, with the exception of reduced hematologic toxicity on the weekly schedule. Thus, each new agent needs to be independently evaluated in the appropriate clinical setting to select the optimal dose and schedule for cancer treatment.

Table 13.13B Impact of Topotecan Infusion Duration and Schedule on Toxicity and Efficacy

Topotecan Dose and Schedule			Dose-Limiting Toxicities				
Infusion Duration (days)	Dose Interval (wk)	Single-Agent Unit Dose (mg/m ² /d)	Neutropenia	Mucositis	Alopecia	Neuropathy	Antitumor Efficacy
21	4	0.40	+++	0	0	0	+++
5	3–4	1.25	+++	0	0	0	+++
3	3	2.00	+++	0	0	0	++
1	3	8.50	+++	0	0	0	+
1	1	1.75	++	0	0	0	–
1	1	4.00	+	0	0	0	+

REFERENCES

- Lissauer A. Zwei Falle von Leucaemie. *Berl Klin Wochenschr.* 1865;2:403.
- Cutler EG, Bradford EH. Action of iron, cod-liver oil, and arsenic on the globular richness of the blood. *Am J Med Sci.* 1878;75:74–84.
- Kandel EV, LeRoy GV. Chronic arsenical poisoning during the treatment of chronic myeloid leukemia. *Arch Intern Med.* 1937;60:846–866.
- Gilman A. The initial clinical trial of nitrogen mustard. *Am J Surg.* 1963;105:574–578.
- Farber S, Diamond LK, Mercer RD, et al. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). *N Engl J Med.* 1948; 238:787.
- Hertz R, Ross GT, Lipsett MB. Primary chemotherapy of nonmetastatic trophoblastic disease in women. *Am J Obstet Gynecol.* 1963;86:808–814.
- Huggins C, Hodges CV. Studies on prostatic cancer. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.* 1941;1:293.
- Tannock I, Frei E 3rd. Possible role of cell kinetics in prediction of the response to cancer therapy. *Natl Cancer Inst Monogr* 1971;34:19–24.
- Lampkin BC, Nagao T, Mauer AM. Synchronization and recruitment in acute leukemia. *J Clin Invest* 1971;50:2204–14.
- Lotem J, Sachs L. Regulation by bc-l2, c-myc and p53 of susceptibility to induction of apoptosis by heat shock and chemotherapy compounds in differentiation-competent and -defective myeloid leukemic cells. *Cell Growth Differ.* 1993;4:41–47.
- Szotek PP, Pieretti-Vanmarcke R, Masiakos PT, et al. Ovarian cancer side population defines cells with stem cell-like characteristics and Mullerian Inhibiting Substance responsiveness. *Proc Natl Acad Sci USA.* 2006;103:11154–11159.
- Glinsky GV. “Stemness” genomics law governs clinical behavior of human cancer: implications for decision making in disease management. *J Clin Oncol.* 2008;26:2846–2853.
- Collins VP, Loeffler RK, Tivey H. Observations on growth rates of human tumors. *AJR Am J Roentgenol.* 1956;76:988–1000.
- Charbit A, Malaise EP, Tubiana M. Relationship between the pathological nature and the growth rate of human tumors. *Eur J Cancer.* 1971;7:307–315.
- Baserga R. The relationship of the cell cycle to tumor growth and control of cell division: a review. *Cancer Res.* 1965;25:581–595.
- Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science.* 2005;307(5706):58–62.

17. Tannock I. Cell kinetics and chemotherapy: a critical review. *Cancer Treat Rep.* 1978;62:1117–1133.
18. Steel GG. Cell loss as a factor in the growth rate of human tumors. *Eur J Cancer.* 1967;3:381–387.
19. Reddy N, Cohen R, Whitehead B, et al. A phase I, open-label, three period, randomized crossover study to evaluate the effect of food on the pharmacokinetics of lapatinib in cancer patients. *Clin Pharmacol Ther.* 2007;81:S16–S17.
20. Ratain MJ, Cohen EE. The value meal: how to save \$1,700 per month or more on lapatinib. *J Clin Oncol.* 2007;25:3397–3398.
21. Lown K, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *J Clin Invest.* 1997;99:2545–2553.
22. Cormio G, Gabriele A, Maneo A, et al. Complete remission of brain metastases from ovarian carcinoma with carboplatin. *Eur J Obstet Gynecol Reprod Biol.* 1998;78:91–93.
23. Murry DJ, Riva L, Poplack DG. Impact of nutrition on pharmacokinetics of anti-neoplastic agents. *Int J Cancer.* 1998;11(suppl):48–51.
24. Engels FK, Sparreboom A, Mathot RA, et al. Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. *Br J Cancer.* 2005;93:173–177.
25. Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. *Lancet Oncol.* 2003;4:277–283.
26. Myers C. The clinical setting and pharmacology of intraperitoneal chemotherapy: an overview. *Semin Oncol.* 1985;12:12–16.
27. TenBokkel Huinink WW, Dubbelman R, Aartsen E, et al. Experimental and clinical results with intraperitoneal cisplatin. *Semin Oncol.* 1985;12:43–46.
28. Howell SB, Zimm S, Markman M, et al. Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. *J Clin Oncol.* 1987;5:1607–1612.
29. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev.* 2011;11:CD005340.
30. Markman M, Brady MF, Spiro NM, et al. Phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube, and peritoneum: a Gynecologic Oncology Group study. *J Clin Oncol.* 1998;16:2620–2624.
31. Knox RJ, Friedlos F, Lydall DA, et al. Mechanism of cytotoxicity of anticancer platinum drugs: evidence that cis-diamminedichloroplatinum(II) and cis-diammine-(1,1-cyclobutanedicarboxylato) platinum(II) differ only in the kinetics of their interaction with DNA. *Cancer Res.* 1986;46:1972–1979.
32. Natarajan G, Malathi R, Holler E. Increased DNA-binding activity of cis-1,1-cyclobutanedicarboxylato-diammineplatinum(II) (carboplatin) in the presence of nucleophiles and human breast cancer MCF-7 cell cytoplasmic extracts: activation theory revisited. *Biochem Pharmacol.* 1999;58:1625–1629.
33. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. *Cancer Control.* 2007;14:32–43.
34. Muss HB, Biganzoli L, Sargent DJ, et al. Adjuvant therapy in the elderly: making the right decision. *J Clin Oncol.* 2007;25:1870–1875.
35. Harlan LC, Clegg LX, Trimble EL. Trends in surgery and chemotherapy for women diagnosed with ovarian cancer in the United States. *J Clin Oncol.* 2003;21:3488–3494.
36. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in trials for cancer drug registration: a 7-year experience by the Food and Drug Administration (FDA). *J Clin Oncol.* 2004;22:4626–4631.
37. Freyer G, Tinker AV. Gynecologic Cancer Inter-Group. Clinical trials and treatment of the elderly diagnosed with ovarian cancer. *Int J Gynecol Cancer.* 2011;21:776–781.
38. Clase CM, Garg AX, Kiberd BA. Prevalence of low glomerular filtration rate in nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol.* 2002;13:1338–1349.
39. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461–470.
40. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31–41.
41. Jelliffe RW. Creatinine clearance: bedside estimate. *Ann Intern Med.* 1973;79:604–605.
42. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis.* 2002;39(suppl. 1):S1–S266.
43. Murray B, Bates J, Buie L. Impact of a new assay for measuring serum creatinine levels on carboplatin dosing. *Am J Health Syst Pharm.* 2012;69:1136–1141.
44. Ivy PS, Zwiebel, Mooney M. Follow-up for Information Letter Regarding AUC-Based Dosing of Carboplatin. Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, 22-October 2010. http://ctep.cancer.gov/content/docs/Carboplatin_Information_Letter.pdf. [Accessed August 20, 2012.]
45. Li YF, Fu S, Hu W, et al. Systemic anticancer therapy in gynecologic cancer patients with renal dysfunction. *Int J Gynecol Cancer.* 2007;17:739–763.
46. Gouyette A, Lemoine R, Adhemar JP, et al. Kinetics of cisplatin in an anuric patient undergoing hemofiltration dialysis. *Cancer Treat Rep.* 1981;65:665–668.
47. Motzer RJ, Niedzwiecki D, Isaacs M, et al. Carboplatin-based chemotherapy with pharmacokinetic analysis for patients with hemodialysis-dependent renal insufficiency. *Cancer Chemother Pharmacol.* 1990;27:234–238.
48. Tanaka E. Clinically important pharmacokinetic drug-drug interactions: role of cytochrome P450 enzymes. *J Clin Pharmacol Ther.* 1998;23:403–416.
49. Boisdron-Celle M, Remaud G, Traore S, et al. 5-fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. *Cancer Lett.* 2007;249:271–282.
50. Nagar S, Blanchard RL. Pharmacogenetics of uridine diphosphoglucuronosyltransferase (UGT) 1A family members and its role in patient response to irinotecan. *Drug Metab Rev.* 2006;38:393–409.
51. Han JY, Lim HS, Shin ES, et al. Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. *J Clin Oncol.* 2006;24:2237–2244.
52. Rouits E, Boisdron-Celle M, Dumont A, et al. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients. *Clin Cancer Res.* 2004;10:5151–5159.
53. Han JY, Lim HS, Yoo YK, et al. Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer. *Cancer.* 2007;110:138–147.
54. Powis G. Effect of human renal and hepatic disease on the pharmacokinetics of anticancer drugs. *Cancer Treat Rev.* 1982;9:85–124.
55. Lee Villano J, Mehta D, Radhakrishnan L. Abraxane induced life-threatening toxicities with metastatic breast cancer and hepatic insufficiency. *Invest New Drugs.* 2006;24:455–456.
56. Hande KR, Wolff SN, Greco FA, et al. Etoposide kinetics in patients with obstructive jaundice. *J Clin Oncol.* 1990;8:1101–1107.
57. Kivisto KT, Kroemer HK, Eichelbaum M. The role of cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. *Br J Clin Pharmacol.* 1995;40:523–530.
58. Fojo AT, Ueda K, Slamon DJ, et al. Expression of multidrug resistance gene in human tumors and tissues. *Proc Natl Acad Sci USA.* 1987;84:265–269.
59. Nunberg JH, Kaufman RJ, Schimke RT, et al. Amplified dihydrofolate reductase genes are localized to a homogeneously staining region in a single chromosome in a methotrexate-resistant Chinese hamster ovary cell line. *Proc Natl Acad Sci USA.* 1978;75:5553–5556.
60. Fojo AT, Whang-Peng J, Gottesman MM, et al. Amplification of DNA sequences in human multidrug-resistant KB carcinoma cells. *Proc Natl Acad Sci USA.* 1985;82:7661–7665.
61. Ling V, Thompson LH. Reduced permeability in CHO cells as a mechanism of resistance to colchicine. *J Cell Physiol.* 1974;83:103–116.
62. Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer.* 2007;7:573–584.
63. Schondorf T, Scharl A, Kurbacher CM, et al. Amplification of the *mdr1*-gene is uncommon in recurrent ovarian carcinomas. *Cancer Lett.* 1999;146:195–199.
64. Rubin SC, Finstad CL, Hoskins WJ, et al. Expression of P-glycoprotein in epithelial ovarian cancer: evaluation as a marker of multidrug resistance. *Am J Obstet Gynecol.* 1990;163:69–73.
65. Bergman AM, Pinedo HM, Talianidis I, et al. Increased sensitivity to gemcitabine of P-glycoprotein and multidrug resistance-associated protein-overexpressing human cancer cell lines. *Br J Cancer.* 2003;88:1963–1970.
66. Belinsky MG, Bain LJ, Balsara BB, et al. Characterization of MOAT-C and MOAT-D, new members of the MRP/cMOAT subfamily of transporter proteins. *J Natl Cancer Inst.* 1998;90:1735–1741.
67. Maliepaard M, van Gastelen MA, de Jong IA, et al. Overexpression of the BCRP/MXR/ABCP gene in a topotecan-selected ovarian tumor cell line. *Cancer Res.* 1999;59:4559–4563.
68. Ishida S, Lee J, Thiele DJ, et al. Uptake of the anticancer drug cisplatin mediated by the copper transporter Ctr1 in yeast and mammals. *Proc Natl Acad Sci USA.* 2002;99:14298–14302.
69. Holzer AK, Howell SB. The internalization and degradation of human copper transporter 1 following cisplatin exposure. *Cancer Res.* 2006;66:10944–10952.
70. Samimi G, Howell SB. Modulation of the cellular pharmacology of JM118, the major metabolite of satraplatin, by copper influx and efflux transporters. *Cancer Chemother Pharmacol.* 2006;57:781–788.
71. Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol.* 2009;27:5431–5438.
72. Green JA, Vistica DT, Young RC, et al. Potentiation of melphalan cytotoxicity in human ovarian cancer cell lines by glutathione depletion. *Cancer Res.* 1984;44:5427–5431.
73. Sadowitz PD, Hubbard BA, Dabrowski JC, et al. Kinetics of cisplatin binding to cellular DNA and

- modulations by thiol-blocking agents and thiol drugs. *Drug Metab Dispos.* 2002;30:183–190.
74. Daubeuf S, Balin D, Leroy P, et al. Different mechanisms for gamma-glutamyltransferase-dependent resistance to carboplatin and cisplatin. *Biochem Pharmacol.* 2003;66:595–604.
 75. Hanigan MH, Lykissa ED, Townsend DM, et al. Gamma-glutamyl transpeptidase-deficient mice are resistant to the nephrotoxic effects of cisplatin. *Am J Pathol.* 2001;159:1889–1894.
 76. O'Dwyer PJ, Hamilton TC, LaCreta FP, et al. Phase I trial of buthionine sulfoximine in combination with melphalan. *J Clin Oncol.* 1996;14:249–256.
 77. Bailey HH, Ripple G, Tutsch KD, et al. Phase I study of continuous-infusion L-S, R-buthionine sulfoximine with intravenous melphalan. *J Natl Cancer Inst.* 1997;89:1789–1796.
 78. Holford J, Beale PJ, Boxall FE, et al. Mechanisms of drug resistance to the platinum complex ZD0473 in ovarian cancer cell lines. *Eur J Cancer.* 2000;36:1984–1990.
 79. Gore ME, Atkinson RJ, Thomas H, et al. A phase II trial of ZD0473 in platinum-pretreated ovarian cancer. *Eur J Cancer.* 2002;38:2416–2420.
 80. Masuda H, Ozols RF, Lai GM, et al. Increased DNA repair as a mechanism of acquired resistance to cis-diamminedichloroplatinum (II) in human ovarian cancer cell lines. *Cancer Res.* 1988;48:5713–5716.
 81. Aebi S, Kurdihaidar B, Gordon R, et al. Loss of DNA mismatch repair in acquired resistance to cisplatin. *Cancer Res.* 1996;56:3087–3090.
 82. Gifford G, Paul J, Vasey PA, et al. The acquisition of hMLH1 methylation in plasma DNA after chemotherapy predicts poor survival for ovarian cancer patients. *Clin Cancer Res.* 2004;10:4420–4426.
 83. Plumb JA, Strathdee G, Sludden J, et al. Reversal of drug resistance in human tumor xenografts by 2'-deoxy-5-azacytidine-induced demethylation of the hMLH1 gene promoter. *Cancer Res.* 2000;60:6039–6044.
 84. Raymond E, Chaney SG, Taamma A, et al. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol.* 1998;9:1053–1071.
 85. Vaisman A, Varchenko M, Umar A, et al. The role of hMLH1, hMSH3, and hMSH6 defects in cisplatin and oxaliplatin resistance: correlation with replicative bypass of platinum-DNA adducts. *Cancer Res.* 1998;58:3579–3585.
 86. Piccart MJ, Green JA, Lacave AJ, et al. Oxaliplatin or paclitaxel in patients with platinum-pretreated advanced ovarian cancer: a randomized phase II study of the European Organization for Research and Treatment of Cancer Gynecology Group. *J Clin Oncol.* 2000;18:1193–1202.
 87. Fracasso PM, Blessing JA, Morgan MA, et al. Phase II study of oxaliplatin in platinum-resistant and refractory ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003;21:2856–2859.
 88. Dabholkar M, Bostick-Bruton F, Weber C, et al. ERCC1 and ERCC2 expression in malignant tissues from ovarian cancer patients. *J Natl Cancer Inst.* 1992;84:1512–1517.
 89. Olausson KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med.* 2006;355:983–991.
 90. Zheng Z, Chen T, Li X, et al. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. *N Engl J Med.* 2007;356:800–808.
 91. Cobo M, Isla D, Massuti B, et al. Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer. *J Clin Oncol.* 2007;25:2747–2754.
 92. Rubatt JM, Darcy KM, Tian C, et al. Pre-treatment tumor expression of ERCC1 in women with advanced stage epithelial ovarian cancer is not predictive of clinical outcomes: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2012;125:421–426.
 93. Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA.* 2012;307:382–390.
 94. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474:609–615.
 95. Penston RT, Oliva E, Skates SJ, et al. Expression of multidrug resistance-1 protein inversely correlates with paclitaxel response and survival in ovarian cancer patients: a study in serial samples. *Gynecol Oncol.* 2004;93:98–106.
 96. Fracasso PM, Brady MF, Moore DH, et al. Phase II study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma: a gynecologic oncology group study. *J Clin Oncol.* 2001;19:2975–2982.
 97. Lhomme C, Joly F, Walker JL, et al. Phase III study of valspodar (PSC 833) combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone in patients with stage IV or suboptimally debulked stage III epithelial ovarian cancer or primary peritoneal cancer. *J Clin Oncol.* 2008;26:2674–2682.
 98. Yusuf RZ, Duan Z, Lamendola DE, et al. Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation. *Curr Cancer Drug Targets.* 2003;3:1–19.
 99. Lamendola DE, Duan Z, Penston RT, et al. Beta tubulin mutations are rare in human ovarian carcinoma. *Anticancer Res.* 2003;23:681–686.
 100. Carrara L, Guzzo F, Roque DM, et al. Differential in vitro sensitivity to paclitaxel versus paclitaxel in uterine and ovarian carcinosarcoma cell lines is linked to tubulin-beta-III expression. *Gynecol Oncol.* 2012;125:231–236.
 101. De Donato M, Mariani M, Petrella L, et al. Class III β -tubulin and the cytoskeletal gateway for drug resistance in ovarian cancer. *J Cell Physiol.* 2012;227:1034–1041.
 102. Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m²) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2006;101:436–440.
 103. Trent JM, Buick RN, Olson S, et al. Cytologic evidence for gene amplification in methotrexate-resistant cells obtained from a patient with ovarian adenocarcinoma. *J Clin Oncol.* 1984;2:8–15.
 104. Cowan KH, Jolivet J. A methotrexate-resistant human breast cancer cell line with multiple defects, including diminished formation of methotrexate polyglutamates. *J Biol Chem.* 1984;259:10793–10800.
 105. Obata T, Endo Y, Murata D, et al. The molecular targets of antitumor 2'-deoxycytidine analogues. *Curr Drug Targets.* 2003;4:305–313.
 106. Zhou B, Mo X, Liu X, et al. Human ribonucleotide reductase M2 subunit gene amplification and transcriptional regulation in a homogeneous staining chromosome region responsible for the mechanism of drug resistance. *Cytogenet Cell Genet.* 2001;95:34–42.
 107. Jung CP, Motwani MV, Schwartz GK. Flavopiridol increases sensitization to gemcitabine in human gastrointestinal cancer cell lines and correlates with down-regulation of ribonucleotide reductase M2 subunit. *Clin Cancer Res.* 2001;7:2527–2536.
 108. Johnston PG, Lenz HJ, Leichman CG, et al. Thymidylate synthase gene and protein expression correlate and are associated with response to 5-fluorouracil in human colorectal and gastric tumors. *Cancer Res.* 1995;55:1407–1412.
 109. Salonga D, Danenberg KD, Johnson M, et al. Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. *Clin Cancer Res.* 2000;6:1322–1327.
 110. Fidler IJ, Kripke ML. Metastasis results from preexisting variant cells within a malignant tumor. *Science.* 1977;197:893–895.
 111. Kern DH, Weisenthal LM. Highly specific prediction of antineoplastic drug resistance with an in vitro assay using suprapharmacologic drug exposures. *J Natl Cancer Inst.* 1990;82:582–588.
 112. Cortazar P, Johnson BE. Review of the efficacy of individualized chemotherapy selected by in vitro drug sensitivity testing for patients with cancer. *J Clin Oncol.* 1999;17:1625–1631.
 113. Nagourney RA, Brewer CA, Radecki S, et al. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol.* 2003;88:35–39.
 114. Levin L, Hryniuk W. Dose intensity analysis of chemotherapy regimens in ovarian cancer. *J Clin Oncol.* 1987;5:756–767.
 115. McGuire WP, Hoskins WJ, Brady MF, et al. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 1995;13:1589–1599.
 116. Schilder RJ, Gallo JM, Millenson MM, et al. Phase I trial of multiple cycles of high-dose carboplatin, paclitaxel, and topotecan with peripheral-blood stem-cell support as front-line therapy. *J Clin Oncol.* 2001;19:1183–1194.
 117. Tiersten A, Sellick M, Smith DH, et al. Phase I/II study of tandem cycles of high-dose chemotherapy followed by autologous hematopoietic stem cell support in women with advanced ovarian cancer. *Int J Gynecol Cancer.* 2006;16:57–64.
 118. Mobus V, Wandt H, Frickhofen N, et al. High-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: results of a phase III intergroup trial of the AGO-Ovar/AIO and EBMT. *J Clin Oncol.* 2007;25(27):4187–4193.
 119. Kummel S, Krocker J, Kohls A, et al. Randomised trial: survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer. *Br J Cancer.* 2006;94:1237–1244.
 120. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet.* 2009;374:1331–1338.
 121. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996;334:1–6.
 122. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003;21:3194–3200.
 123. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2004;22(11):2159–2166.
 124. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without

- paclitaxel in stage IVB, recurrent or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol*. 2004;22(15):3113–3119.
125. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009;27:4649–4655.
 126. Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25:526–531.
 127. Muggia FM, Braly PS, Brady ME, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2000;18:106–115.
 128. The International Collaborative Ovarian Neoplasm (ICON) Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet*. 2002;360:505–515.
 129. Young RC, Brady ME, Nieberg RK, et al. Adjuvant treatment for early ovarian cancer: a randomized phase III trial of intraperitoneal ^{32}P or cyclophosphamide-cisplatin: A Gynecologic Oncology Group study. *J Clin Oncol*. 2003; 21(23):4350–4355.
 130. Trimbos JB, Vergote I, Bolis G, et al. EORTC-ACTION collaborators. European Organisation for Research and Treatment of Cancer—Adjuvant ChemoTherapy in Ovarian Neoplasm. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer—Adjuvant ChemoTherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst*. 2003;95:113–125.
 131. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2006;24:36–44.
 132. Wolfson AH, Brady ME, Rocereto T, et al. A Gynecologic Oncology Group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I–IV carcinosarcoma (CS) of the uterus. *Gynecol Oncol*. 2007;107(2):177–185.
 133. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25:2804–2810.
 134. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med*. 2010;363:943–953.
 135. Eisenhauer EA, Therasse P, Bogaerts J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
 136. Rustin GJ, Bast RC Jr, Kelloff GJ, et al. Use of CA-125 in clinical trial evaluation of new therapeutic drugs for ovarian cancer. *Clin Cancer Res*. 2004;10:3919–3926.
 137. Vergote I, Rustin GJ, Eisenhauer EA, et al. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). Gynecologic Cancer Intergroup. *J Natl Cancer Inst*. 2000;92:1534–1535.
 138. Rustin GJ. Use of CA-125 to assess response to new agents in ovarian cancer trials. *J Clin Oncol*. 2003;21(suppl. 10):187–193.
 139. Tsao AS, Garland L, Redman M, et al. A practical guide of the Southwest Oncology Group to measure malignant pleural mesothelioma tumors by RECIST and modified RECIST criteria. *J Thorac Oncol*. 2011;6:598–601.
 140. Hunter RJ, Namjo MA, Thaker PH, et al. Dosing chemotherapy in obese patients: actual versus assigned body surface area (BSA). *Cancer Treat Rev*. 2009;35:69–78.
 141. Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2012;30:1553–1561.
 142. Fanucchi M, Gaspy J, Crawford J, et al. Effects of polyethylene glycol-conjugated recombinant human megakaryocyte growth and development factor on platelet counts after chemotherapy for lung cancer. *N Engl J Med*. 1997;336:404–409.
 143. Del Mastro L, Venturini M, Lionetto R, et al. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. *J Clin Oncol*. 1997; 15:2715–2721.
 144. Barosi G, Marchetti M, Liberato NL. Cost-effectiveness of recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia. *Br J Cancer*. 1998;78:781–787.
 145. Khuri FR. Weighing the hazards of erythropoiesis stimulation in patients with cancer. *N Engl J Med*. 2007;356:2445–2448.
 146. Steinbrook R. Erythropoietin, the FDA, and oncology. *N Engl J Med*. 2007;356:2448–2451.
 147. Food and Drug Administration. FDA Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Procrit, Epogen, and Aranesp. Published February 26, 2010. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm>. [Accessed August 20, 2012.]
 148. Center for Medicare and Medicaid Services. National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (110.21). Published July 30, 2007. <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=322>. [Accessed August 20, 2012.]
 149. Bonnetterre J, Chevallier B, Metz R, et al. A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. *J Clin Oncol*. 1990;8:1063–1069.
 150. du Bois A, Vach W, Kiechle M, et al. Pathophysiology, severity, pattern, and risk factors for carboplatin-induced emesis. *Oncology*. 1996; 53(suppl. 1):46–50.
 151. Friedlander ML, Sims K, Kearsely JH. Impairment of recall improves tolerance of cytotoxic chemotherapy. *Lancet*. 1983;2:686.
 152. Dodd MJ, Miaskowski C, Greenspan D, et al. Radiation-induced mucositis: a randomized clinical trial of micronized sucralfate versus salt & soda mouthwashes. *Cancer Invest*. 2003; 21:21–33.
 153. Nottage M, McLachlan SA, Brittain MA, et al. Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. *Support Care Cancer*. 2003;11:41–47.
 154. Rosen LS, Abdi E, Davis ID, et al. Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. *J Clin Oncol*. 2006;24:5194–5200.
 155. Henke M, Alfonsi M, Foa P, et al. Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: a randomized, placebo-controlled trial. *J Clin Oncol*. 2011; 29:2815–2820.
 156. Le QT, Kim HE, Schneider CJ, et al. Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: a randomized, placebo-controlled study. *J Clin Oncol*. 2011;29:2808–2814.
 157. Muggia FM, Hainsworth JD, Jeffers S. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol*. 1997;15:987–993.
 158. Kassner E. Evaluation and treatment of chemotherapy extravasation injuries. *J Pediatr Oncol Nurs*. 2000;17:135–148.
 159. Schulmeister L, Camp-Sorrell D. Chemotherapy extravasation from implanted ports. *Oncol Nurs Forum*. 2000;27:531–538.
 160. Langer SW, Sehested M, Jensen PB. Treatment of anthracycline extravasation with dexrazoxane. *Clin Cancer Res*. 2000;6:3680–3686.
 161. Mouridsen HT, Langer SW, Buter J, et al. Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. *Ann Oncol*. 2007;18:546–550.
 162. Verstappen CC, Heimans JJ, Hoekman K, et al. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs*. 2003;63:1549–1563.
 163. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol*. 2002; 249:9–17.
 164. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol*. 2006;24:1633–1642.
 165. Hausheer FH, Schilsky RL, Bain S, et al. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. *Semin Oncol*. 2006;33:15–49.
 166. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23:7794–7803.
 167. Wilding G, Caruso R, Lawrence TS, et al. Retinal toxicity after high-dose cisplatin therapy. *J Clin Oncol*. 1985;3:1683–1689.
 168. Land SR, Kopec JA, Cecchini RS, et al. Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. *J Clin Oncol*. 2007; 25:2205–2211.
 169. Pasetto LM, D'Andrea MR, Rossi E, et al. Oxaliplatin-related neurotoxicity: how and why? *Crit Rev Oncol Hematol*. 2006;59:159–168.
 170. Krishnan AV, Goldstein D, Friedlander M, et al. Oxaliplatin and axonal Na⁺ channel function in vivo. *Clin Cancer Res*. 2006;12:4481–4484.
 171. Hochster HS, Grothey A, Childs BH. Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. *J Clin Oncol*. 2007; 25:4028–4029.
 172. Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the functional assessment of cancer therapy/Gynecologic Oncology Group—neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer*. 2003;13:741–748.

173. Pachman DR, Barton DL, Watson JC, et al. Chemotherapy-induced peripheral neuropathy: prevention and treatment. *Clin Pharmacol Ther.* 2011;90:377–387.
174. Moore DH, Donnelly J, McGuire WP, et al. Limited access trial using amifostine for protection against cisplatin- and three-hour paclitaxel-induced neurotoxicity: a phase II study of the Gynecologic Oncology Group. *J Clin Oncol.* 2003;21:4207–4213.
175. van Deventer H, Bernard S. Use of gabapentin to treat taxane-induced myalgias. *J Clin Oncol.* 1999;17:434–435.
176. Pelgrims J, De Vos F, Van den Brande J, et al. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer.* 2000;82:291–294.
177. Santoso JT, Lucci JA 3rd, Coleman RL, et al. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. *Cancer Chemother Pharmacol.* 2003;52:13–18.
178. Andriole GL, Sandlund JT, Miser JS, et al. The efficacy of mesna as a uroprotectant in patients with hemorrhagic cystitis receiving further orazaphosphorine chemotherapy. *J Clin Oncol.* 1987;5:799–803.
179. Bookman MA, Kloth DD, Kover PE, et al. Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. *Ann Oncol.* 1997;8:611–614.
180. Weiss RB, Donehower RC, Weirnik PH, et al. Hypersensitivity reactions from Taxol. *J Clin Oncol.* 1990;8:1263–1268.
181. Markman M, Kennedy A, Webster K, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol.* 1999;17:1141–1145.
182. Rose PG, Fusco N, Smrekar M, et al. Successful administration of carboplatin in patients with clinically documented carboplatin hypersensitivity. *Gynecol Oncol.* 2003;89:429–433.
183. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol.* 2005;99:393–399.
184. Joly F, Ray-Coquard I, Fabbro M, et al. Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin compared to carboplatin-paclitaxel combination: analysis from the GCG CALYPSO relapsing ovarian cancer trial. *Gynecol Oncol.* 2011;122:226–232.
185. Sikora K, Advani S, Koroltchouk V, et al. Essential drugs for cancer therapy: a World Health Organization consultation. *Ann Oncol.* 1999;10:385–390.
186. Cragg GM, Newman DJ, Weiss RB. Coral reefs, forests, and thermal vents: the worldwide exploration of nature for novel antitumor agents. *Semin Oncol.* 1997;24:156–163.
187. Wani MC, Taylor HL, Wall ME, et al. Plant antitumor agents. VI. The isolation and structure of Taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc.* 1971;93:2325–2327.
188. Wall ME, Wani MC, Cook CE, et al. Plant antitumor agents. I. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*. *J Am Chem Soc.* 1966;88:3888–3890.
189. Gehan EA. The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. *J Chronic Dis.* 1961;13:346–353.
190. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clin Trials.* 1989;10:1–10.
191. Estey EH, Thall PF. New designs for phase 2 clinical trials. *Blood.* 2003;102:442–448.
192. Steinberg SM, Venzon DJ. Early selection in a randomized phase II clinical trial. *Stat Med.* 2002;21:1711–1726.
193. Strauss N, Simon R. Investigating a sequence of randomized phase II trials to discover promising treatments. *Stat Med.* 1995;14:1479–1489.
194. Bookman MA. First-line chemotherapy in epithelial ovarian cancer. *Clin Obstet Gynecol.* 2012;55:96–113.
195. Rowinsky EK, Gilbert M, McGuire WP, et al. Sequences of Taxol and cisplatin: a phase I and pharmacologic study. *J Clin Oncol.* 1991;9:1692–1703.
196. Rowinsky EK, Citardi M, Noe DA, et al. Sequence-dependent cytotoxicity between cisplatin and the antimicrotubule agents Taxol and vincristine. *J Cancer Res Clin Oncol.* 1993;119:737–743.
197. Jekunen AP, Christen RD, Shalinsky DR, et al. Synergistic interaction between cisplatin and Taxol in human ovarian carcinoma cells in vitro. *Br J Cancer.* 1994;69:299–306.
198. Rowinsky EK, Kaufmann SH, Baker SD, et al. Sequences of topotecan and cisplatin: phase I, pharmacological and in vitro studies to examine sequence dependence. *J Clin Oncol.* 1996;14:3074–3084.
199. Bookman MA, McMeekin DS, Fracasso P. Sequence-dependence of hematologic toxicity using carboplatin and topotecan for primary therapy of advanced epithelial ovarian cancer: a phase I study of the Gynecologic Oncology Group. *Gynecol Oncol.* 2006;103:473–478.
200. Zamboni WC, Egorin MJ, Van Echo DA, et al. Pharmacokinetic and pharmacodynamic study of the combination of docetaxel and topotecan in patients with solid tumors. *J Clin Oncol.* 2000;18:3288–3294.
201. Markman M, Rose PG, Jones E, et al. Ninety-six-hour infusional paclitaxel as salvage therapy of ovarian cancer patients previously failing treatment with 3-hour or 24-hour paclitaxel infusion regimens. *J Clin Oncol.* 1998;16:1849–1851.
202. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol.* 1994;12:2654–2666.
203. Fennelly D, Aghajanian C, Shapiro F, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol.* 1997;15:187–192.
204. McGuire WP, Blessing JA, Bookman MA, et al. Topotecan has substantial antitumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2000;18:1062–1067.
205. Markman M, Blessing JA, Alvarez RD, et al. Phase II evaluation of 24-h continuous infusion topotecan in recurrent, potentially platinum-sensitive ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2000;77:112–115.
206. Miller DS, Blessing JA, Lentz SS, et al. Phase II evaluation of three-day topotecan in recurrent platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. *Cancer.* 2003;98:1664–1669.
207. Hochster H, Wadler S, Runowicz C, et al. Activity and pharmacodynamics of 21-day topotecan infusion in patients with ovarian cancer previously treated with platinum-based chemotherapy: New York Gynecologic Oncology Group. *J Clin Oncol.* 1999;17:2553–2561.
208. Herzog TJ, Sill MW, Walker JL, et al. A phase II study of two topotecan regimens evaluated in recurrent platinum-sensitive ovarian, fallopian tube or primary peritoneal cancer: a Gynecologic Oncology Group Study (GOG 146Q). *Gynecol Oncol.* 2011;120:454–458.
209. Sehouli J, Stengel D, Harter P, et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol.* 2011;29:242–248.

Pharmacology and Therapeutics in Gynecologic Cancer

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The determinants of effective cancer drug therapies include drug disposition, tumor kinetics, and drug resistance. These factors profoundly influence the cytotoxicity of each anticancer drug and must be considered in designing therapeutic regimens. These principles are discussed in Chapter 15. In this chapter, we elaborate on the basic and clinical pharmacology of cancer chemotherapeutic and biologic agents and provide a limited discussion of cytotoxic, molecularly targeted antiangiogenesis and modulating/supportive care drugs useful in the treatment of patients with gynecologic cancer.

DETERMINANTS OF EFFECTIVE DRUG THERAPIES

Drug Disposition Factors

The term *pharmacokinetics* describes the time course of drug disposition in body fluids and tissues through the use of mathematical models. These models use an equation or set of equations to describe the concentration-versus-time profile of a specific drug after administration into the body. The models are often illustrated by box diagrams, with each box or compartment corresponding to a region of the body, although the compartments may not represent real anatomic regions. A drug is considered to be uniformly distributed within a compartment if its concentration within tissues has reached homogeneity.

Pharmacokinetic models may be useful in predicting the plasma or tissue concentrations of drugs in the body after any one of several routes or methods of drug administration. The simplest model has one compartment into which the drug is assumed to be instantaneously introduced, and elimination occurs by one linear route. The disappearance of the drug from this compartment can be described by a straight line if plotted on semilogarithmic graph paper. As discussed by Tozer (1), no one-compartment pharmacokinetic model can be used to describe the disposition of commonly used anticancer drugs; nevertheless, the one-compartment pharmacokinetic model lends itself to an understanding of the concept of plasma half-life (i.e., $t_{1/2}$), which represents the time required for the concentration of a drug at any point on the plasma concentration · time elimination curve to achieve half its value. This constant may be applied repeatedly, so that, for instance, only 25% of the drug remains in 2 half-lives. The equation for plasma half-life that can be applied to any linear plasma concentration-time elimination curve is as follows: $t_{1/2} = 0.693/\text{slope of the linear elimination curve}$ (i.e., λ_z or rate constant for that part of the curve). Unfortunately, the determination of the terminal half-life of a drug is often poorly reproducible because it is highly

dependent on measuring multiple plasma levels, often at the limit of drug assay sensitivity.

Pharmacokinetic Models

The pharmacokinetics of virtually all anticancer drugs requires 2- or 3-compartment models for their mathematic description. These models are commonly referred to as biphasic or triphasic models (i.e., 2 or 3 phases observed on semilogarithmic plots). Conceptually, the one-compartment model relates to a drug that remains confined to the intravascular space after intravenous injection, and the 2- or 3-compartment model allows the pharmacokinetic description of anticancer drugs whose ultimate targets are beyond the intravascular space in tumor tissues.

Drug Clearance and AUC Concepts

Wisdom dictates using the simplest mathematical model that can provide the “best” fit of the actual plasma concentration time data using nonlinear least squares regression. After the mathematic model is selected, it is possible to generate the important pharmacokinetic parameters that describe the disposition of a specific anticancer drug within the body. Besides the determination of the terminal-phase plasma half-life (i.e., half-life related to the second or third phase of biphasic or triphasic plasma concentration time data), the area under the plasma disappearance curve ($AUC_{0-\infty}$) and total body plasma clearance (CL_T) are the most significant and clinically useful pharmacokinetic parameters. The relationship between AUC and clearance is simplified to: $\text{dose} = \text{clearance} \times \text{area}$.

Although the height of an anticancer drug’s peak plasma level ($C_{\max}$) generally correlates with peak dose and the degree of toxicity, the drug’s plasma AUC tends to correlate better with its ultimate antitumor activity and normal tissue side effects. For example, when identical doses of melphalan are administered first orally and then intravenously at a 1-month interval, because of its poor oral availability, the melphalan plasma AUC after the oral dose would be only one-third of that after the intravenous dose (Fig. 14.1). As would be anticipated, the equivalent intravenous dose of melphalan was associated with a two-fold to threefold deeper nadir in granulocytes and a greater than twofold increase in objective response rates in various cancer types (e.g., myeloma).

The plasma AUC (in $\text{mg/mL} \cdot \text{hour}$) can be estimated through the use of a pharmacokinetic model or measured directly by plotting the drug’s plasma concentrations against time on semilogarithmic graph paper. Then, it is possible to calculate the areas of successive trapezoids under the concentration vs. time

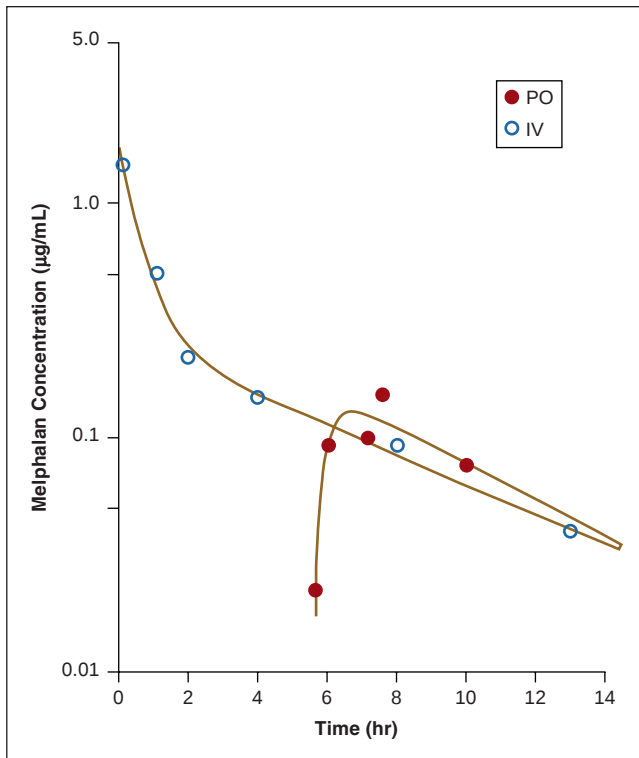


FIGURE 14.1. Plasma disappearance curves for intravenous and oral (tablets) melphalan (0.6 mg/kg) in a patient with ovarian cancer. The melphalan plasma AUC associated with the bolus oral dose was only one-third of that associated with the intravenous dose.

Source: Reprinted with permission from Alberts DS, Chang SY, Chen HS, et al. Oral melphalan kinetics. *Clin Pharmacol Ther.* 1979;26:737–745.

curve wherein the upper surface of the trapezoid is a line that connects 2 successive plasma concentration data points. By convention, when the plasma AUC is measured in this way, the terminal part of the AUC is calculated using a triangular area, rather than a trapezoid.

After the plasma AUC has been determined, it is possible to derive the anticancer drug's total body clearance rate based on the following formula: $CL_T = \text{dose (mg)}/\text{AUC (mg/mL} \cdot \text{hour)}$. The resulting CL_T is measured in units of milliliters or liters per minutes or hours, sometimes with normalization to the body surface area. The total body clearance of an anticancer drug depends on the drug's dose and plasma AUC and represents the rate at which the drug is eliminated from the entire body. The drug's total body clearance is made up of the combination of renal clearance (CL_R) plus nonrenal clearance (CL_{NR}). The renal clearance of a drug can be calculated by the following equation: $CL_R = Ae_c/\text{AUC}$, where Ae_c is the total amount of the unchanged drug that is excreted in the urine. For many drugs that are glomerularly filtered but not reabsorbed, renal clearance is proportional to creatinine clearance. In a patient with severe renal impairment, if nonrenal clearance is unaltered, the total body clearance of the drug is diminished significantly. This phenomenon is observed in patients with relatively severe renal impairment who receive drugs like methotrexate and carboplatin, both of which are eliminated mainly through renal excretion.

Volume of Distribution

The volume of distribution (Vd) of an anticancer drug is another important pharmacokinetic parameter that relates the drug plasma concentration (measured at the time of administration through

extrapolation of the terminal phase of the concentration-time curve to 0 time) to the total amount of drug in the body. Thus, Vd_{area} represents the volume of distribution of a drug in the terminal phase of its elimination from the body, and in its simplest form, $Vd = \text{amount of drug in the body} \div \text{plasma concentration}$. Since drug levels are typically measured only in the plasma compartment and not in tissues, most reported Vd values represent the "apparent" Vd of the drug in the plasma. Thus, these Vd values represent a theoretic plasma volume that would account for the drug's plasma levels after administration. The volume of distribution in the terminal phase can be derived using the following equation: $Vd_{area} = \text{dose}/\text{AUC slope } (\lambda_z)$, where λ_z is the rate constant in the terminal phase of a biphasic or triphasic elimination curve.

Linear and Nonlinear Kinetics

Most drugs exhibit linear pharmacokinetics, which in its simplest configuration means that the C_{max} and AUC are proportionate to the dose, and the $T_{1/2}$, Vd and clearance are constant; that is, they do not change with the dose. Linearity helps make predictions about the effects of changes in doses since the AUC (and the biological effects) of the drug should change in proportion to the dose. Drugs with nonlinear pharmacokinetics such as aspirin, ethanol, and phenytoin, have saturable elimination patterns. This means that small dose changes can disproportionately increase the AUC and the drug's biologic effects. Drugs with nonlinear pharmacokinetic patterns may therefore have longer $T_{1/2}$ s and much lower clearance values when the dose is increased.

As discussed by Collins and Dedrick (2), there are at least 2 explanations for nonlinear kinetics. First, nonlinearity may be caused by changes in drug excretion at high doses. For example, at extremely high doses of methotrexate (i.e., 7 to 8 g/m²), the drug load outstrips renal tubular secretion capacity. Second, nonlinearity may be observed for drugs that depend almost completely on elimination through a specific degradative enzyme system (e.g., antimetabolites). Drugs like cytarabine and 5-fluorouracil administered in high doses may overcome the capacity of their respective degradative enzymes with a resultant decrease in their total body clearance rates and an increase in plasma levels that are more than proportionate to their doses.

Intraperitoneal Drug Pharmacokinetics

Intraperitoneal drug administration has become an increasingly important therapeutic strategy in the management of patients with advanced ovarian cancer who have minimal residual intraperitoneal disease after primary or secondary exploratory laparotomies. Three large phase III trials in the Gynecologic Oncology Group (GOG) and the Southwest Oncology Group (GOG-104/SWOG-8501, GOG-114, and GOG-172) comparing various cisplatin-based combination chemotherapeutic regimens administered intravenously (IV) or intraperitoneally (IP) have documented significant survival advantages for the IP cisplatin treatment arms (3–5). In GOG-172, an IP regimen (IV paclitaxel on day 1, IP cisplatin on day 2, and IP paclitaxel on day 8) was associated with a 25% reduction in the risk of death compared to the intravenously administered regimen (IV paclitaxel plus cisplatin) ($p = 0.03$) (4). A meta-analysis of IP cisplatin-based randomized trials found that both overall and progression-free survival were significantly improved with IP regimens ($p = 0.0007$ and $p = 0.001$, respectively) (6).

Despite the superior activity of this IV paclitaxel/IP cisplatin-paclitaxel regimen evaluated in GOG-172, there was significantly

more hematologic, gastrointestinal, metabolic, and neurologic toxicity compared to intravenous paclitaxel and cisplatin (7); however, the dose of cisplatin on the IP arm was 33% higher than that of the IV arm. When combining the toxicity data across IP randomized trials, only acute gastrointestinal toxicity ($p = 0.01$) and fever ($p = 0.04$) are significantly higher among patients treated with IP therapy and ototoxicity was significantly higher among patients receiving IV treatment as compared to those receiving IP therapy ($p = 0.004$) (6). A study of patient quality of life within GOG-172 demonstrated that patient quality of life was significantly lower during IP treatment compared to IV therapy, but 1 year after treatment, the overall quality of life of patients receiving IP or IV therapy was equivalent (8). However, long-term neurotoxicity remained higher among patients treated with IP therapy. These short- and long-term effects should be balanced against the documented 16-month improvement in survival compared with IV cisplatin/paclitaxel ($p = 0.03$) (7). This increase in survival is similar to that achieved when IV cisplatin was initially added to primary combination chemotherapeutic regimens for the treatment of this disease (9).

The incremental increase in cisplatin efficacy associated with IP administration likely results from the delivery of approximately 20-fold greater concentrations of cisplatin into the IP space than is achievable with IV administration. Anticancer drugs with known activity against ovarian cancer that undergo slow clearance from the IP space into the systemic circulation without causing significant chemical peritonitis are the favored IP compounds. Clearly, paclitaxel falls into this category. IP administration of this large taxane molecule results in 1,000-fold greater concentration time products in the IP space than is achievable with IV administration (10). In contrast, cisplatin undergoes rapid clearance from the systemic circulation after administration via the IP route. Caution must be taken when considering other agents for research-based IP administration, as some cytotoxic agents have not demonstrated efficacy and have been associated with excessive toxicity when given IP (e.g., mitoxantrone, doxorubicin) (11–14).

As with the IV administration of anticancer drugs, the drug clearance rate from the IP space is the most useful pharmacokinetic parameter for comparing drugs that are administered by the IP route in the treatment of ovarian cancer. The peritoneal clearance rate can be calculated by dividing the drug dose by its IP concentration $\cdot$ time product, which must be measured with repeated IP fluid content sampling. Intraperitoneal drugs with slow clearance rates are favored because they result in prolonged exposure of the IP tumor bed to high concentrations of anticancer drug. It is also possible to assess the pharmacokinetic characteristics of drug doses by comparing their peak IP concentration with peak plasma concentration after IP dosing or comparing their IP concentration $\cdot$ time product (AUC_{IP}) with their plasma concentration $\cdot$ time products (AUC_{IV}) after IP dosing. Virtually all commonly used drugs administered intraperitoneally in patients with ovarian cancer have peak or concentration $\cdot$ time product ratios of more than 20. In some cases, the peritoneal exposures can be much greater. For example, paclitaxel IP exposure with IP therapy is 300 to nearly 3,000 times greater than with IV treatment (15).

Except for drugs whose cytotoxicity depends on continuous exposure, such as cytarabine and methotrexate, drugs used by the IP route should be administered relatively rapidly in at least 2 L of peritoneal dialysate and remain within the peritoneal space without removal. For schedule-independent drugs, it is important to maintain high concentrations as long as possible within the IP space to improve efficacy. It is of considerable interest that as the IP dialysate volume decreases, a drug's IP clearance rate increases rapidly. Thus, large volumes of IP fluid increase the chances for uniform drug distribution throughout

the IP space and optimize the IP clearance rates. Generally, it is suggested to administer the IP drug dose in the first liter of peritoneal dialysate, followed by a second liter of dialysate to the point of mild abdominal discomfort.

Ultimately, the effectiveness of IP therapy depends on the inherent cytotoxic potency of the individual agent and its ability to penetrate from the outer surface to the inner core of IP tumors. The degree of tumor penetration depends on the molecular weight, charge, and chemical structure of the compound. There is an inverse relationship between molecular weight and tumor penetration. The higher the molecular weight of the anticancer drug, the lower the degree of tumor penetration. Indeed, one advantage of cisplatin over carboplatin as an IP agent is its lower molecular weight. Los and colleagues (16) demonstrated in IP ovarian cancer animal studies that it requires almost 10 times more IP carboplatin than cisplatin to achieve similar intratumoral concentrations; however, there is renewed interest to develop IP carboplatin plus IP and IV paclitaxel regimens to reduce the potential for cisplatin-paclitaxel-induced peripheral neuropathy (see Special Applications, in Carboplatin section below) (17).

PERIOPERATIVE CHEMOTHERAPY AS A PLANNED PART OF THE CYTOREDUCTIVE SURGICAL INTERVENTION FOR PERITONEAL METASTASES

Oncologists agree that a combination of meticulous cytoreductive surgery plus treatment with cancer chemotherapy is necessary for optimal treatment of gynecologic malignancies. The prevention and treatment of peritoneal metastases from ovarian cancer is the most obvious challenge for this combined treatment plan. Also, endometrial cancer frequently causes peritoneal metastases and has been considered for not only systemic but also local-regional (IP) chemotherapy administration. Uterine sarcoma is another gynecologic malignancy that may be significantly benefited. Finally, low malignant potential ovarian cancers that fail a surgery alone approach may progress with disease confined to the abdominal and pelvic surfaces. Cytoreductive surgery with perioperative chemotherapy is a treatment option for these patients.

The principles of cytoreductive surgery utilizing visceral resections and peritonectomy procedures have been well described in the gynecologic oncology and surgical oncology literature. Surgical cytoreduction is an essential part of optimal treatment. However, chemical cytoreduction with cancer chemotherapy employed as a planned part of the operative intervention presents a new dimension in an attempt to optimize the management of gynecologic malignancy (18). Hyperthermic perioperative chemotherapy (HIPEC) is used in the operating room as part of the surgical procedure. In addition, normothermic early postoperative IP chemotherapy (EPIC) is administered in the first few postoperative days. As surgeons have ascended the learning curve for this combination of extensive surgery combined with perioperative chemotherapy, the mortality rate has been reduced to 1% or less. Also, grade III and grade IV adverse events have been reduced to 20% (19). Most recent publications associate the morbidity and mortality with the extensive cytoreductive surgery and estimate the adverse outcomes from the perioperative chemotherapy to be unusual. Of course, knowledgeable management of both aspects of the combined treatment is an absolute requirement for success.

Hyperthermic Perioperative Chemotherapy

The drugs used with the surgical procedure are those whose maximal cytotoxic effect is completed with a 60- to 120-minute treatment in the operating room. These chemotherapy agents should be augmented by moderate heat of approximately 42°C, which is maintained in the whole abdomen through the use of a hyperthermia pump (20). The chemotherapy agents used through an IP route or through an IV route as a multiagent HIPEC regimen include the following drugs:

Mitomycin C

The greatest experience with HIPEC comes with the IP administration of mitomycin C (21). The drug is used at 15 to 30 mg/m², depending on the other chemotherapy agents used simultaneously and the patient's history of prior systemic chemotherapy. The AUC ratio of peritoneal fluid concentration times time to plasma concentration times time is approximately 25. Over 90 minutes, 67% of the drug is retained within the body compartment. Approximately 9% will be excreted in the urine, and 29% will be removed when the chemotherapy solution is removed from the abdominal and pelvic space after the 90-minute hyperthermic treatment. The drug is administered either by an open or closed technique. Data suggest that patients with extensive prior surgery and limited peritoneal space are best treated using a closed technique, which produces moderate IP pressure to expand the abdominopelvic space and maximize distribution of both heat and chemotherapy. Large visceral resections, such as total colectomy, will diminish the clearance of mitomycin C from the peritoneal space. With increasing peritonectomy, a small increase (approximately 15%) in clearance from the abdominopelvic space into the plasma has been reported. The abdominopelvic temperature (normothermic vs. hyperthermic) has little effect on the pharmacokinetics of IP mitomycin C (22).

Cisplatin

Cisplatin has been utilized for 3 decades through the IP route with and without heat. The AUC ratio of IP concentration times time compared to plasma concentration times time is approximately 8. Sometimes ultra-high doses of IP or intrapleural cisplatin (250 mg/m²) can be administered as HIPEC or hyperthermic thoraco-abdominal chemotherapy (HITAC) when an infusion of thiosulfate is used via the IV route (23,24). If thiosulfate is given prior to or concomitant with cisplatin, bleeding within the cavity treated by chemotherapy must not occur or the thiosulfate will neutralize cisplatin activity local-regionally. The drug is augmented by heat, with a thermal enhancement ratio estimated at 2.9 at 41.5°C (25). The penetration of cisplatin into tumor tissue has been well documented (26).

Doxorubicin

Doxorubicin has received a large amount of preclinical and clinical investigation when used with hyperthermia. The drug is compatible in solution with cisplatin and has been frequently used as a 2-drug regimen with hyperthermia in the abdominal and pelvic space. The AUC ratio of concentration times time in the peritoneal fluid compared to plasma concentration times time is approximately 150. The dose of doxorubicin is limited by its known sclerotic effects. The optimal dose for IP administration is 15 mg/m² in 1.5 L/m² of fluid. The clearance will decrease

with extensive visceral resection and will increase approximately 10% with extensive peritonectomy. After 90 minutes of abdominopelvic treatment, 88% of the drug has entered the body compartment and 12% will be removed with suctioning of the chemotherapy solution from the body cavity at the close of HIPEC treatment.

Melphalan

Melphalan is a candidate for HIPEC because of its marked thermal enhancement with moderate hyperthermia (25). The drug has been successfully used with limb perfusion for melanoma and sarcoma and with liver perfusion for ocular melanoma. Howell et al. established the dose of drug at 60 mg/m², with a slight dose reduction in patients who have had extensive prior chemotherapy treatments (27). The AUC ratio of peritoneal fluid concentration times time over plasma concentration times time is approximately 90, but can be quite variable. The tissue concentration in peritoneal surface tissue or in tumor is approximately 50% of the IP fluid concentration and 10 times the plasma concentration (28). Clinical trials to estimate durable response using HIPEC with melphalan have not been done, but phase I/II investigations suggest benefit with melphalan used as a single agent.

One caveat in administering this drug concerns its rapid degradation by hydrolysis after mixing in a large volume of carrier solution. The drug should be hand-delivered promptly to the operating room from the pharmacy and instilled into the peritoneal cavity without delay. The temperature of the hyperthermic chemotherapy solution should not exceed 42°C.

Gemcitabine

Pharmacokinetic studies suggest that gemcitabine may be one of the most appropriate drugs for HIPEC. Its AUC ratio of peritoneal fluid concentration times time to plasma concentration times time is approximately 500. Nevertheless, 90% of the drug was cleared into the body compartment by 90 minutes (29). The cytotoxicity of the drug is synergized by heat, but the timing for the hyperthermia is not clear. The optimal interval between intraperitoneal drug administration and heat application has not been determined. It is possible that delayed heat may result in optimal cytotoxicity because of the intracellular metabolism of the drug as a requirement for its cytotoxicity (29).

Oxaliplatin

The administration of oxaliplatin differs considerably from the hyperthermic IP administration of other drugs. It is usually administered as a short pulse of high-dose drug over approximately 30 minutes. The dose is usually 460 mg/m² at 42°C. The drug is rapidly absorbed from the peritoneal cavity. The AUC ratio of peritoneal fluid concentration times time to plasma concentration times time is approximately double that of cisplatin (30).

The drug is not administered as a single agent within the peritoneal space. The systemic circulation is primed with a bolus of 5-fluorouracil shortly before the IP administration of oxaliplatin. The combined IV administration of 5-fluorouracil and abdominopelvic administration of oxaliplatin with heated peritoneal surfaces is designed to target small cancer nodules on peritoneal surfaces. The 5-fluorouracil reaches the carcinomatous nodule via a capillary network. The hyperthermic oxaliplatin gains access to the tumor nodule by simple diffusion from the chemotherapy solution within the abdomen and pelvis.

Bidirectional Hyperthermic Perioperative Chemotherapy

Ifosfamide

Intravenous ifosfamide as part of a cancer treatment regimen for ovarian malignancy was pioneered by Zylberberg et al. (31). When used IV as a continuous infusion, the dose is usually 1,300 mg/m². Approximately 20% of this dose should be matched by Mesna, which is given 15 minutes before and 4 hours and 8 hours after the ifosfamide infusion. Ifosfamide is an unusual drug with an extremely high thermal enhancement ratio (25). This may be as high as 10. It is an ideal IV drug for the heat targeting to the warm peritoneal surfaces by HIPEC. High concentrations of the active agent for hydroxy-ifosfamide are found within the peritoneal space and have been documented to be present within tumor nodules on peritoneal surfaces (32). Toxicities from the use of ifosfamide in combination with hyperthermic IP chemotherapy have been observed to be minimal.

5-fluorouracil

Heated IP chemotherapy for gastrointestinal cancer has been augmented through the use of IV 5-fluorouracil (30). Oxaliplatin alone is ineffective for gastrointestinal cancer and produces the greatest cytotoxicity when used in combination with a full dose of 5-fluorouracil. Drugs augmented by 5-fluorouracil include cisplatin, oxaliplatin, mitomycin C, and irinotecan. Van der Speeten et al. showed that IV 5-fluorouracil given as a bolus with HIPEC maintained a higher IP level compared to the IV drug level over 90 minutes of drug sampling. The AUC ratio of peritoneal fluid to plasma was 2.3 (± 1.3). The AUC ratio of peritoneal fluid to tumor nodules was 9.9 (± 9.8). The AUC ratio of plasma to tumor nodules was 5.2 (± 4.7). By modulating the route and timing of administration of 5-fluorouracil, it becomes a pharmacologic advantageous molecule in patients with peritoneal metastases (33).

Early Postoperative Intraperitoneal Chemotherapy

Cancer chemotherapy administered in the early postoperative period into the abdomen and pelvis in a large volume of fluid may gain access to all peritoneal surfaces because no significant wound healing has occurred at this point in time. Adhesions between bowel loops should be separated at the time of cytoreductive surgery so that loculations within the abdominopelvic space do not occur (22). The drugs are used in the absence of hyperthermia. Distribution within the peritoneal space may be augmented by gravity distribution. This means that the patient turns from an extreme right lateral to left lateral position postoperatively in a repeated manner. The drugs selected for EPIC should have a high molecular weight to cause a long dwell time and should be cell cycle-specific, resulting in their maximal effect over 4 or 5 days.

Paclitaxel

From a pharmacologic perspective, paclitaxel may be the most promising drug for administration in a large volume of fluid into the abdominopelvic space. The AUC of peritoneal fluid concentration times time to plasma concentration times time is approximately 1,000 (34). Also, a remarkable penetration of drug up to 80 cell layers has been published (35). Because of the long retention of paclitaxel within the abdominopelvic space, use of high-molecular-weight carrier solutions has been suggested to increase drug exposure to peritoneal surfaces over

time without increased systemic toxicity. With hetastarch as a carrier solution, a larger total volume of chemotherapy solution is retained in the peritoneal space with its high concentration of paclitaxel. The longer the ascites fluid remains, the longer the drug has to reach its maximal effect within the abdominopelvic space (36). When combined with other chemotherapy agents, IP paclitaxel is associated with a marked prolongation of median survival in peritoneal mesothelioma (36).

Docetaxel

Another taxane that has promise as normothermic IP chemotherapy as a planned part of postoperative management is docetaxel. The drug is minimally enhanced by heat but is retained within the peritoneal space for up to 24 hours. The AUC ratio of peritoneal fluid concentration times time to plasma concentration times time is 550 (34). This drug has been successfully used as a neoadjuvant IP chemotherapy agent for patients with gastric cancer.

5-fluorouracil

Undoubtedly, one of the oldest and best studied IP agents for gastrointestinal cancer is 5-fluorouracil. Because of its complete metabolism within a single pass through the liver, it has been suggested that the drug may not only treat cancer cells on peritoneal surfaces but also cause beneficial effects within the liver. The drug used is 400 to 600 mg/m² in the early postoperative period in 1 L of 1.5% dextrose peritoneal dialysis solution. Use of the drug intravenously with HIPEC and then intraperitoneally with EPIC can increase the total dose of 5-fluorouracil to 2 g/m² over the perioperative treatment cycle. This may be the optimal dose of 5-fluorouracil to use in combination with other drugs, such as oxaliplatin, cisplatin, or mitomycin C. The drug has been used not only to treat peritoneal metastases but in an adjuvant setting to diminish the incidence of carcinomatosis in patients at high risk for disease progression on peritoneal surfaces (37).

Floxuridine

Floxuridine is a unique chemotherapy agent because of its complete metabolism within a single pass through the liver by uptake of the drug into the portal vein. In phase I/II trials, IP floxuridine and systemic fluorouracil were successfully used to treat patients at high risk for locoregional recurrence after the resection of colon cancer (38). No liver metastases and no peritoneal carcinomatosis occurred during this treatment. The drug has a large potential for prophylaxis of peritoneal and liver metastases in a wide variety of malignancies.

Pemetrexed

Pemetrexed is a large-molecular-weight antifolate chemotherapy agent that has great promise for management of gynecologic malignancy. It is approved for treatment of peritoneal mesothelioma and is used intraperitoneally in combination with IV cisplatin for that disease. Its use in the perioperative period has not been fully explored. The AUC concentration times time after IP administration is 40 times the AUC for IV concentration times time. The half-life of pemetrexed in peritoneal fluid is 2 hours, suggesting prolonged activity within the abdominal and pelvic space (39,40).

Summary

An important consideration for HIPEC and EPIC concerns the selection of cancer chemotherapy agents that may show drug synergy. The bidirectional treatment with HIPEC and the continuing treatment postoperatively with EPIC present an opportunity to eradicate the peritoneal surface component of

gastrointestinal malignancy from the natural history of the disease. As surgeons learn to modify their surgical procedures in order to ensure a safe cytoreductive procedure, more effective combinations of both IV and IP chemotherapy used as HIPEC and EPIC become promising clinical approaches.

CLINICAL PHARMACOLOGY OF ACTIVE DRUGS AGAINST GYNECOLOGIC CANCERS

We discuss below in alphabetical order the clinical pharmacology of cytotoxic, biologic/molecularly targeted and modulating/supportive care drugs with demonstrated activity against gynecologic cancers. We also include several U.S. Food and Drug Administration (FDA)-approved drugs for other indications that may prove active against gynecologic cancers.

Cytotoxic Agents

Albumin-bound Paclitaxel

Chemistry

Albumin-bound paclitaxel (Abraxane, ABI-007) is a protein-bound form of paclitaxel that measures approximately 130 nm. Each vial of albumin-bound paclitaxel contains 100 mg of paclitaxel and 900 mg of human albumin. The chemical name of paclitaxel is 5 β ,20-Epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine, and the empirical formula and molecular weight are C₄₇H₅₁NO₁₄ and 853.91, respectively. Albumin-bound paclitaxel is FDA approved for the treatment of breast cancer after failure of treatment for metastatic disease or recurrence within 6 months of adjuvant chemotherapy. Phase III trials have demonstrated superior efficacy to castor-oil-based paclitaxel and a more favorable toxicity profile (41). Clinical trials in gynecologic cancer (e.g., ovarian and cervical cancer) are ongoing. Please refer to the Paclitaxel section for details on the mechanism of action of this agent.

Drug Disposition

According to the Abraxane package insert, comparison studies showed that the clearance of albumin-bound paclitaxel (260 mg/m² over 30 minutes) was larger (43%) than that for the clearance of paclitaxel injection (175 mg/m² over 3 hours), and the volume of distribution of the albumin-bound form was 53% higher; however, there was no difference in the terminal half-life of the active agent.

Administration and Dosage

The recommended dosage of albumin-bound paclitaxel is 260 mg/m² IV over 30 minutes every 3 weeks. No premedication to prevent hypersensitivity reactions is needed. Albumin-bound paclitaxel should be carefully reconstituted according to the manufacturer instructions. Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel. The exact total dosing volume of 5 mg/mL for the patient should be calculated using the following formula: total dose (mg) ÷ 5 (mg/mL). Reconstituted agent should be used immediately, but can be refrigerated for up to 8 hours. If precipitates are observed, the solution should be discarded.

Side Effects and Toxicities

Neutropenia and sensory neuropathy are dose-dependent. In drug approval studies, grade 4 neutropenia occurred among approximately 9% of patients compared to 22% of patients

receiving 175 mg/m² paclitaxel. Infection (generally oral candidiasis and respiratory system events) occurred in approximately 23% of patients receiving albumin-bound paclitaxel. Anemia occurred among 33% of patients (severe anemia in 1% of cases). Severe cardiotoxicity occurred in approximately 3% of patients. Dyspnea (12%) and cough (6%) were also reported among patients receiving albumin-bound paclitaxel. Patients with neutrophil counts of less than 1,500 cells/mm³ should not receive albumin-bound paclitaxel, as it may lead to bone marrow suppression, which can result in infection.

Altretamine

Chemistry

Altretamine (hexamethylmelamine, Hexalen), a synthetic cytotoxic antineoplastic s-triazine derivative, is FDA approved for the treatment of persistent or recurrent ovarian cancer after first-line chemotherapy with cisplatin or other alkylating agents. The drug also exhibits antitumor activity against breast cancer, lymphomas, small-cell carcinoma of the lung, and endometrial and cervical cancer. The empiric formula of altretamine is C₉H₁₈N₆ (molecular weight = 210.28).

Mechanism of Action

The mechanism of action of altretamine is not completely elucidated. Although it bears structural similarity to and cross reactivity with triethylene-melamine, a classic alkylating agent, evidence demonstrating altretamine to be an alkylating agent is inconclusive. Altretamine does not consistently demonstrate cross-resistance with classic alkylating agents used in rodent tumors or in human cancer treatment, but its clinical antitumor spectrum resembles that of an alkylating agent. Altretamine is inactive against most common murine and human tumor cell lines *in vitro*. Ruddy and Connors (42,43) presented definitive evidence that metabolic activation of altretamine is necessary for its cytotoxic activity. It is extensively demethylated *in vivo* in the presence of liver enzymes, and these N-methylolmelamine derivatives are more cytotoxic than the parent compound (43). Additional studies have shown that the reactive methyl intermediates, formed during altretamine N-demethylations, covalently bind to tissue macromolecules, including DNA, and that the cytotoxicity against certain human solid tumor cells *in vitro* is dependent on the metabolic formation of the reactive intermediates or their direct addition to cell culture incubate (44).

Drug Disposition

Altretamine is practically insoluble in water and, therefore, it has only been administered orally in clinical studies, precluding absolute bioavailability studies. After administration of altretamine to laboratory animals by any route, urinary recovery of parent drug was very low (<1%), and urinary recovery of total dose or total radioactivity after administration of ¹⁴C-labeled drug was as high as 90%. Ames (44) determined that the bioavailability of the parent compound in rabbits after oral administration was 25% of that obtained after IV administration. Moreover, after giving the rabbits labeled altretamine by stomach tube, 85% of labeled drug equivalents was recovered in the urine. The high rate of recovery suggests efficient gastrointestinal absorption.

The urinary recovery and bioavailability data demonstrate that altretamine is well absorbed after oral administration and that the drug is extensively metabolized, regardless of route of administration. The low bioavailability of intact altretamine is due to first-pass metabolism rather than to poor absorption.

After oral administration in doses of 120 to 300 mg/m², peak plasma levels, measured by gas chromatographic assay, from 0.2 to 20.8 mg/L are reached between 0.5 and 3.0 hours.

The terminal-phase plasma half-life ranges from 4.7 to 10.2 hours (45). The interpatient variability of AUCs, ranging from 1.2 to 60.1 mg/L · h, is most likely due to the differences in the rate at which the drug is metabolized.

Administration and Dosage

The recommended dose for altretamine as a single agent for use in the palliative treatment of patients with ovarian cancer is 260 mg/m²/day, orally, for 14 to 21 consecutive days in a 28-day cycle (46). The total daily doses should be given as 4 divided oral doses after meals and at bedtime. Compliance to this regimen in a small group of patients with relapsed ovarian cancer was documented at greater than 95% (47). There is no pharmacokinetic information on this dosing regimen and the effect of food on altretamine bioavailability in humans. In combination regimens, altretamine is typically used at a dose of 150 mg/m²/day for 7 to 14 days of monthly cycles (48,49).

Altretamine should be temporarily discontinued for 14 days or longer and subsequently restarted with a 20% to 25% dose reduction for any of the following side effects: gastrointestinal intolerance unresponsive to symptomatic measures; leukocyte count less than 2,000/mm³ or granulocyte count less than 1,000/mm³; platelet count less than 75,000/mm³; or progressive neurotoxicity. If neurologic symptoms fail to stabilize on the reduced-dose schedule, altretamine should be discontinued.

Side Effects and Toxicities

Altretamine is administered at a dose of 260 mg/m² (single agent) or 150 mg/m² (in combination) on an intermittent schedule and is relatively well tolerated. Single-agent data for this drug are available for 1,014 patients (50). With high, continuous daily dosing, nausea and vomiting were the dose-limiting toxic effects, and a form of reversible peripheral neurotoxicity occurred occasionally. Myelosuppression was mild to moderate. Leukocyte and platelet counts usually recovered within 1 week of therapy discontinuation.

In a study of 395 patients with advanced ovarian cancer treated with altretamine-containing combination regimens with or without cisplatin, no additional effect of altretamine on the incidence or severity of neurotoxicity could be demonstrated (51). Peripheral neuropathy and central nervous system symptoms are more likely to occur in patients receiving continuous, high-dose daily altretamine administered on an intermittent schedule than in those receiving moderate doses. Neurologic toxicity reverses after the drug is discontinued. Pyridoxine should not be used concomitantly with altretamine to reduce neurotoxicity because clinical trials data suggest it may inhibit cytotoxic activity. Concurrent administration of altretamine and antidepressants of the monoamine oxidase (MAO) inhibitor class may cause severe orthostatic hypotension. Cimetidine, an inhibitor of microsomal drug metabolism, increased altretamine's half-life and toxicity in a rat model.

In 2 phase II studies of single-agent altretamine, at a dose of 260 mg/m² for 14 to 21 days of each monthly cycle, the most common toxicity was grade 2 to 3 nausea (23%) (52,53). In a consolidation therapy phase II trial, only 3 patients (4%) experienced any grade 4 toxicity: granulocytopenia (2 patients) and anxiety/depression (1 patient). The most common grade 3 toxicities were malaise, fatigue, or lethargy in 7 patients (7%) and nausea in 6 patients (6%). Aside from these, there were no other grade 3 or 4 toxicities in more than 5% of patients (53).

With continuous high-dose daily drug administration, nausea and vomiting of gradual onset occur frequently. Although in most instances these symptoms are controllable with antiemetics, the severity sometimes requires altretamine dose reduction or, rarely, discontinuation.

Data from 3 large clinical trials demonstrated that altretamine can be added to full therapeutic doses of cyclophosphamide,

doxorubicin, and cisplatin (CHAP) without evidence of increased hematologic toxicity (54–56). Leukopenia below 3,000 cells/mm³ occurred in less than 15% of the patients on a variety of intermittent- or continuous-dose altretamine regimens. Less than 1% had leukopenia below 1,000 cells/mm³. When given in high doses over a 21-day course, nadirs of leukocyte and platelet counts were reached by 3 to 4 weeks, and normal counts were observed by 6 weeks. With continuous administration, nadirs are reached in 6 to 8 weeks.

Bleomycin

Chemistry

Bleomycin (Blenoxane), an antineoplastic, is a mixture of complex glycopeptides originally isolated from a strain of the fungus *Streptomyces verticillaris*. The primary components are bleomycins A₂ and B₂. The family of bleomycin glycopeptides have a relatively high molecular weight and are quantitated in units of cytotoxic activity (i.e., roughly 1 U/mg of polypeptide protein). Bleomycin is used as palliative treatment in patients with advanced cervical (57) and vulvar cancers. Other clinical indications include squamous-cell carcinomas of the head and neck, lymphomas, and testicular carcinoma. The molecular formula of bleomycin A₂ is C₅₅H₈₄N₁₇O₂₁S₃ (molecular weight = 1,414), and the molecular formula of bleomycin B₂ is C₅₅H₈₄N₂₀O₂₁S₂ (molecular weight = 1,425).

Mechanism of Action

Although the exact mechanism of action is unknown, a key to its activity is the isolation of native compounds from *S. verticillaris* as coordinated Cu(II) complexes, which are inactive as anti-tumor agents. When complexed with ferrous iron, bleomycin becomes a potent oxidase, producing DNA strand breaks by oxygen free radicals. Its unique mechanism of action is schedule dependent and cell cycle dependent for the G₂ phase.

The oxygen radicals produced by the bleomycin-iron complex bound to DNA primarily cause single-strand breaks and to a lesser degree, double-strand breaks. There is a subsequent release of base propenals of all 4 DNA bases: guanine, thymine, adenine, and cytosine. These modified free bases result from cleavage of the deoxyribose sugar at the 3' to 4' bond. There is an apparent specificity for the release of thymine and for DNA binding at guanine-rich sequences in actively transcribed genes (58). The linker regions of DNA between nucleosomes comprise an important site for specific strand cleavage by bleomycin (59). Several mechanisms have been theorized to explain the development of resistance to bleomycin. Less important mechanisms appear to include DNA repair, membrane alterations, and decreased drug accumulation. The primary mechanism probably involves metabolic inactivation of bleomycin by a cytosolic hydrolase, which is in the cysteine proteinase family. The enzyme inactivates bleomycin by replacing a terminal amine with a hydroxyl group. The distribution of bleomycin hydrolase appears to explain some of the relative resistance and sensitivity to bleomycin in normal tissues. Normal tissues with high intrinsic hydrolase activities, such as the liver, spleen, intestine, and bone marrow, are not targets for bleomycin's toxic effects. In contrast, lung tissues and skin have low levels of hydrolase activity and are particularly susceptible to bleomycin-induced toxicity. However, there appears to be no direct correlation between hydrolase levels in tumor cells and bleomycin-induced cytotoxicity (59). The development of other methods of bleomycin metabolism by tumor cells may be responsible for the emergence of drug resistance (60).

Drug Disposition

Bleomycin is eliminated predominantly by urinary excretion. This accounts for 45% to 62% of a dose after 24 hours. In

the blood, the drug is rapidly cleared, and 2 phases of elimination are apparent. As a practical point, this means that greater than 95% of a dose has been completely eliminated by 24 hours (about 6 half-lives) (61). If administered by an intracavitary route, a large percentage of a bleomycin dose is absorbed, and the fractional systemic bioavailability is approximately 45% for intrapleural or intraperitoneal injections. The drug appears to efflux more slowly from the peritoneal cavity. This suggests that there is significantly greater local drug retention in the intraperitoneal space. This may explain some of the drug's unique efficacy by intracavitary administration (62,63). An increased exposure to drug in these local compartments is also reflected by the tenfold higher drug levels achieved with IP or intrapleural therapy than with equivalent IV dosing.

Renal insufficiency markedly alters bleomycin elimination (64,65). This effect becomes most pronounced in patients with creatinine clearance values less than 25 to 35 mL/min (64). In these patients, the volume of distribution is unaltered at about 20 L, but the half-life varies as the inverse exponent of creatinine clearance. Thus, significant bleomycin dose reductions are required in all patients with reduced renal function.

Dosage

Bleomycin (in combination with cisplatin and etoposide or vinblastine) is used most commonly by bolus IV administration at dosages of as high as 30 mg/week for up to 12 weeks in the treatment of patients with germ-cell tumors of ovary. These 30-mg doses often are associated with delayed febrile episodes that can be inhibited successfully with a morning dose of dexamethasone or prednisone.

Bleomycin remains to be used commonly by continuous IV infusion at dosages of 10 mg/m²/day for 4 consecutive days, with courses repeated every 4 weeks. This schedule has been proven to be successful in the treatment of women with metastatic cervical cancer. Total bleomycin doses should usually not exceed 400 mg to avoid serious pulmonary toxicity.

Bleomycin can also be administered by the intramuscular route in doses of 15 to 30 mg. Absorption appears to be complete, and because of its lack of vesicant activity, the intramuscular route has been proven to be extremely safe (66).

Side Effects and Toxicities

Bleomycin's dose-limiting side effect is pulmonary toxicity, which occurs in approximately 10% of treated patients and in rare instances can result in death. The likelihood of lung damage increases with advanced age, chest irradiation (67), hyperoxia during surgical anesthesia (68,69), renal insufficiency, and cumulative doses greater than 400 U. However, pulmonary toxicity can occur in younger patients following low cumulative doses. Bleomycin-induced lung damage presents as pneumonitis with dry cough, dyspnea, and rales and may progress within weeks to pulmonary fibrosis. Bleomycin should be discontinued at the first clinical signs of lung toxicity. Acute pneumonitis is often responsive to corticosteroid therapy; however, there is no effective therapy for the chronic pulmonary fibrosis that may result from bleomycin therapy (70).

Evidence from preclinical models of bleomycin-induced pulmonary thrombosis has documented that pretreatment with amifostine can abrogate this dose-limiting toxicity (71,72).

Bleomycin is nonmyelosuppressive (a factor that facilitates its use in combination chemotherapeutic regimens). Mucocutaneous toxicities, including mucositis, are the primary acute side effects of bleomycin. Manifestations of cutaneous reactions include hyperpigmentation, erythema, rash, striae, pruritus, thickening of the nail beds, and in rare instances, scleroderma (73). Fever, chills, and alopecia are common. Mild nausea, vomiting, and anorexia may also occur but are typically self-limiting.

Infrequent side effects include headache, pain at tumor site, and anaphylactoid reactions. An idiosyncratic reaction consisting primarily of mucositis and skin rash has also been reported (74).

Special Precautions

Bleomycin should be used with extreme caution in patients with significant renal impairment or compromised pulmonary function; frequent radiographs are recommended. Because up to 70% of a bleomycin dose is eliminated by renal excretion, the bleomycin dose should be reduced for individuals with severe renal insufficiency. Unfortunately, there are no prospectively evaluated dosing nomograms for bleomycin dose adjustment. An empiric dose-adjustment formula has been described (64). The percentage dose reductions that are indicated by applying this formula to a "normal" creatinine clearance (CrCl) of 120 mL/min and a fractional urinary drug excretion of 0.45 are as follows: CrCl > 35 mL/min, no dose reduction required; CrCl = 20 mL/min, 50% dose reduction; CrCl = 15 mL/min, 52% dose reduction; CrCl = 10 mL/min, 55% dose reduction; and CrCl = 5 mL/min, 60% dose reduction. This is only a general guide, and it has not been clinically validated in a prospective study or retrospective analysis. Patients over 65 years of age may be at increased risk of developing orthostatic hypotension, especially when the recommended rate of IV infusion is exceeded.

Drug Interactions

Nephrotoxic drugs may significantly reduce the rate of bleomycin clearance and thus increase toxicity. Yee and coworkers (75) observed markedly reduced bleomycin clearance in children who had received 6 courses of a regimen including cisplatin (cumulative dose 300 mg/m²). In another case report, fatal bleomycin pulmonary toxicity occurred in a patient with cisplatin-induced acute renal failure (76). Similar toxic interactions should be anticipated for combinations of bleomycin with other nephrotoxic drugs, such as aminoglycosides, amphotericin, or cyclosporine.

Special Applications

Because of its nonvesicant nature, bleomycin has been administered by a number of nonvascular routes, including intramuscular (66), subcutaneous (77), and, most significantly, intrapleural routes for the management of malignant effusions. When compared with tetracycline, intrapleurally administered bleomycin, 60 to 120 U, had greater therapeutic benefit for the management of malignant pleural effusions (62,63). When compared with tetracycline, intrapleurally administered bleomycin, 60 to 120 U, had greater therapeutic benefit as evidenced by a longer time to effusion recurrence (46 vs. 32 days, $p = 0.037$) and a lower 3-month effusion recurrence rate (30% vs. 53%, $p = 0.047$). Because toxicities were similar for both therapies, bleomycin was selected as the preferred intrapleurally administered therapy for malignant pleural effusions (62,63).

There is evidence that a cytosolic hydrolase in the cysteine protein family inactivates bleomycin by replacing a terminal amine with a hydroxyl group. The distribution of bleomycin hydrolase appears to explain some of the relative resistance and sensitivity to bleomycin in normal tissues. Normal tissues with high intrinsic hydrolase activities, such as the liver, spleen, intestine, and bone marrow, are not targets for bleomycin's toxic effects. In contrast, lung tissues and skin have low levels of hydrolase activity and are particularly susceptible to bleomycin-induced toxicity. However, there appears to be no direct correlation between hydrolase levels in tumor cells and bleomycin-induced cytotoxicity (59). The development of other methods of bleomycin metabolism by tumor cells may be responsible for the emergence of drug resistance (60).

Capecitabine

Chemistry

Capecitabine (Xeloda) is an orally administered antineoplastic agent. In patients with metastatic breast cancer, capecitabine in combination with docetaxel is indicated after failure of prior anthracycline-containing chemotherapy, and monotherapy is indicated for those who are resistant to paclitaxel and are resistant to anthracycline-containing chemotherapy (or further anthracycline-containing chemotherapy is not indicated). Capecitabine is a fluoropyrimidine carbamate prodrug form of 5'-deoxy-5-fluorouridine (5'-DFUR) that is enzymatically converted to 5-fluorouracil (5-FU) *in vivo*. Its chemical name is 5'-deoxy-5-fluoro-N-[(pentoxyl) carbonyl]-cytidine and its molecular weight is 359.35.

Mechanism of Action

Capecitabine itself is inactive, but after absorption in the gastrointestinal tract it is metabolized to 5-FU by 3 enzymes: carboxylesterase, which converts capecitabine to 5'-deoxy-5-fluorocytidine in the liver; to 5'-deoxy-5-fluorouridine by cytidine deaminase in the liver and tumor tissue; and thymidine phosphorylase, which in many cases is highly expressed in tumors, completes the final step of conversion to 5-FU. Theoretically, capecitabine therapy is likely to be most effective in patients with tumors that express high concentrations of thymidine phosphorylase (resulting in greater 5-FU being generated in the tumor) and low concentrations of dihydropyrimidine dehydrogenase (which rapidly breaks down 5-FU) (78). 5-FU acts as a false pyrimidine or antimetabolite ultimately to inhibit the formation of the DNA-specific nucleoside base thymidine. The metabolites of 5-FU, 5-fluoro-21-deoxyuridine-5'-monophosphate (FdUMP), and 5-fluorouridine triphosphate (FUTP) inhibit thymidylate synthase (TS) and are incorporated into cellular RNA (FUTP). DNA synthesis and function is inhibited by the incorporation of FdUMP into cellular DNA (79). A pharmacogenetic study of capecitabine in 105 consecutive patients has shown an increase in toxicity in patients homozygous for the TS 3RG allele and also that a patient with a DPD IVS14 + 1G>A mutation died from toxicity emphasizing the importance of polymorphisms in the metabolizing enzymes of this drug (80).

Drug Disposition

After oral administration, capecitabine reaches peak blood levels in about 1.5 hours, and peak 5-FU levels are reached at about 2 hours. Food reduces the rate and extent of absorption for both capecitabine and 5-FU. Plasma protein binding is not dose dependent and is less than 60% for capecitabine and its metabolites. Capecitabine (95.5% of administered dose) and its metabolites are excreted in urine. Capecitabine has no effect on the pharmacokinetics of docetaxel or vice versa. The precise pharmacokinetics of capecitabine have been difficult to establish, which is thought to be due to the large interindividual and intraindividual variation in expression of the enzyme dihydropyrimidine dehydrogenase (78).

Administration and Dosage

Capecitabine is available as 150- and 500-mg tablets for oral use. The recommended dose is 2,500 mg/m² daily to be administered as 2 doses: 1,250 mg/m² in the morning and 1,250 mg/m² in the evening for 2 weeks followed by a 1-week rest (21-day cycle). Because of the high rate of grade 2 or greater capecitabine-induced palmar-plantar erythrodysesthesia (PPE), recommendations have been made to reduce the starting dose to 2,000 mg/m² daily. It should be taken with water within 30 minutes after a meal. The same dosage of capecitabine should be used when combined

with docetaxel, which should be administered at 75 mg/m² as a 1-hour infusion on day 1 of the 21-day cycle. Premedication (per docetaxel labeling) should be started prior to docetaxel administration for patients receiving the combination therapy.

Side Effects and Toxicities

The only side effect that occurs more frequently with capecitabine than with IV 5-FU is PPE (15% to 20% of patients). The other more common side effects of capecitabine include diarrhea (40%) and nausea and vomiting (30% to 40%). Grade 3 hyperbilirubinemia occurred in 15.2% and grade 4 in 3.9% of patients in the clinical safety database of Xeloda. Of those patients experiencing grades 3 and 4 hyperbilirubinemia, many (64% and 71%, respectively) had liver metastases at baseline, and 57.5% and 35.5% had elevations in alkaline phosphatase or transaminases, respectively. Other less common side effects include myelosuppression (less frequent than with IV 5-FU), leukopenia, and cardiotoxicity. In general, capecitabine is relatively well tolerated.

Special Precautions

Because capecitabine is administered orally, patients should be informed about how to monitor their toxicity symptoms and be instructed to maintain the prescribed dosing regimen. Capecitabine has been shown to alter coagulation parameters in patients undergoing treatment concomitantly with coumarin-derivative anticoagulants (e.g., warfarin) (78). Therefore, patients taking oral coumarin-derivative anticoagulant therapy should be monitored regularly with regard to coagulation parameters (international normalized ratio or prothrombin time). Patients over the age of 80 years and those with mild to moderate liver dysfunction should also be closely monitored.

Carboplatin

Chemistry

Carboplatin (Paraplatin) is platinum-based agent that is approved by the Food and Drug Administration for the treatment of patients with advanced ovarian cancer of epithelial origin. It is also active against metastatic endometrial and cervical cancer. Carboplatin has a molecular formula of C₆H₁₂N₂O₄ Pt and a molecular weight of 371.25. Its chemical name is cis-diammine-(1,1-cyclobutanedicarboxylato) platinum(II). The water solubility of carboplatin (14 mg/mL) is approximately 10 times that of cisplatin.

Mechanism of Action

Carboplatin, like cisplatin, produces an equal number of predominantly interstrand DNA cross-links rather than DNA-protein cross links, causing equivalent lesions and biologic effects. The differences in potencies appear to be related to the aquation rate, which is significantly higher for cisplatin compared to carboplatin (81). It covalently binds to DNA with preferential binding to the N-7 position of guanine and adenine (79). Like cisplatin, carboplatin must first undergo sequential losses of the nonamine carboxylato ligands. Although this process proceeds readily with the loss of the chlorides in cisplatin, the rate of leaving or "opening" of the carboxylato moieties in carboplatin is much slower (82). The molar potency of carboplatin in creating DNA lesions and cytotoxicity was observed to be roughly 2% of cisplatin *in vitro* and 25% to 33% of cisplatin *in vivo* (83,84). A more striking difference is the markedly delayed onset of peak cross-linking for carboplatin compared with cisplatin. With carboplatin, maximal DNA cross-linking occurs 18 hours after exposure compared with 6 to 12 hours for cisplatin (84). In addition, carboplatin-induced DNA cross-links appear to

have a slower rate of resolution than cisplatin-induced cross-links. This slower onset and offset of carboplatin cross linking is believed to be a direct result of a slow rate of monofunctional adduct formation or a slower rate of conversion of monoadducts to cross-links.

Although the final DNA adducts formed by cisplatin and carboplatin are the same, there are large differences in the kinetics of their formation and the rate of conversion of mono- to di-adducts (85), which could impact the ability of various DNA repair enzymes to cause resistance. Further, cell membrane transport proteins are thought to be critical determinants of platinum drug sensitivity and resistance. It is known that cisplatin and carboplatin differ in their transport characteristics (86). Leblanc et al. (87) showed that substantial hepatic P450 induction occurred in rats following cisplatin treatment, but not following carboplatin treatment. Waxman et al. (88) showed that cisplatin induced GST Yc expression in the liver of rats, but carboplatin did not. These data may be significant because GSTs are thought to contribute to platinum resistance. Natarajan et al. (89) extended the latter observation by showing that S-containing nucleophiles (thiourea, glutathione, and human breast cancer MCF-7 cell cytoplasmic extracts) significantly decreased the formation of DNA platinum adducts from cisplatin, but significantly increased them from carboplatin. Despite the pharmacokinetic and mechanistic differences between carboplatin and cisplatin, phase III studies and meta-analyses of clinical studies reveal equivalent activity between carboplatin and cisplatin in all prognostic subgroups of ovarian cancer patients (90,91). However, meta-analysis is performed on pooled data. It is entirely plausible that subsets of ovarian cancers with differing genetic phenotypes will respond differently to cisplatin and carboplatin.

Harrap (92) described nuclear protein phosphorylation after treatment with both cisplatin and carboplatin. These events appear to correlate with cell killing (93). Carboplatin reacts with 2 sites on DNA to produce cross-links, as has been observed with cisplatin (94). The formation of DNA adducts results in the inhibition of DNA synthesis and function and inhibits transcription (79). These lesions involve a bifunctional platinum adduct to a single-strand DNA. This may produce transcriptional miscoding and an inhibition of DNA synthesis. It is possible that the cytotoxic effects of carboplatin are the result of binding to nuclear and cytoplasmic proteins. Carboplatin-induced cytotoxicity is not cell cycle phase specific, but it can be maximized by exposing cells in S phase to the drug.

Drug Disposition

The pharmacokinetics of carboplatin differs significantly from that of cisplatin. Table 14.1 shows that the plasma clearance of carboplatin is biphasic and slower than that of cisplatin, with a much higher percentage of drug being excreted in the urine. Unlike cisplatin, carboplatin binds to plasma proteins relatively slowly so that in the first 24 hours after administration there is a considerable concentration of the free drug in circulation. The major route of elimination of carboplatin is glomerular filtration and tubular secretion. There is little or no true metabolism of the drug. The carboxylate bonds in carboplatin are slowly hydrolyzed to yield transient aquated intermediates. These activated platinum species are believed to lead directly to irreversible adducts to DNA or protein. Overall, the rate of hydrolysis of carboplatin is significantly slower than that of cisplatin, leading to much slower reactivity with DNA (95). Because at least 65% of a carboplatin dose is excreted in the urine, significant dose adjustments are recommended for patients with creatinine clearance values less than 60 mL/min. However, since the widespread use of formula-based dosing (see below) these reductions are implicit in the use of the formula and need not be separately calculated.

Table 14.1 Carboplatin Pharmacokinetics

Cumulative 24-hr Urinary Excretion	65% (if Creatinine Clearance >60 mL/min)
<i>In vitro</i> half-life (H ₂ O)	~24 hr
Plasma half-life β phase (free drug)	180 min
Protein-bound drug	>5 days
Volume of distribution	16–20 L
Protein binding	30% (slow equilibration)

Carboplatin is widely distributed in body fluids and achieves good penetration into pleural effusions and ascites fluid (96,97). Pharmacokinetic studies in patients receiving continuous carboplatin infusions show that although total platinum levels increase over the course of the infusion, free or active platinum levels can decrease from 78% on day 1 to 38% on day 4 of a 4-day infusion.

Administration and Dosage

Carboplatin is usually administered as a brief infusion in a solution of 0.9% sodium chloride or 5% dextrose in water. The drug is typically diluted in 500 mL of fluid and infused IV over 15 to 30 minutes to 1 hour without further hydration (98,99). Carboplatin also has been administered as a continuous 24-hour IV infusion for 1, 4, or 5 days or as a continuous IV infusion for 21 days.

The Calvert equation is the most frequently used formula for carboplatin dosing as it requires minimal calculations, results in predictable levels of myelosuppression, and prevents underdosing or overdosing in patients with excellent or poor renal function, respectively (100). The Calvert formula appears below along with general guidelines for selecting the specific carboplatin AUC.

Carboplatin total dose (mg) = AUC(mg/mL · min) · [GFR(mL/min) + 25] AUC = 7 when carboplatin is used as a single agent in patients with good bone marrow reserve; 6 when carboplatin is used in combination regimens in patients with good bone marrow reserve or when used as a single agent in patients who have had prior moderate chemotherapy; and 4 when carboplatin is used as a single agent in patients with prior heavy chemotherapy exposure.

Glomerular filtration rate (GFR) can be determined by measuring creatinine clearance (i.e., [⁵¹Cr]-ethylenediamine-tetraacetic acid) for all patients or estimated creatinine clearance for patients who have had no prior cisplatin exposure or have not had cisplatin for at least 2 months prior to carboplatin dose determination.

For example, if the desired carboplatin AUC is 6 for a patient with an estimated creatinine clearance (CrCl) of 75 mL/min, the total carboplatin dose would equal 6 × (75 + 25), or 600 mg.

As noted above, the Calvert formula uses the following estimate of carboplatin clearance: Cl = GFR + 25. Although the method may be optimal (101), isotopic determination of the GFR as measured by [⁵¹Cr]-ethylenediamine-tetraacetic acid (⁵¹Cr-EDTA) is not available in many countries and the estimated creatinine clearance is often substituted for the GFR. A commonly used method for estimating creatinine clearance is the Cockcroft-Gault (CG) equation (102):

$$CrCl = \frac{(140 - Age) \times Wt \times (1 - 0.15 \times Sex)}{72 \times SCr \times 0.0113}$$

CrCl = Creatinine clearance; Age = Age in years; Sex = 1 if female, 0 if male; SCr = Serum Creatinine in mmol/L; Wt = Weight in kg.

Both the CG calculation of creatinine clearance and creatinine clearance based on a 24-hour urine collection result in a systematic underestimation of the carboplatin AUC by approximately 10% (103–105). This level of bias may be deemed acceptable in view of the clinical utility of substituting creatinine clearance for GFR. Significantly, the accuracy of the CG calculation depends on the method used for measuring creatinine. When the CG formula was derived, a colorimetric reaction was used that significantly overestimates the plasma level of creatinine. A more accurate measurement uses an enzymatic method (106). The use of a more accurate method combined with the CG formula leads to an unexpectedly high dose of carboplatin. Recently, creatinine measurements in the United States have been standardized using isotope dilution mass spectrometry, leading to potential overdosage in some trial protocols and a recommendation for a dose cap (107). The issue of using a creatinine-based estimate of the GFR has been approached by Wright et al. (106) where alternatives to the CG formula are proposed for use with differing creatinine assays.

The Calvert formula has been prospectively evaluated by Sorenson et al. (108) in 24 previously untreated ovarian cancer patients and was found to predict more accurately carboplatin exposure than calculation of dose based on body surface area. The AUC of carboplatin as calculated by the Calvert formula accurately predicted the level of myelosuppression as determined by the relative decrease in the platelet count (108).

Although formula-based dosing is normally used, the recommendation dosage for single-agent carboplatin in mg/m² in ovarian cancer patients with good bone marrow reserve, based on body surface area, is 360 mg/m² given IV every 4 weeks. Because renal excretion is the primary route of carboplatin elimination, the carboplatin dose must be reduced for patients with compromised kidney function. The drug manufacturer's package insert recommends carboplatin doses of 250 and 200 mg/m² for patients with creatinine clearances of 41 to 59 and 16 to 40 mL/min, respectively.

The most frequently used primary chemotherapeutic regimen for advanced ovarian cancer is a combination of paclitaxel (175 mg/m² by 3-hour IV infusion) followed by carboplatin (at a targeted AUC of 5 or 6 by 30- to 60-minute IV infusion) every 21 days (if blood counts are adequate) for 6 cycles (109).

Side Effects and Toxicities

Although the activity is comparable to cisplatin, carboplatin is better tolerated, as measured by toxicity [e.g., low incidence of alopecia (110)] and quality of life analysis (91). The usual dose-limiting toxicity of carboplatin is bone marrow suppression, particularly thrombocytopenia (111). Leukopenia and anemia also occur but are less severe.

The platelet nadir is achieved 2 to 3 weeks after an IV bolus injection, and recovery is generally complete 4 to 5 weeks after dosing. However, patients with poor bone marrow reserve from previous chemotherapy or radiation therapy can have more profound thrombocytopenia and leukopenia with carboplatin treatment. Cell depletion may persist for several weeks after dosing.

Nausea and vomiting induced by carboplatin is much less severe than with cisplatin and rarely lasts beyond 24 hours. In a study of 943 ovarian cancer patients randomized to carboplatin, only 9% experienced greater than grade 2 nausea and/or vomiting (110). Emesis can usually be blocked entirely with aggressive therapy using antiemetic drug combinations (112). Diarrhea has been reported in only 6% of patients and constipation in 3% of carboplatin-treated patients (113).

Nephrotoxicity has been reported with carboplatin, but it is much less common and less severe than with cisplatin. In a large

review, transient elevations in serum creatinine and blood urea nitrogen were described in 7% and 16% of patients, respectively (113). Measured creatinine clearances dropped in 25% of patients, and a slight increase in uric acid was described in the same percentage of patients. However, there can be a significant loss of serum electrolytes, including potassium (16% of patients) and magnesium (37%). Serum calcium is only rarely decreased after carboplatin treatment (113).

A few cases of carboplatin-induced hematuria have been described. Hepatic enzyme elevations occasionally occur with carboplatin (113). Alkaline phosphatase was transiently increased in 36% of patients and serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) in about 15% of patients. Serum bilirubin levels are rarely elevated (4%) (113).

Neurotoxicity is uncommon after carboplatin and was described in only 25 of 428 (6%) patients treated on a variety of schedules for different tumor types (113). Mild paresthesias have been reported in a few patients receiving cumulative carboplatin doses of more than 1.6 g/m² (111). Unlike cisplatin, these peripheral nerve toxicities rarely produce any disabling symptoms. In most cases, no neurotoxicity was attributed to the drug.

Ototoxicity does not appear to be problematic with carboplatin, and only 8 of 710 (1.1%) patients have described clinical hearing deficits, mainly tinnitus (113). However, if pretreatment and serial audiometric tests are performed, as many as 15% of the patients may have some decrease in audio acuity. Fortunately, ototoxicity from carboplatin sometimes improves after therapy is halted. Like cisplatin, greater ototoxicity from carboplatin can be expected in patients with preexisting hearing loss or in those concurrently being given other ototoxic drugs, such as aminoglycosides.

Other rare carboplatin toxicities include alopecia (2% of patients), mucositis (2%), skin rash (1.7%), injection-site irritation without extravasation necrosis (0.4%), and a flu-like syndrome (1.3%) (113). The same study described alterations in taste sensation. Skin disorders from carboplatin treatment may appear as an erythematous rash in exposed areas and do not occur in all patients who had developed similar rashes on cisplatin (111).

Although carboplatin-associated hypersensitivity reactions rarely occur when the drug is administered as part of an initial chemotherapeutic regimen, subsequent administration of carboplatin in the setting of second-line or salvage therapy is associated with an increased risk of hypersensitivity. It has been estimated that greater than 25% of patients who receive more than 6 courses of platinum-based (i.e., cisplatin or carboplatin) chemotherapy develop sensitivity to carboplatin (114). The onset of symptoms may occur during the carboplatin infusion or up to 3 days after drug administration. Mild reactions consist of localized itching and erythema, primarily of the palms and soles, and/or facial flushing, whereas severe reactions can cause diffuse erythema, tachycardia, wheezing, facial edema, chills, rigors, throat and chest tightness, dyspnea, vomiting, alterations in blood pressure (both hypotension and hypertension), and in extreme cases, respiratory arrest. Mild cases may respond to IV diphenhydramine (50 mg) or oral diphenhydramine (25 to 50 mg every 4 to 6 hours), and additional courses of carboplatin can be administered. Severe hypersensitivity reactions typically necessitate the discontinuance of carboplatin; however, some patients are able to receive additional courses of carboplatin with administration of corticosteroids for several days prior to carboplatin administration. Hypersensitivity reactions may also occur when carboplatin is administered by the IP route (115).

Platinum-based chemotherapy (either cisplatin or carboplatin) has been shown to increase the risk of leukemia in ovarian cancer patients (116). Following carboplatin-based chemotherapy, the estimated relative risk of leukemia is 6.5 (95% confidence interval, 1.1 to 9.4). The relative risk increases as a function of

both cumulative dose and duration of treatment. Patients who receive 4,000 mg or more of carboplatin have a relative risk of 7.6 of developing leukemia, whereas patients who receive more than 12 months of carboplatin-based chemotherapy have a relative risk of 7.0. Although radiation therapy alone does not increase the risk of leukemia, radiation therapy administered in combination with platinum-based chemotherapy is associated with a significantly higher risk of leukemia than platinum-based chemotherapy without radiation ($p = 0.006$). The average time to onset of secondary leukemia is 4 years after the diagnosis of ovarian cancer. Although the potential benefits of platinum-based chemotherapy for ovarian cancer far outweigh the risk of secondary leukemia, the dose-dependent leukemogenic potential of platinum-based chemotherapy should be considered during its administration to patients with early-stage disease.

With the high doses of carboplatin used in autologous bone marrow transplantation programs, other severe toxicities may occur. These include hepatotoxicity (both hepatitis and cholestasis) and severe renal dysfunction (96,117). Nausea, vomiting, and electrolyte wasting are also more profound with high-dose carboplatin treatments. In addition, other unusual toxic effects may occur. These include hemorrhagic colitis, optic neuritis, and interstitial pneumonitis.

As noted below (see Drug Interactions), paclitaxel ameliorates carboplatin-induced thrombocytopenia.

Drug Interactions

Although the pharmacokinetics of carboplatin is not altered by coadministration of paclitaxel, patients who receive combination chemotherapy with carboplatin plus paclitaxel experience less thrombocytopenia than would be expected if carboplatin was administered as a single agent (103,118). The relationship between free platinum exposure and thrombocytopenia following carboplatin/paclitaxel chemotherapy can be described by a sigmoid maximum effect model (103). In that the degree of neutropenia appears to be unaffected by coadministration of paclitaxel and carboplatin, this pharmacodynamic interaction is believed to occur at the megakaryocyte level (118).

The cytoprotective agent amifostine reduces carboplatin-induced thrombocytopenia (119) but also extends the plasma half-life of carboplatin (120). In a randomized trial of carboplatin with or without amifostine, the median platelet nadir of patients treated with carboplatin 500 mg/m² was 88,000/ μ L, whereas the nadir in patients who received amifostine 910 mg/m² was 127,000/ μ L ($p = 0.023$) (119). Pharmacokinetic studies have shown that amifostine administered just before the carboplatin infusion and 2 to 4 hours thereafter is associated with a significant increase in the terminal half-life of the ultrafiltrable platinum species (e.g., in patients with a creatinine clearance less than 80 mL/min the platinum half-life increased from 4.2 to 5.6 hours with the addition of amifostine). In patients with good renal function, the impact of the increase in terminal half-life was associated with a minimal effect on the AUC. However, patients with impaired renal function experienced significant increases in the AUC of the ultrafiltrable platinum species (120).

Special Applications

Patients with advanced ovarian cancer have been treated with IP carboplatin in doses ranging from 200 to 650 mg/m² (121). Pharmacologic studies have demonstrated that serum concentrations are equivalent between IV and IP carboplatin regimens, but IP administration results in more than 10 times the concentration in the peritoneal cavity compared to IV administration (122). However, cisplatin may be a better choice for IP delivery in that it appears to have significantly better penetration into tumor masses than carboplatin (123). Several early-phase trials have shown potentially promising results (17,124); however, there is a need for phase III research to determine the

possible efficacy of IP carboplatin and trials to determine the optimal dosing schedule.

Because of its relative lack of nonhematologic side effects, carboplatin has become the platinum analog of choice for bone marrow transplantation regimens. A regimen developed at Loyola University that consists of high-dose carboplatin combined with cyclophosphamide, mitoxantrone, and autologous bone marrow support was selected for an intergroup phase III study of high-dose versus standard-dose chemotherapy for ovarian cancer patients with low-volume, persistent disease following primary chemotherapy (GOG-164). Although this study was closed in May 1999 because of inadequate patient accrual, the high-dose regimen was well tolerated among the 24 patients on the trial. With adequate hydration and mannitol diuresis to prevent nephrotoxicity, nonhematologic side effects were predominantly mucositis, ototoxicity, and diarrhea (117).

Cisplatin

Chemistry

Cisplatin (Platinol, *cis*-diamminedichloroplatinum II) is a primary drug in the treatment of advanced cancer of the ovary, cervix, and endometrium. It has the molecular formula PtCl₂H₆N₂ (molecular weight = 300.1). It is a planar inorganic heavy metal complex containing a central atom of platinum surrounded by 2 chloride atoms and 2 ammonia molecules in the *cis* position. It is soluble in water at a concentration of 1 mg/mL. Only the *cis*-isomer is therapeutically active.

Mechanism of Action

Cisplatin's interaction with DNA is probably its primary mode of action. The antitumor effect of cisplatin has been correlated with binding to DNA and the production of intrastrand cross-links and formation of DNA adducts, similar to carboplatin (94,125). Intrastrand cisplatin adducts can cause changes in DNA conformation that may affect DNA replication (126). Platinum DNA adduct levels have been measured in patients' leukocytes and correlated with clinical response (125).

Mechanisms of cisplatin drug resistance are an area of concentrated research. Methods by which tumor cells may develop resistance to platinum agents include decreased drug accumulation, increased glutathione levels, enhanced DNA repair, and increased capacity to tolerate DNA damage (127,128).

The ERCC1 repair protein is part of the nucleotide excision repair system, which takes part in single-strand break repair. It is thought that this system may be responsible for the removal of intrastrand DNA platinum adducts from DNA. High expression of ERCC1 has been associated with platinum resistance and poorer survival in ovarian cancer patients treated with platinum-based regimens (129) [H10]. ERCC1 has also been identified as playing a critical role in the synergy of gemcitabine and cisplatin. Phase II data suggest that gemcitabine may reverse cisplatin resistance, as gemcitabine-cisplatin combination therapy was active in platinum-resistant ovarian cancer patients (130).

Resistance to platinum drugs has also been associated with the activity of the double-strand break repair system, homologous recombination repair (HR). Tumors arising in patients with germline BRCA1 and BRCA2 mutations respond better to platinum-based therapy and survive longer on treatment than their BRCA wild-type counterparts (131–133). Both BRCA1 and BRCA2 are involved in HR, and patients whose tumors contain somatic BRCA1/2 mutations or who show impaired HR ("BRCAness") also respond better and survive longer on platinum-based therapy than case controls (134,135). The idea that platinum resistance may be mediated by HR is supported by the observation of secondary mutations that re-activate either the BRCA1 (136) or the BRCA2 (137,138) proteins when these patients eventually become resistant to platinum drugs.

In vitro studies have shown that the copper transporter, CTR1, plays a regulatory role with respect to the uptake of platinum drugs (139). In a study of 40 patients with ovarian carcinoma, Yoo-Young Lee et al. showed that high CTR1 expression was specifically associated with sensitivity to platinum-based therapy and prolonged progression-free survival while low CTR1 expression and high STR2 expression were associated with resistance to platinum-based therapy and shorter survival (140).

Mechanisms of resistance also include the increased inactivation of thiol-containing proteins such as glutathione and glutathione-related enzymes, a deficiency in mismatch repair enzymes (e.g., hMLH1, hMSH2), and decreased drug accumulation due to alterations in cellular transport (79).

A study of hMLH1 methylation in the plasma DNA of ovarian cancer patients at presentation and relapse showed no correlation with outcome at presentation, but high methylation was associated with poorer outcome following relapse (141). Whether this was due to resistance to platinum drugs is not clear because the report does not document the treatments given following relapse. Further, a follow-on randomized phase II study using decitabine to induce demethylation of the HMLH1 promoter showed an inferior outcome in the decitabine arm (142). The clinical relevance of mismatch repair defects in the response to platinum agents remains uncertain.

Recent evidence also suggests that resistance to platinum and other agents may be mediated by factors in the tumor environment rather than in the tumor cell itself. Roodhart et al. have identified 2 distinct platinum-induced polyunsaturated fatty acids (PIFAs), 12-oxo-5,8,10-heptadecatrienoic acid (KHT) and hexadeca-4,7,10,13-tetraenoic acid (16:4[n-3]), that in minute quantities induce resistance to a broad spectrum of chemotherapeutic agents, including platinum agents (143).

Drug Disposition

Cisplatin demonstrates a triphasic disappearance curve with a $t_{1/2\alpha}$ of 20 minutes, a $t_{1/2\beta}$ of 48 to 70 minutes, and a terminal-phase half-life of 24 hours (144). The first 2 phases of disappearance represent clearance of free drug from the plasma, and the third phase is probably removal of drug from the plasma proteins. The ratio of cisplatin to total free platinum in plasma has a great deal of interpatient variability: from 0.5 to 1.1 after a dose of 100 mg/m². Three hours after a bolus injection and 2 hours after a 3-hour infusion, 90% of the plasma protein is bound to the platinum in cisplatin, not the cisplatin itself. The complexes between albumin and platinum are slowly eliminated with a minimum half-life of 5 days or more (145). Ninety percent of the drug that is excreted is removed by renal mechanisms (i.e., glomerular filtration and tubular secretion), and less than 10% is removed by biliary excretion. Fecal excretion appears to be insignificant. The total proportion of a given dose that is excreted is variable and has been reported to be between 31% and 85% after 51 days (146). The remainder stays bound to tissues for very long periods. Schierl et al. reported 2 long-term biological half-lives of platinum of 16 and 720 days and showed that, of an administered dose of 800 mg cisplatin, 1 mg remained in a long-term pool after 3,000 days (147). There is a potential for accumulation of ultrafilterable platinum plasma concentrations whenever cisplatin is administered on a daily basis but not when dosed on an intermittent schedule.

Administration and Dosage

Cisplatin may be administered IV or IP. Cisplatin should be mixed only in solutions containing 0.9% or more sodium chloride, because drug stability is directly related to the concentration of the salt. When admixed with dextrose-containing solutions, by chromatographic analysis, the drug appears to be relatively unstable, with decomposition evident by 2 hours (148). Platinum also can form significant, colored

complexes if directly admixed with mannitol and stored for 2 to 3 days (149). Short-term (<24 hours) admixtures, however, have been successfully used. Needles or IV sets containing aluminum should not be used in the preparation or administration of cisplatin, because this drug rapidly reacts with aluminum, resulting in a loss of drug potency and the formation of a black precipitate (150).

To protect against nephrotoxicity, it is critical that a high urinary output be maintained during cisplatin therapy. Several methods of accomplishing this have been recommended; however, the most widely practiced method involves prehydration and mannitol diuresis (151). If cisplatin is administered in a hospital setting, patients should receive hydration with 1 to 2 L of fluid prior to cisplatin. Mannitol diuresis is accomplished by diluting the cisplatin in 2 L of normal saline containing 37.5 g of mannitol. The solution is then infused over 6 to 8 hours. Adequate hydration and urinary output should be maintained during the next 24 hours. A safe outpatient procedure using concurrent mannitol that appears to prevent serious nephrotoxicity has also been reported (152). The desired dose of cisplatin plus 50 g mannitol is diluted to 1 L with 5% dextrose plus 0.45% sodium chloride, USP. This solution may then be infused at a rate of no more than 1 mg/min. For patients with known cardiac disease, the dose may be placed in 200 mL of a 10% mannitol solution and infused at a rate of no more than 1 mg/min. This is followed by 200 mL of additional 10% mannitol. An alternative is to add the drug to 400 mL of 10% mannitol that is then brought up to a 1-L volume with normal saline containing 3 g of magnesium sulfate and administered IV over 1 hour (153).

Intraperitoneal cisplatin administration and nursing guidelines are described in detail elsewhere (154,155), using the GOG-172 regimen adapted to a 3-hour paclitaxel infusion (IV paclitaxel 135 mg/m² over 3 hours day 1 + IP cisplatin 100 mg/m² day 2 + IV paclitaxel 60 mg/m² day 8). A totally implantable device (IV port, such as single-lumen venous-access catheter: 9.6F, Port-A-Cath or Bardport) is surgically placed in the IP space at least 2 days before cisplatin administration. Placement can be done at the time of surgery or postoperatively (e.g., laparoscopically). It is important to note that peritoneal or fenestrated catheters can lead to fibrous sheath formation, small bowel obstruction and perforation, and should be avoided (156). Day 2 IP administration requires that cisplatin be mixed in 1 L of normal saline and then warmed to body temperature. The 1-L cisplatin solution is instilled as rapidly as possible into the IP space via the catheter and should be followed by up to one additional liter of saline to the point of mild abdominal discomfort. The cisplatin solution is allowed to remain in the IP cavity (i.e., the fluid is not drained). Concurrently, at least 1 L normal saline must be administered IV along with 40 gm mannitol to assure a brisk diuresis to eliminate the cisplatin. Since cisplatin has the potential to be highly emetogenic, it is important to consider an aggressive antiemetic regimen (154,157).

A retrospective analysis by Levin and Hryniuk (158) strongly suggests that cisplatin efficacy against ovarian cancer is directly correlated with cisplatin dose intensity (i.e., mg/m²/wk). Typical high-dose regimens include 20 mg/m² daily for 5 days repeated every 3 weeks, 100 to 120 mg/m² IV every 3 to 4 weeks, or 100 mg/m² on day 1 and day 8 repeated every 20 days (159,160). Holleran and DeGregorio (161) prepared an excellent review of high-dose (200 mg/m²/course) cisplatin. Dose-limiting toxicities with the higher dose regimens include severe, relatively irreversible neurotoxicity and myelosuppression. Responses have been seen in conventional-dose cisplatin-refractory patients, but they generally are of relatively short duration.

Side Effects and Toxicities

Dose-related nephrotoxicity is the major dose-limiting toxicity of cisplatin. It is manifested by renal tubular damage resulting in

an elevation of BUN (blood urea nitrogen) or serum creatinine. The peak detrimental effect on renal function usually occurs between the tenth and twentieth day after treatment. The renal damage is usually reversible. Patients concomitantly receiving gentamicin and cephalothin have been shown to be at greater risk of developing acute renal failure (162).

Madias and Harrington (163) have characterized the renal damage of cisplatin as being similar to mercury nephrotoxicity. Pathologically, renal tubular necrosis, degeneration, and interstitial edema without glomerular changes are observed. Although clinically overt renal toxicity may be common, it is usually reversible. However, some degree of long-term damage is likely. The renal-protective effect of hydration and mannitol is well established in animals and humans, and renal impairment can be prevented (152).

Ototoxicity, manifested by high-frequency hearing loss (above the frequency of normal speech), may be seen in as many as 30% of patients treated with cisplatin (164). Hearing impairment may be dose related and can be unilateral or bilateral. Occasional tinnitus (but not vestibular dysfunction) has been reported. The ototoxicity may be partially reduced by adequate hydration and the use of mannitol diuresis. Patients with lower than average threshold before chemotherapy with cisplatin are more likely to experience greater threshold shifts (164).

Neurotoxicity can be a dose-limiting side effect of cisplatin, particularly with high-dose regimens (165). The range of cisplatin-induced neurologic deficits include peripheral sensory neuropathy, ototoxicity, autonomic neuropathy manifested by orthostatic hypotension and gastric paresis, Lhermitte's syndrome, and rarely focal encephalopathy, often accompanied by cortical blindness. Peripheral neuropathy is by far the most common cisplatin-induced neurotoxicity. Neurotoxicity is dose dependent, with symptoms typically developing after cumulative doses of 300 mg/m² or more. A review of published literature (166) found that neurotoxicity occurred in 85% of patients at cumulative doses of 300 mg/m² or more but occurred in only 15% of patients who had received a cumulative dose below this level. Initial symptoms are usually numbness and tingling in the distal fingers and toes. If cisplatin is continued, proximal extension of the peripheral neuropathy occurs, and the sense of joint position becomes impaired, resulting in more severe neurologic symptoms, including ataxia, gait disturbances, loss of manual dexterity, and wheelchair dependency. Symptoms may begin and progress up to 4 or more months after discontinuation of cisplatin. In 30% to 50% of patients, cisplatin neuropathy is irreversible.

Early clinical data suggest that a number of investigational agents may ameliorate cisplatin-induced neurotoxicity (165). Agents that have been associated with positive preclinical results include ORG2766 (167), an ACTH analog, and the sulfhydryl-based compounds amifostine and glutathione. Only amifostine has been associated with a significant reduction of grades 2 and 3 neurotoxicity in the setting of an adequately designed phase III trial (168). Further development of a neuroprotective agent, such as amifostine, could significantly enhance the clinical effectiveness of cisplatin, enabling dose-intensive therapy and greater cumulative doses to be delivered to more patients with sensitive tumors. In 2003, the GOG initiated a phase III trial of low-dose, IV bolus amifostine 3 times weekly to reverse grade 2 or greater peripheral neuropathy (GOG-192).

Symptomatic hypomagnesemia frequently occurs with cisplatin. In a study to determine the effects of magnesium supplementation on cisplatin-induced hypomagnesemia, the administration of magnesium (oral and IV) with cisplatin to one group of patients produced less renal tubular damage and no compromise in efficacy than that seen in a group not supplemented with magnesium (169).

Without adequate antiemetic therapy, most patients who receive cisplatin experience nausea and vomiting. This reaction may be severe and usually starts within the first hour after

treatment and may persist for 24 to 48 hours. Delayed nausea and vomiting, lasting from 3 to 5 days, also may occur. The combination of a 5-HT₃ inhibitor (e.g., ondansetron or granisetron) with dexamethasone (10 to 40 mg IV) has reduced the incidence of severe nausea and vomiting by as much as 75% (170). Delayed nausea and vomiting can be eradicated by continuation of oral low-dose dexamethasone (with or without a 5-HT₃ inhibitor) for the first 5 days after platinum treatment (171). Other less effective antiemetic regimens to prevent cisplatin-induced nausea and vomiting include prochlorperazine, dexamethasone, and lorazepam; metoclopramide and dexamethasone; metoclopramide and methylprednisolone; or metoclopramide and lorazepam (112,172).

Anaphylactic hypersensitivity reactions consisting of tachycardia, wheezing, hypotension, and facial edema, occurring within a few minutes of IV administration, have occurred occasionally after a dose of cisplatin given to previously treated patients (173,174). These hypersensitivity reactions have been controlled with corticosteroids, epinephrine, or antihistamines. Wiesenfeld and colleagues (175) reported successful retreatment with cisplatin after apparent allergic reactions in 2 patients. *In vivo* and *in vitro* tests in one patient could not demonstrate an immunologic basis for the initial reaction. Both patients were successfully rechallenged with cisplatin after only diphenhydramine pretreatment. This suggests a nonallergic cause of the acute hypersensitivity reactions occasionally seen with platinum.

Myelosuppression occurs in 25% to 30% of patients receiving the recommended dose, and is more pronounced at higher doses. Coombs-positive hemolytic anemia also occurs as a result of cisplatin treatment. Cisplatin-induced anemia has been shown to respond to recombinant erythropoietin (176).

Drug Interactions

When cisplatin is given in combination with other agents, the order of drug sequence can affect the severity of drug-induced myelosuppression. Rowinsky and Donehower (177) conducted a phase I study of sequential escalating doses of paclitaxel and cisplatin therapy and determined that myelosuppression was more severe when cisplatin administration preceded paclitaxel than when given after paclitaxel. Another phase I study was conducted to evaluate the effects of drug sequence of treatment with cisplatin in combination with topotecan (178). This study also found a significantly higher incidence of myelosuppression when cisplatin was administered first.

Cisplatin-induced nephrotoxicity should be considered whenever this agent is given prior to or in combination with other cytotoxic drugs that are cleared by renal elimination (e.g., bleomycin, ifosfamide, etoposide, methotrexate). Cisplatin reduces the renal clearance of these agents, resulting in an increased accumulation of these drugs. Yee and coworkers (75) observed markedly reduced bleomycin clearance in children who had received 6 courses of a regimen including cisplatin (cumulative dose 300 mg/m²). In another case report, fatal bleomycin pulmonary toxicity occurred in a patient with cisplatin-induced acute renal failure (76).

Cisplatin is directly inactivated by mesna and amifostine (79). The FDA has approved amifostine to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer. In a phase III randomized study of ovarian cancer patients, amifostine treatment prior to IV cisplatin plus cyclophosphamide did not appear to reduce cisplatin's anticancer activity (179). However, there are only limited data in other chemotherapeutic settings, and the FDA recommends that amifostine should not be administered to patients in settings where chemotherapy could produce a significant survival advantage or cure, except in a clinical trial (180).

Special Applications

The efficacy of cisplatin can be increased significantly in patients with stage III, optimal disease (i.e., <1 cm² residual

tumor) epithelial ovarian cancer when it is administered by the IP route as part of a primary, combination chemotherapy regimen. A pivotal phase III trial, GOG-172, determined that the IP administration of cisplatin 100 mg/m² (on day 2, preceded by IV paclitaxel 135 mg/m² over 24 hours on day 1 and followed by IP paclitaxel 60 mg/m² on day 8, every 3 weeks for 6 cycles) was associated with a highly significant 16-month increase in overall survival compared with the standard treatment arm (IV cisplatin 75 mg/m² plus IV paclitaxel 135 mg/m² over 24 hours every 3 weeks for 6 cycles) in patients with advanced, optimal ovarian cancer (4). Despite the higher incidence of toxicity in the IP arm, these effects appear to be of short duration, as patients treated IP and IV reported equivalent quality of life 1 year post treatment (8). As a result, the National Cancer Institute issued a Clinical Announcement on January 5, 2006 recommending IP therapy as the preferred treatment for optimal, advanced ovarian cancer (181).

Intraperitoneal therapy is not recommended for patients who have suboptimal cytoreductive surgery (i.e., >1 cm in largest diameter of a tumor nodule), because IP cisplatin (as well as other cytotoxic agents) only penetrates a few millimeters into tumor plaques (16). Additional considerations regarding the appropriate patient selection for consideration of IP therapy are discussed in detail elsewhere (154,155,182).

Multiple phase III studies have shown that cisplatin-based chemotherapy as an adjunct to radiation therapy improves survival in cervical cancer patients (47,183–185).

Cyclophosphamide

Chemistry

Cyclophosphamide (Cytosan, Neosar, CTX, CPM, and Endoxan) is an alkylating agent that before the advent of paclitaxel was used in the primary chemotherapy of advanced, epithelial-type ovarian and endometrial cancer. It is no longer often used in the treatment of gynecologic cancers because of the more effective agents currently available (e.g., paclitaxel). It is occasionally used in the third-line treatment of ovarian cancer and as a second-line agent in the treatment of choriocarcinoma. It is a cyclic phosphamide ester of nitrogen mustard and is referred to chemically as 2-[bis-(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Its molecular weight is 279.1. The monohydrate is unionized and lipid soluble; in normal saline or water, it is soluble to a maximum of 4% at room temperature.

Mechanism of Action

Cyclophosphamide, a bifunctional substituted nitrogen mustard, was synthesized in 1958 in an attempt to achieve greater selective toxicity for tumor tissue. The N-methyl moiety of nitrogen mustard is replaced with a cyclic phosphamide group, resulting in a stable, inactive compound. The bis-(2-chloroethyl) group cannot ionize until the cyclic phosphamide is opened at the phosphorus-nitrogen linkage.

Activation of cyclophosphamide is a multistep process. The liver microsomal P450 mixed-function oxidase system converts the parent drug to 4-hydroxycyclophosphamide. This metabolite exists in equilibrium with the acyclic tautomer, aldophosphamide. These compounds may be further oxidized by hepatic aldehyde oxidase to the inactive metabolites of carboxyphosphamide and 4-ketocyclophosphamide. Nonenzymatic conversion to the cytotoxic compounds of phosphoramidate mustard and acrolein occurs in susceptible peripheral tissues.

Most of the alkylating agents, like cyclophosphamide, are bifunctional, which facilitates their reaction with 2 cellular molecules. Accordingly, they can cross-link the 2 opposite strands of DNA to give an interstrand cross-link, react with 2 sites on the same strand (intrastrand cross-link), or cross-link DNA to

protein. The latter type of lesion is generally considered to be innocuous, but the relative significance of the other cross-links is still in contention. DNA intrastrand cross-links are more frequent than interstrand cross-links and are more often considered to be the critical lesions.

These 2 classes can be differentiated by the structure of the cross-links in DNA. Generally, the entire mustard is involved in the cross-link, with the 2 mustard “arms” linked usually to the N7 position of guanine. Since these guanines can be separated by several bases in DNA, the linkages represent particularly bulky lesions.

Drug Disposition

After IV administration, approximately 15% of the drug is excreted unchanged in the urine and the remainder as metabolites. The plasma half-life of the parent compound after doses of 6 to 80 mg/kg appears to range from 4.0 to 6.5 hours (186,187). Approximately 50% of the alkylating metabolites (but not parent drug) is bound to plasma proteins.

Although cyclophosphamide is exclusively excreted by the kidney, because of the unionized nature of the intact drug molecule, tubular reabsorption is avid. Hepatic inactivation appears to be the major mechanism of active drug elimination. The mean renal clearance of intact drug is approximately 11 mL/min, or 15% of creatinine clearance, but renal elimination remains the major route of disposition of the more polar, less lipid-soluble metabolites (188). There can be significantly prolonged retention of active (alkylating) metabolites in patients with severe renal failure, and doses should be adjusted accordingly.

Dosage

Cyclophosphamide is active in many different types of malignancies. The dosing schemes are numerous and depend on the particular disease. There are two general categories of treatment schedules exist. In the method generally used to treat ovarian and endometrial cancers, an intermediate dose (600 to 1,000 mg/m²) is given all at once over a short period. This treatment approach usually involves other drugs, such as cisplatin, carboplatin, or doxorubicin, whose additive toxic effects must be considered in selecting the dose and frequency of cyclophosphamide administration. Adequate hydration for 72 hours before and following high-dose treatment with cyclophosphamide is recommended to reduce cyclophosphamide-induced hemorrhagic cystitis (189).

An alternative continuous low-dose regimen for cyclophosphamide has been developed. Doses of 25 to 50 mg/day are given on a continuous basis. Used in this way, it was originally thought that cyclophosphamide acted as an “accidental” antiangiogenic agent (190). It is usually well tolerated with few side effects. Colleoni and colleagues published the results of a trial of continuous low-dose cyclophosphamide with methotrexate in breast cancer and showed antitumor activity that correlated with vascular endothelial growth factor levels (191). Further, Miscoria and colleagues found an association between progression-free survival and thymidine phosphorylase levels (192). A suggestion has been made that the acrolein metabolite of cyclophosphamide acts as an antiangiogenic agent (193). The use of cyclophosphamide in this way has come to be known as “metronomic” dosing. In addition to the antiangiogenic effect, metronomic cyclophosphamide may also have an immune regulatory function (194). Ge et al. (195) showed that metronomic cyclophosphamide induced an increase in the number of breast cancer reactive t-cells and that this correlated with disease stabilization in breast cancer.

There have been a large number of trials of the metronomic approach in a range of tumor types, including ovarian cancer. These have been reviewed (196). Activity is frequently reported, but the heterogeneous nature of the trials, the frequent combination with established antiangiogenic agents,

and the lack of randomized trials makes the overall role of this approach undefined.

Side Effects and Toxicities

Myelosuppression consisting primarily of leukopenia is the usual dose-limiting toxic effect of cyclophosphamide. Both the nadir and time of bone marrow recovery are rapid at 8 to 14 and 18 to 21 days, respectively. Although this drug has long been considered to be “platelet sparing,” significant thrombocytopenia can also occur at very high doses ($>1.5 \text{ g/m}^2$).

Acute, sterile hemorrhagic cystitis, believed to be due to the acrolein metabolite, is an infrequent toxic manifestation, but is occasionally dose limiting. It is understandably more common in poorly hydrated or renally compromised patients. The onset of this complication may be delayed from 24 hours to several weeks. It is detected by gross hematuria or a microscopic hematuria of greater than 20 erythrocytes per high-power field. The bleeding may persist but is usually transient. Prophylactic hydration with intake of at least 3 L/day appears to offer the best protection. With continued therapy, patients characteristically develop a fibrotic “small bladder,” and urinary frequency may become a permanent problem. There is a definite increase in the risk of bladder cancer in these patients. The availability of the sulfhydryl mesna as a prophylactic treatment of patients at high risk for developing cyclophosphamide-induced cystitis has almost completely eliminated this side effect.

A syndrome of inappropriate antidiuretic hormone (SIADH), or “water intoxication,” has been reported after cyclophosphamide treatment. This is more common with IV doses greater than 50 mg/kg and is both a limitation to and consequence of fluid loading (197). Alopecia occurs to some degree in all patients receiving cyclophosphamide and is significant in at least half of all patients treated. Regrowth of hair may occur even with continuing treatment. Gastrointestinal problems are more common with high doses given orally. Anorexia, nausea, and vomiting are all common reactions, but they are usually controlled with IV antiemetic regimens. A rare pulmonary toxic effect has been reported with a pneumonitis picture similar to “busulfan lung.” The typical clinical presentation is that of an interstitial pneumonitis, usually occurring after long-term and continuous low-dose therapy (198). The onset of symptoms is insidious. Pathologically, there can be alveolitis with eventual fibrosis and atypical type II pneumocytes. Steroids may be beneficial. Other toxic effects include testicular atrophy, sometimes with reversible oligospermia and azospermia. Amenorrhea also has been reported. As with all alkylating agents, drug-induced congenital abnormalities are possible. With high-dose therapy used for bone marrow transplant (120 to 180 mg/kg), cyclophosphamide-associated cardiac toxicity has been reported (199).

Special Precautions

It is important to keep the patient well hydrated during cyclophosphamide therapy to reduce the potential for hemorrhagic cystitis. It is advisable to administer at least 1 L of additional IV fluids (usually normal saline) to assure an adequate urine volume to excrete the cyclophosphamide metabolite acrolein, which can otherwise alkylate bladder mucosa and cause hemorrhagic cystitis. The patient should be instructed to drink at least 8 glasses of fluid daily during the 2 days after cyclophosphamide administration. In patients prone to developing cystitis, consider administering prophylactic IV mesna, a sulfhydryl-containing compound that can neutralize acrolein.

Drug Interactions

Cyclophosphamide must be metabolized to be active. Although some cyclophosphamide may be activated by phosphatases and phosphamidases peripherally, most of the drug is metabolized

by microsomal enzymes in the liver (200,201). These enzymes may be activated by drugs like phenobarbital or inhibited by drugs like proadifen (SKF 525A). Because active and toxic metabolites are generated by the reactions of these enzymes and cyclophosphamide, many potential drug interactions may exist.

Barbiturates and other inducers of hepatic microsomal enzymes, such as phenytoin and chloral hydrate, may increase the rate of hepatic conversion of cyclophosphamide to its toxic metabolites. Similarly, cyclophosphamide may block the metabolism of barbiturates, increasing sedative effects. Although the clinical significance of these reactions is not clear, cyclophosphamide toxicity may be increased by the H_2 -histamine blocker cimetidine (202). Cimetidine, but not ranitidine, may increase cyclophosphamide’s myelotoxicity through an increase in the concentration time product of its active metabolites (e.g., 4-hydroxycyclophosphamide and phosphoramidate mustard) (203). Thus, H_2 -blockers such as ranitidine may be safer to use than cimetidine when high doses of cyclophosphamide are administered.

Dactinomycin

Chemistry

Dactinomycin (actinomycin D, ACT-D, Cosmegen) has been shown to be active in the treatment of patients with germ-cell tumors of the ovary and endometrium and those with gestational trophoblastic disease (204–206). It has a molecular weight of 1,255 and an empiric formula of $\text{C}_{62}\text{H}_{86}\text{N}_{12}\text{O}_{16}$. The drug is an antitumor antibiotic isolated from *Streptomyces parvulus*. The molecular structure includes 2 peptide loops linked to a 3-ring chromophoric phenoxazone ring system (actinocin). The drug is highly soluble in water, forming an amber- to gold-colored solution.

Mechanism of Action

Dactinomycin becomes anchored into or around a purine-pyrimidine base pair in DNA by intercalation. DNA-dependent ribosomal RNA synthesis and new messenger RNA synthesis is inhibited. The peptide loops appear to allow tight drug binding to DNA because the actinocin (phenoxazone) moiety alone is inactive. This can occur adjacent to any G–C pair in DNA.

Bound dactinomycin molecules dissociate very slowly from DNA owing to electrostatic interactions of the cyclic peptide rings with each strand of the DNA double helix. This process, which stabilizes the intercalative interaction, appears to be crucial for cytotoxicity.

Dactinomycin on a molar basis is one of the most potent antineoplastic agents available. The drug possesses some hypocalcemic activity, similar to mithramycin. Although maximal cell killing is observed in the G_1 phase, the cytotoxic action is thought to be primarily cell cycle nonspecific. Actively proliferating cells are more sensitive than quiescent cells to the lethal effects of the drug (207).

In that dactinomycin is a natural product, it is not surprising that the primary mode of tumor cell resistance to dactinomycin is mediated through overexpression of P-glycoprotein (208).

Drug Disposition

Tattersall and colleagues (209) studied the pharmacokinetics of radiolabeled [^3H] dactinomycin in patients, and the drug appeared to be only minimally metabolized and was concentrated in nucleated cells. There was a greater drug uptake into bone marrow than in plasma. Drug penetration into the central nervous system was not observed. Urinary and fecal recovery totaled only 30% each after 9 days, and there was significant drug retention in lymphocytes and granulocytes. This may explain the prolonged terminal plasma half-life of 36 hours observed after single dactinomycin doses. There appears to be little metabolism, because approximately 90% of excreted drug

is collected as the intact molecule. Some monolactone forms of dactinomycin are recovered in the urine.

Using a more specific radioimmunoassay, a much shorter dactinomycin half-life is described ($t_{1/2\alpha} = 0.78$ minutes, $t_{1/2\beta} = 3.5$ hours) (210). The discrepancies between these and Tattersall's findings reflect the differences in the assays used.

Administration and Dosage

Dactinomycin is administered by slow IV push or, preferably, into the tubing of a freely running IV solution. A 5- to 10-mL flush of 5% dextrose in water (D₅W) or normal saline is recommended before and after IV push administration to assure vein patency and to flush any remaining drug from the tubing.

Dactinomycin is commonly given IV in short "pulse" doses of 500 $\mu\text{g}/\text{m}^2$ daily for as long as 5 days in adults. The dose for each 2-week cycle should not exceed 15 $\mu\text{g}/\text{kg}/\text{day}$ or 400 to 600 $\mu\text{g}/\text{m}^2/\text{day}$ for 5 days.

A wide variety of dosing regimens have been employed. Several clinical studies have documented equal efficacy and toxicity for single-dose dactinomycin regimens (211,212). In non-metastatic gestational trophoblastic cancer, a single IV dose of 1.25 mg/m^2 every 14 days produced a 99% remission rate after 4 courses of therapy (212). Compared with 5 divided doses of 500 $\mu\text{g}/\text{m}^2/\text{day}$, the single-dose method produced slightly greater mild-to-moderate toxic effects.

Side Effects and Toxicities

Bone marrow depression is the usual dose-limiting toxic effect of dactinomycin. It is usually manifested 7 to 10 days after dosing. All blood elements are affected, but primarily, the platelets and leukocytes are depressed. Combined with gastrointestinal reactions, myelosuppression appears to be dose limiting as well as dose dependent (213). Immunosuppression is another well-known effect of dactinomycin. Patients should not receive this drug during viral infection because of the risk of developing disseminated disease.

Severe gastrointestinal consequences, such as vomiting, can occasionally represent the acute dose-limiting toxic effects of dactinomycin. Vomiting can persist for 4 to 20 hours, but it can be controlled by combination antiemetic regimens (214). Mucositis can also be severe. It is characterized by severe oral ulcerations and diarrhea in 30% of patients. Reversible alopecia may occur with dactinomycin. A variety of other skin manifestations have been reported, including acneiform changes, erythema, and hyperpigmentation.

Dactinomycin is toxicologically similar to the anthracyclines and characteristically interacts with radiation therapy, producing delayed "radiation recall" skin damage. Previously irradiated or even irritated skin may become reddened and inflamed after drug administration. Frank necrosis is sometimes reported. Oral ulcers may also develop after radiation therapy. These reactions may occur months after radiation therapy. Experimentally, radiation therapy given after dactinomycin does not produce this effect.

Dactinomycin potentiates pulmonary radiation and decreases radiation tolerance by at least 20%. Reintroduction of dactinomycin following pulmonary radiation has resulted in fatal pulmonary fibrosis (215). As noted in the "Special Precautions" section below, dactinomycin is highly ulcerogenic if extravasated.

Special Precautions

Dactinomycin is extremely damaging to soft tissue, and every effort should be made to assure vein patency during administration. Extravasations characteristically result in immediate pain and swelling followed by indolent, poorly healing necrotic ulcers (214).

Dactinomycin is highly potent and is typically dosed in micrograms per kilogram. Doses must be calculated and prepared carefully to prevent inadvertent overdosage. No specific antidote to overdosage is known, although granulocyte colony-stimulating factors may be useful.

Dactinomycin is a potent immunosuppressant and can inhibit the effectiveness of vaccinations given after drug administration. The drug also produces radiation recall skin and soft-tissue damage if given after ionizing radiation.

Docetaxel

Chemistry

Docetaxel (Taxotere) is a semisynthetic analog of paclitaxel and has a FDA-approved indication for locally advanced or metastatic breast cancer after failure of prior chemotherapy. It is also FDA approved for locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. It also has shown marked antitumor activity against a variety of solid tumors, including both platinum-sensitive and platinum-refractory epithelial ovarian cancer (216,217). The natural component of docetaxel is 10-deacetyl baccatin III, which is extracted from the needles of the European yew tree (*Taxus baccata* L.) (217). Docetaxel has a molecular weight of 861.9 and the empirical formula $\text{C}_{43}\text{H}_{53}\text{NO}_{14} \cdot 3\text{H}_2\text{O}$. Unlike paclitaxel, which uses a polyoxyl compound (Cremophor) as a diluent, docetaxel is formulated in Tween 80 and alcohol.

Mechanism of Action

In a manner similar to paclitaxel, docetaxel promotes microtubule assembly and inhibits the depolymerization of tubulin. However, compared with paclitaxel, the microtubules formed by docetaxel are more slowly reversible, and there are differential effects on tau binding sites and on microtubule-associated proteins. Docetaxel-induced stabilization of microtubules halts cellular division in M phase, thereby preventing cell replication.

Drug Disposition

The pharmacokinetics of docetaxel when administered as an IV infusion lasting from 1 to 24 hours has been investigated in a number of studies (218). When administered as a typical 1-hour infusion at doses of 70 to 100 mg/m^2 , pharmacokinetics reveals triphasic elimination with plasma AUC of 3.13 to 4.83 $\text{mg}/\text{mL}/\text{hour}$, a peak plasma concentration of 2.57 to 3.67 $\mu\text{g}/\text{mL}$, and a terminal-phase plasma half-life of 13.6 hours. There is very limited renal excretion of docetaxel; the 24-hour urinary excretion was 1.4% of the dose administered. Plasma drug clearance was determined to be 21.3 $\text{L}/\text{hour}/\text{m}^2$ (219).

Administration and Dosage

All patients receiving docetaxel should be premedicated with oral corticosteroids such as dexamethasone 16 mg/day (e.g., 8 mg BID) for 3 days beginning 1 day prior to docetaxel administration in order to reduce fluid retention and the risk of hypersensitivity reactions.

Docetaxel is commercially available in single-dose 20- and 80-mg vials with accompanying diluent vials. Both the docetaxel vials and the diluent vials should stand at room temperature for approximately 5 minutes prior to mixing. The entire contents of the diluent vial should be aseptically transferred to the docetaxel vial, and the resulting contents should be gently rotated for 15 seconds to promote complete mixture. The resulting concentration of docetaxel is 10 mg/mL . Foam may be present owing to the Tween 80; however, it should largely dissipate within a few minutes. The infusion solution is prepared by aseptically withdrawing the proper amount of docetaxel with a calibrated syringe and adding it to a 250-mL infusion bag or

bottle containing either 0.9% sodium chloride or 5% dextrose solution to produce a final concentration of 0.3 to 0.9 mg/mL. The infusion solution should be mixed by manual rotation and inspected for particulate formation and/or discoloration. Solutions that are cloudy or that contain particulate matter should be discarded.

The recommended dose of docetaxel for salvage chemotherapy of breast cancer is 60 to 100 mg/m² IV as a continuous 1-hour infusion every 3 weeks. For non-small cell lung cancer, the recommended dose is 75 mg/m² IV as a continuous 1-hour infusion every 3 weeks. The optimal dosing schedule for docetaxel in gynecologic cancers is presently undefined. A 100-mg/m² dose administered as a 1-hour infusion every 3 weeks has been used in phase II trials. Other tolerable docetaxel dose schedules that have been identified in phase I studies are: 50 mg/m²/day on days 1 and 8 every 3 weeks; 70 to 90 mg/m² by 24-hour continuous IV infusion every 3 weeks; 80 to 100 mg/m² by 6-hour infusion every 3 weeks; 14 mg/m²/day for 5 days by 1-hour infusion every 21 days (220); and 30 to 35 mg/m² weekly (221,222). Docetaxel has been administered in combination with cisplatin using the following schedule: docetaxel 85 to 100 mg/m² as a 1-hour IV infusion followed (3 hours after completion) by cisplatin 75 mg/m² as a 3-hour IV infusion, with cycles being repeated every 3 weeks (223).

A number of clinical trials have explored the use of docetaxel given weekly in doses of 30 to 40 mg/m² (224–234). Weekly schedules have a different toxicity profile, with myelosuppression being less prominent, but fatigue becoming the dose-limiting side effects. Nail changes and excessive lacrimation are also more common. The response rates and dose intensities observed have been similar to those seen with the every-3-weeks schedule.

The docetaxel dose should be reduced for patients with moderate liver impairment (see Special Precautions section below).

Side Effects and Toxicities

The major dose-limiting toxicity of docetaxel is neutropenia, which is noncumulative and generally resolves within 7 to 8 days. The combined results of early phase II studies of docetaxel (without steroid premedication) in ovarian cancer revealed that at a dose level of 100 mg/m² every 3 weeks, greater than 90% of patients developed grades 3 to 4 neutropenia, with febrile neutropenia occurring in 8% to 44% of patients (235). The incidence of other grade 3 to 4 toxicities was stomatitis in 0% to 5%, diarrhea in 6% to 20%, dermatitis in 4% to 8%, acute hypersensitivity reactions 7% to 12%, and fluid retention in 8% to 12%. Other docetaxel-induced side effects include alopecia, anemia, neurosensory effects (paresthesia, dysesthesia, pain), and asthenia (220).

In early phase II studies, slow-onset (i.e., after 3 to 5 courses), cumulative fluid retention leading to peripheral or generalized edema with possible development of pleural effusion and/or ascites was a common dose-limiting toxicity. However, a 5-day premedication regimen with corticosteroids, starting the day before docetaxel administration, significantly reduces this side effect. In a retrospective analysis, severe fluid retention occurred in 20% of patients who received no premedication compared with 5% of patients who received steroid prophylaxis. Additionally, the percentage of patients who discontinued treatment secondary to fluid retention was reduced from 32% to 2% ($p < .00001$) with the use of a 5-day corticosteroid regimen (220). Steroid prophylaxis also reduces the incidence and severity of dermatologic side effects and hypersensitivity reactions.

The spectrum of docetaxel-induced hypersensitivity reactions is less severe than that associated with paclitaxel. In the absence of prophylactic medication, mild hypersensitivity reaction as characterized by flushing, rash, and pruritus occurs in approximately 5% of docetaxel administrations. Moderate reactions with dyspnea and/or slight hypertension occur in 8% of treatments, and severe reactions (with bronchospasm, angioedema,

and/or severe hypertension) occur in less than 2% of docetaxel administrations (236). Initial symptoms of hypersensitivity to docetaxel therapy generally occur within minutes of the start of the first or second course of docetaxel and resolve rapidly with interruption of the infusion. Patients can be successfully rechallenged with docetaxel therapy following medication with corticosteroids, antihistamines, and H₂-agonists.

Dermatologic toxicities typically appear as maculopapular eruptions and desquamation generally localized to the extremities. Nail changes, including onycholysis, may also occur. Skin changes are largely self-limiting and may be alleviated with glycerin/chlorhexidine ointment or oral pyridoxine. This side effect can often be prevented with prophylactic oral steroids and H₁- and H₂-agonists (237). Recurrent skin toxicity refractory to oral prophylactic medication and pyridoxine therapy may respond to local hypothermia during docetaxel administration (238).

Special Precautions

Patients with impaired liver function have a significant reduction in docetaxel clearance and an increased risk of life-threatening side effects. Analysis of the overall safety database revealed that patients with moderately impaired liver function (defined as transaminase levels more than 1.5 times the upper limit of normal and alkaline phosphatase more than 2.5 times the upper limit of normal) have a 27% reduction in docetaxel clearance and a 38% increase in the area under the concentration-time curve (220). When compared with patients with normal liver function, patients with at least moderately impaired liver function had a significantly greater incidence of febrile neutropenia (40% vs. 16%) and toxic death (20% vs. 1.4%). Grades 3 to 4 nausea/vomiting, stomatitis, and thrombocytopenia were also increased in patients with impaired liver function (220).

The recommended docetaxel dose level for a patient with moderate hepatic impairment (defined as transaminases between 1.5 and 3.5 times the upper limit of normal and an alkaline phosphatase between 2.5 and 6.0 times the upper limit of normal) is 75 mg/m² over 1 hour. No safe docetaxel dose can be recommended for patients with greater than moderate liver impairment (239).

Special Applications

Verschraegen and colleagues (240) published preliminary evidence that patients with ovarian cancer may respond to docetaxel even though they have had progression of their disease on paclitaxel. They noted a partial response rate of 37.5% in 8 eligible patients. A phase II study conducted by the GOG of 60 patients with paclitaxel-resistant ovarian and peritoneal carcinoma observed responses in 22.4% of patients, with 5.2% achieving complete response and 17.2% achieving partial response (at a dose of 100 mg/m² IV over 1 hour every 21 days) (241). However, the 75% incidence of grade 4 neutropenia in this study suggests that further study is needed to determine the appropriate dose and schedule.

Doxorubicin

Chemistry

Doxorubicin (Adriamycin), a primary agent in the treatment of metastatic endometrial cancer and advanced ovarian cancer, is an anthracycline antibiotic obtained from *Streptomyces peuceitii* var. *caesius*. It has a molecular weight of 580. The doxorubicin structure includes a water-soluble basic reducing amino sugar, daunosamine, linked by a glycosidic bond to carbon atom number 7 on the D-ring of the water-insoluble chromophore aglycone, adrimycinone.

Structural changes in the side groups of doxorubicin alter anti-tumor potency and pharmacokinetic properties. The aglycone is inactive, and modifications in the amino sugar substituents can also alter antitumor or toxic potency (242).

In DNA, the amino sugar projects into the minor groove and can interact electrostatically with negatively charged phosphate groups in the DNA strand to stabilize the aglycone moiety. Doxorubicin can also form complexes with iron or copper by means of the hydroquinone moieties (243). Metal-iron doxorubicin complexes may contribute to cardiotoxicity by enhancing redox cycling of the quinone moiety to produce membrane-damaging oxygen free radicals (244).

Doxorubicin hydrochloride is freely soluble in water, slightly soluble in normal saline, and very slightly soluble in alcohol.

Doxorubicin also is commercially available in a polyethylene glycol (PEG)-coated (pegylated, Stealth) liposomal form (see Liposomal Encapsulated Doxorubicin section below).

Mechanisms of Action

DNA Binding. The anthracyclines, including doxorubicin, probably have several modes of action. The anthracycline portion of the molecule appears to intercalate between stacked nucleotide pairs in the DNA helix by means of P-P-type bonds (245). The drug may also bind ionically around certain base pairs of DNA (adlination). The overall effect of this is interference with nucleic acid synthesis, specifically an inhibition of DNA synthesis (246). However, preribosomal RNA synthesis is also affected by the drug binding to DNA, preventing DNA-directed RNA and DNA transcription (247).

Mechanisms other than intercalation may also contribute to the antitumor effect of the doxorubicin molecule. The contribution of alkylation to antitumor effects has not been established.

Free-Radical Formation. Oxygen free-radical intermediates containing an unpaired electron can be formed by doxorubicin. This can react rapidly with oxygen to form superoxide, and with hydrogen peroxide, highly reactive hydroxyl radicals can form. These radicals damage membrane lipids by peroxidation, break DNA strands by attacking ribose-phosphate bonds, and directly oxidize purine or pyrimidine bases, thiols, and amines (244,248). Free-radical mechanisms have most often been associated with cardiotoxicity.

Doxorubicin appears to be active in all phases of the cell cycle, and although maximally cytotoxic in S phase, it is not phase specific (249). Cells exposed to lethal doxorubicin concentrations in G₁ can proceed through S phase but are then blocked and die in G₂. Higher concentrations can also produce an S-phase blockade (250).

Inhibition of DNA Topoisomerase II. Topoisomerases are enzymes capable of covalent binding to DNA, forming transient breaks in one strand (TOPO-I) or 2 strands (TOPO-II). This activity is highly phase dependent for G₂, and in the case of TOPO-II, normally mediates strand passage to facilitate DNA condensation or decondensation (251). Doxorubicin and other DNA intercalators inhibit the strand-passing activity of TOPO-II by increasing and stabilizing the initial enzyme-DNA (cleavable) complexes. This leads to protein-linked DNA double-strand breaks that are roughly proportional to the cytotoxic potency of the drug *in vitro* (252).

Drug Disposition

Doxorubicin pharmacokinetics is usually described using a 2-compartment or 3-compartment open model. The drug is rapidly distributed in body tissues, and approximately 75% of the drug is bound to plasma proteins, principally albumin (253). In the blood, the free doxorubicin fraction depends on the hematocrit, with more free drug being available in patients with reduced hematocrit (254). The avid binding to DNA is believed to explain the prolonged terminal elimination half-life of 30 to 40 hours, the large apparent volume of distribution of up to 28 L/kg, and the incomplete (50%) total recovery of drug in urine,

bile, and feces (255). Human tissues with high drug concentrations (in descending order) include liver, lymph nodes, muscle, bone marrow, fat, and skin (256). The drug does not distribute into the central nervous system.

There is a significant distribution of doxorubicin into human breast milk (257). Doxorubicin levels of 0.24 μM and 0.2 μM of doxorubicinol have been measured in human milk. They produce cumulative AUCs in breast milk of 9.9 and 16.5 $\mu\text{M} \cdot \text{hour}$, respectively. Both of these values were greater than concurrent plasma AUC values. However, doxorubicin does not appear consistently to pass the placenta. Except for one study reporting low drug levels in placental blood of 0.78 to 1.19 nmol/g and no drug in cord blood plasma, several other trials detected no drug in amniotic fluid after doxorubicin administration to pregnant patients (258–260).

Doxorubicin is extensively metabolized and eliminated primarily as glucuronide conjugates of the parent aglycone or its hydroxylated congener, doxorubicinol (255,261). The conjugated metabolites are exclusively excreted in the bile and feces. Overall, biliary excretion accounts for approximately 40% of an administered dose (262). Approximately 42% of the biliary drug is parent doxorubicin, 22% is doxorubicinol, and 36% is other metabolites (262). Only 5% to 10% of the administered drug is excreted in the urine as doxorubicin (40%), doxorubicinol (29%), and other metabolites (31%).

In liver disease, patients with cholestasis have delayed doxorubicin clearance and experience exaggerated toxic reactions from standard doses (263). However, hepatoma patients with cirrhosis or simple hepatocellular enzyme elevation appear to have normal doxorubicin clearance and toxic effects from standard doses (264). Although obesity reduces clearance of doxorubicin in adult cancer patients (265), there were no differences in doxorubicin toxicity between normal, mildly obese, and obese patients.

There is some evidence that repeated doxorubicin dosing alters pharmacokinetics (266,267). In these reports, doxorubicin levels were lower after repeated dosing, which suggests increased drug clearance. However, because neither toxicity nor response rates are altered, the clinical significance of these observations has not been established. Age may also be a factor. In one trial, the highest clearances of doxorubicin were observed in the younger patients (268). These observations suggest that higher peak doxorubicin levels may be achieved in older patients.

The hepatic extraction ratio for doxorubicin in humans is 0.45 to 0.50, and systemic drug levels are approximately 25% lower with intraarterial administration compared with IV dosing (269). Several studies have shown that the pharmacokinetics of intraarterial drug is similar to that of IV doses (256,270). The relatively low hepatic extraction rate and similar overall disposition patterns provide little pharmacokinetic rationale for intraarterial administration as a means of localizing doxorubicin effects to the liver (271).

Administration and Dosage

Short IV push infusions and IV bolus injections have been used with doxorubicin. A slow IV push over several minutes, with constant monitoring of the patient and blood return, can help minimize the chance of serious tissue damage from extravasation. A 5- to 10-mL flush of normal saline or D₅W before and after administration is strongly recommended to test vein patency and flush any remaining drug from the tubing. Alternatively, injection into the side port of a running IV infusion has also been recommended. The patient should be asked to report immediately any change in sensation during the administration. Old venipuncture sites or infusion sites previously used for administering blood, antibiotics, or other medications should not be used to administer doxorubicin. Heparin locks (unless recently inserted) are not recommended because the drug is chemically incompatible with sodium heparin.

Table 14.2 Intravenous Dosing Guidelines for Doxorubicin

Dose (mg/m ²) ^a	Intravenous Method	Schedule	Average Cumulative Tolerable Dose ^c (mg/m ²)
60–75 ^b	Bolus	Every 3 wk	550
30	Bolus	3 successive days, every 3 wk	550
20	Bolus	Weekly	750
60	96-hr infusion	Every 3–4 wk	1,000

^aLower doses should be administered to patients with hepatobiliary dysfunction and for poor bone marrow reserve or performance status.

^bAllows for greater dose intensity in breast cancer.

^cRepresents average total cumulative dose tolerated without clinical evidence of doxorubicin cardiotoxicity.

Prolonged infusions increase the incidence and severity of stomatitis and dermatologic reactions. Administration through tunneled central venous catheters or indwelling vascular access ports is mandatory for all prolonged infusions. Careful patient and site monitoring are required because doxorubicin extravasation from central vascular access devices can occur.

Numerous dosing schedules have been reported. The individual doxorubicin dose depends on clinical variables, including the cumulative dose administered to date and the potential for interaction with other drugs or radiation (Table 14.2). As a single agent, doses of 60 to 75 mg/m² as a single IV injection have been used and repeated no more often than every 3 weeks. An alternative scheme uses 20 to 30 mg/m² given daily for 3 consecutive days and repeated in 3 weeks (272). When used in combination therapy, the most commonly used dosage is 40 to 60 mg/m² given as a single IV injection every 21 to 28 days.

Both the dose and rate of dosing (dose intensity) can have therapeutic impacts for different agents and tumors (273). Clinical studies with doxorubicin show that greater dose intensity is associated with enhanced response rates in breast cancer (274). The doses compared in this trial were 70 mg/m² every 21 days for 8 cycles versus 35 mg/m² every 21 days for 16 cycles.

Dose adjustments are required in a number of clinical settings (Table 14.3), specifically in the case of hyperbilirubinemia. A 50% dose reduction is indicated if plasma bilirubin concentration is 1.2 to 3.0 mg/dL, and the dose must be reduced by 75% if plasma bilirubin concentration reaches 3.1 to 5.0 mg/dL.

Side Effects and Toxicities

The single acute dose-limiting toxicity for doxorubicin is bone marrow suppression. The most commonly seen dose-limiting toxicity is leukopenia, with a nadir at 10 to 14 days. Other hematologic toxicities, such as anemia and thrombocytopenia, have been reported, but they are rare and generally less severe. Recovery from myelosuppression is usually prompt, with resolution often within about 1 week after the nadir.

Doxorubicin is known to produce local skin and deep-tissue damage at the site of inadvertent extravasations (275,276). Ulcers result in 33% of extravasations. The lesions undergo a slow, indolent expansion and occasionally involve tendons and other deep structures. They characteristically do not heal and are associated with prolonged local drug retention (277). Reilly and colleagues (275) recommend early surgical debridement, with skin grafting and tendon repair for serious infiltrations. Numerous pharmacologic antidotes have been evaluated, but few have demonstrated unequivocal clinical efficacy. The application of cold, topical dimethylsulfoxide is recommended (278).

Table 14.3 Modifications of Doxorubicin Doses

Condition	Recommended Dose Modification
Prior doxorubicin	Limit total cumulative lifetime dose (by IV bolus) to 550 mg/m ² (285)
Prior chest Radiation therapy	Reduce total dose limit to 300–350 mg/m ²
Obesity	Base dose on ideal body weight (265)
Heptabillary dysfunction	Reduce dose for elevated serum bilirubin (give 50% of dose for serum bilirubin of 1.2–1.9 µg/dL, and give 25% of dose for serum bilirubin ≥ 3.0 mg/dL (282) Use indocyanine green disappearance rate as an Indicator of doxorubicin clearance
Infusion method	Greater cumulative (total) dose may be afforded by weekly bolus doses or continuous (96-hr) infusions ^a (Legha, 1982)

Note: Average safe cumulative doxorubicin dose is 750 mg/m² using standard infusion schedules.

^aAverage safe cumulative doxorubicin dose is 1,000 mg/m² when administered with a 96-hour infusion schedule.

Cardiac consequences from the drug have included acute effects, such as a rare pericarditis-myocarditis syndrome or electrophysiologic aberrations, and a total-dose-related cardiomyopathy (279,280). Nonspecific electrocardiographic changes during infusion or immediately afterward may be seen. These include T-wave flattening, ST depression, supraventricular tachyarrhythmias, and extra systolic contractions (281). These conduction abnormalities are generally transient, not associated with severe morbidity, and do not require dose modification.

Cardiomyopathy from doxorubicin is dose related. It presents initially as a clinical syndrome identical to classic congestive heart failure. It is usually irreversible, but symptoms can be managed with standard medical therapy involving digitalis, glycosides, and diuretics. Potential risk factors for doxorubicin cardiotoxicity include cumulative doses greater than 550 mg/m², prior mediastinal irradiation (≥20 Gy), age greater than 70 years, and preexisting cardiovascular diseases, such as prior myocardial infarction or long-standing hypertension (282). Anthracycline-induced cardiomyopathy can also occur 4 to 20 years after the drug is stopped at standard dose limits (283). The administration of anthracyclines incorporated into liposomes is one method that may significantly reduce the risk of cardiac toxicity (see Liposomal Encapsulated Doxorubicin section below) (284).

At total doses under 500 mg/m², the incidence of cardiomyopathy is less than 1%; between 501 and 600 mg/m², it is 11%; and the incidence is 30% for doses above 600 mg/m². In a retrospective cardiotoxicity study of 4,018 patient records, Von Hoff and associates (285) described an overall incidence of 2.2% for doxorubicin-induced congestive heart failure. In this analysis, there was no influence of performance status, sex, race, and tumor type on the incidence of cardiomyopathy. However, elderly patients were at greater risk even after adjustment for the normally decreased cardiac function in this group. The major determinants were the dose, the schedule of administration, and the age of the patient. A weekly doxorubicin dosing schedule was associated with significantly less congestive heart failure than an every-3-week dosing schedule. Continuous IV infusions over 96 hours also can significantly lessen doxorubicin cardiotoxicity (286).

Dexrazoxane (Zinecard) is a chemoprotective agent with an FDA-approved indication for reducing doxorubicin-associated cardiomyopathy in women with metastatic breast cancer who have received a cumulative doxorubicin dose of ≥300 mg/m² and

who, in their physician's opinion, would benefit from further doxorubicin therapy (see Modulating Agents section below).

There is evidence that doxorubicin is a radiosensitizing or "radiomimetic" agent and can cause reactivation of tissue reactions in areas previously irradiated (287,288). Radiation recall reactions have also been reported in areas of previous drug infiltration. A particularly sensitive area for serious recall toxicity is the esophagus (289).

Other toxic effects are observed in rapidly proliferating normal tissues. These include marked alopecia in all hairy body areas. Stomatitis may occur at high doses and is more pronounced when the drug is given on consecutive days. It generally begins in the sublingual and lateral tongue regions as a burning sensation with noticeable erythema. The initial inflammation typically progresses to ulceration after a few days. Anal fissures or proctitis have been rarely reported. Nausea and vomiting are common but of moderate intensity. Diarrhea is rare with consecutive daily dosing, and the emetic effects are generally limited to the first day of treatment. Hyperpigmentation of the skin, especially the nail beds, may occur. Extravasations of doxorubicin are known to cause severe ulceration and soft-tissue necrosis (275,276). Vein patency should be assured before injection and constantly monitored during administration.

As discussed later in this chapter, pegylated liposomal encapsulation dramatically alters the pharmacokinetic profile of doxorubicin and, hence, the drug's toxicity profile.

Drug Interactions

Doxorubicin is believed to interact with numerous other drugs. Most of these effects have been described only in experimental systems, and their clinical significance is, therefore, unknown. However, several potentially significant interactions have been described in cancer patients. Altered doxorubicin disposition is postulated with α -interferon, and substantial doxorubicin dose reductions are required (290). The combination of doxorubicin with H_2 -antihistamines, such as ranitidine or cimetidine, may also increase toxicities significantly and necessitate drug dose reduction.

Special Applications

Doxorubicin has been investigationally administered intrapleurally to patients with malignant pleural effusions (291). Doses of 30 mg were diluted in 20 mL of saline and administered by paracentesis needle as a bolus. Eight of 11 patients responded to doxorubicin, including one complete response. This response rate was superior to nitrogen mustard or tetracycline. Toxicity included pain or fever in 20% of patients and nausea or vomiting in 45% of patients. No alopecia or hematologic toxicity was reported. Markman and colleagues (292) combined doxorubicin (3 mg) with cytarabine (61 mg) and cisplatin (100 mg/m²) in the treatment of 7 cancer patients with malignant pleural effusions. Two ovarian cancer patients responded, and no significant systemic toxicities were reported. All injections were given in 250 mL of saline, and aggressive hydration was given to counteract cisplatin nephrotoxicity.

Etoposide

Chemistry

Intravenous etoposide (VP-16) is used commonly in combination chemotherapy regimens for the treatment of patients with germ-cell tumors of the ovary (206). Oral etoposide has activity as a salvage agent for refractory or recurrent ovarian cancer (293). It is a semisynthetic epipodophyllotoxin derived from the root of *Podophyllum* (the May apple plant, or mandrake). The chemical name is demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene- β -D-glucopyranoside]. Etoposide has the molecular formula of $C_{29}H_{32}O_{13}$ and a molecular weight of 588.58. It is

highly soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water. Because of poor water solubility, the commercial drug is dissolved in an ethanol-based cosolvent system.

Etoposide was originally synthesized from *P. embodi* (294). Structure-activity studies show that the hydroxyl group at the C-4' position is required for activity and that alterations at this site can dramatically affect activity.

Mechanism of Action

There is marked schedule dependence for etoposide cell killing, and cytotoxic effects are maximal in G_2 phase (295). There is also some activity against cells in late S phase, and the drug can halt cell cycle traverse at the S- G_2 interphase (296).

Etoposide produces protein-linked DNA strand breaks by inhibiting DNA TOPO-II enzymes (297). This normal mammalian enzyme mediates double-strand-passing activities in G_2 phase to condense or decondense supercoiled DNA (298). Drug-induced inhibition of TOPO-II is an energy-dependent process that is influenced by dose and duration of exposure.

Etoposide does not bind directly to DNA, but rather stabilizes a transition form of the DNA-TOPO-II complex (297). The number of single and double DNA strand breaks reflects the cytotoxic dose-response curve (299). Etoposide and intercalative drugs, such as doxorubicin, "poison" TOPO-II enzymes by stabilizing an otherwise transient form of TOPO-II covalently linked with DNA (252). Normal TOPO-II strand-passing activity is thereby blocked, and cell progression out of G_2 phase is halted (251,300). The production of cytotoxicity by etoposide may ultimately involve chromosomal breaks characterized as sister chromatid exchanges (301).

Another postulated etoposide mechanism involves microsomal activation to reactive intermediates capable of generating oxygen free radicals (299). Nucleoside transport is also inhibited at high drug concentrations, but whether this makes a major contribution to the antitumor effect is unknown (302).

Drug Disposition

A 2-compartment open pharmacokinetic model appears to describe adequately etoposide disposition in cancer patients (303). The terminal half-life of the drug appears to be approximately 7 hours and is independent of the dose, route, or method of administration (304). Renal excretion appears to account for approximately 30% of overall drug elimination. Approximately 42% to 66% of radiolabeled drug is recovered in the urine, of which less than half is parent etoposide.

With standard doses of etoposide, no drug is detectable in the cerebrospinal fluid (CSF), and even after doses of 400 to 800 mg/m², CSF levels were less than 2% of concurrent plasma levels (305). Despite the low distribution of drug into the CSF, mean levels of 1.4 μ g/g (range, undetectable to 5.9 μ g/g) have been measured in brain tumor tissue (306). The drug also distributes into myometrial carcinoma and normal myometrium, achieving levels 50% of those in the blood (307).

Biliary secretion of parent drug accounts for 2% or less of the dose, although fecal recovery of drug and metabolites is variable, ranging from 1.5% to 16.3% (308). However, patients with obstructive jaundice excrete a larger fraction of the dose in urine (46%) than do unaffected patients (35%), which suggests that there is a slight decrease in hepatic drug metabolism with a commensurate increase in renal clearance (305).

The plasma protein binding of etoposide is normally high, averaging 95% in typical patients (309). The free (unbound) fraction of etoposide can vary from 6% to 37% among patients. Patients with increased bilirubin or decreased albumin may have an increase in the free fraction even though systemic clearance is unaltered (309). Myelosuppression may also be commensurately increased in these patients. Other conditions that may decrease

etoposide clearance include prior cisplatin therapy, obesity, and elevated alkaline phosphatase levels (310).

The absolute oral bioavailability of etoposide gelatin capsules ranges from 25% to 74%, with a mean of 48% (311). Some patients experience a 30% change in overall bioavailability (both increased and decreased) with repeat dosing. Neither food nor other chemotherapeutic agents appear to alter etoposide absorption (312). Wide variations in peak levels and AUC values were also described in this trial.

Administration and Dosage

Etoposide must be diluted prior to use with either 0.5% dextrose or 0.9% sodium chloride to give a final concentration of 0.2 to 0.4 mg/mL. Etoposide should be given by IV infusion over a 30- to 60-minute period. Severe hypotension may occur if the drug is given too rapidly. Although not a vesicant, extravasation of the drug should be avoided (313). Examine all solutions for fine precipitates; mix before use. Precipitation may occur if the solution is prepared at the concentration of 0.4 mg/mL. Continuous infusions of etoposide have been used as a means of enhancing efficacy because of its phase-specific mode of antitumor action. Most infusions have used 5-day courses, although 72-hour infusions have also been employed (314,315).

Oral administration of etoposide capsules may be useful if patient compliance is high, and low-emetogenic drug regimens are used. The capsules may be taken all at once to achieve the desired dose. Neither food nor other chemotherapeutic drugs appear to alter oral absorption of the drug (312). The GOG has investigated multiple trials of oral etoposide at various dosing regimens. Based on a cumulative review of these trials and schedules, it was found to be active in platinum-resistant ovarian cancer patients (overall response rate 26.8%; 7.3% clinical complete remission rate) and in platinum-sensitive patients (overall response rate 34.1%; 14.6% clinical complete remission rate) (314). One of these trials that demonstrated activity used an oral etoposide dosing schedule of 50 mg/m²/day for 21 days every 28 days with dose escalation to 60 mg/m²/day when feasible (316). Studies using similar oral etoposide dosing schedules in patients with cervical cancer and endometrial cancer failed to show significant activity in these tumor types (317–319).

The variety of doses and schedules that have been used with etoposide are presented in Table 14.4. General principles of

dosing include more frequent administration to take advantage of cell cycle-dependent cytotoxicity, an approximate doubling of oral doses due to 50% bioavailability for the gelatin capsules, and significant dose reductions for combinations of etoposide with other myelosuppressive drugs or for patients with poor bone marrow reserve or poor performance status. In general, etoposide doses can be repeated every 3 to 4 weeks depending on the leukocyte count. A pharmacokinetic study in patients with obstructive jaundice showed that no significant dose reductions are needed if renal function is normal (320).

Side Effects and Toxicities

Side effects and toxicities for oral and IV administration of etoposide as a single agent are similar. The principal toxicity of etoposide is dose-related and dose-limiting bone marrow suppression. Leukopenia and thrombocytopenia can occur, but leukopenia consistently predominates, with a nadir at approximately 16 days and with recovery usually beginning by days 20 to 22.

Gastrointestinal complaints of nausea, vomiting, or anorexia are usually minor and are more frequent with the oral preparations (321). Other adverse effects include alopecia in 20% to 90% of patients, headache, fever, and hypotension (322). Severe hypotension can occur if the drug is infused too rapidly (<30 minutes) (308). Stomatitis has been infrequently reported. Rare instances of generalized allergic reactions and anaphylaxis have occurred (323). A few episodes of cardiotoxicity, including myocardial infarction and congestive heart failure, have been described (324). Immune suppression appears to be minimal with this drug (322). Bronchospasm with severe wheezing has been rarely observed and has usually been responsive to antihistamines and glucocorticosteroids. Chemical phlebitis also has been associated with etoposide, although the reaction is most likely related to solubilizers in the diluent. Diluted solutions of etoposide are not vesicants. For inadvertent extravasations of highly concentrated etoposide solution, hyaluronidase may be effective (325).

Neurotoxicity has been rarely reported with etoposide. This has consisted of somnolence and fatigue in 3% of patients and peripheral neuropathy in less than 1% of patients. However, the drug may exacerbate preexisting neuropathy caused by vincristine (326). Predisposing factors included advanced age, impaired nutritional status, and poor performance status. Degradation of myelin lamellae has been observed in affected nerves.

Table 14.4 Intravenous and Oral Dosing Schedules for Etoposide

Administration Method	Dose		Repeat Dosing Interval (wk)	Clinical Application
	mg/m ² /day	Days		
Short single-dose IV infusion	200–250	1	7	Single agent, small-cell lung cancer
Short multiple-dose IV infusion	100	1–5	3–4	Testicular cancer
	100	1, 3, 5	3–4	With other drugs
	45	1–7	3	Phase I
Continuous IV infusion	125	1–5	4	Phase I, single agent
	30	1–5	4	With cisplatin in advanced cancer
	80	1–5	4	Phase I, good-risk patients
	50	1–5	4	Poor-risk patients
	125	1–3	4	Adult patients with advanced cancer (240)
	500	1 (24-hr)	3	Small-cell lung cancer
Oral	160	1–5	3–4	Small-cell lung cancer
	50	1–21	4	Ovarian cancer (243)

Special Applications

Despite preclinical data showing peritonitis with IP injections, combinations of etoposide and cisplatin have been administered safely by the IP route. Barakat et al. (327) performed a phase II study of 3 courses of IP cisplatin 100 mg/m² plus etoposide 200 mg/m² as consolidation therapy in patients with stages II to IV epithelial ovarian cancer with negative second-look surgeries. When compared with a similar group of contemporaneous patients who did not receive consolidation therapy, the disease-free survival distribution between the 2 groups (using the log-rank test) was found to be significant ($p = 0.03$) in favor of consolidation therapy (327). European researchers have used a combination of etoposide 350 mg/m² IP followed by cisplatin 200 mg/m² IP with IV sodium thiosulfate (4 g/m² bolus followed by 12 g/m² over 6 hours) protection every 4 weeks for 4 to 6 cycles in ovarian cancer patients with either no residual disease or minimal residual disease at second-look surgery. The regimen was fairly well tolerated, although there was one study-related patient death from a bowel perforation and resulting complications. Other major clinical complications were nausea, vomiting, and the formation of intra-abdominal adhesions. Grade 3 to 4 leukopenia and thrombocytopenia occurred in 30% and 6% of cycles, respectively (328).

Etoposide in combination with other chemotherapeutic agents and autologous stem-cell rescue is often used in salvage therapy for germ-cell tumors or metastatic trophoblastic disease. Two commonly used regimens are bleomycin, etoposide, and cisplatin (BEP); and ifosfamide, carboplatin, and etoposide (ICE) (329,330).

5-Fluorouracil and Floxuridine

Chemistry

5-Fluorouracil (5-FU) is a fluorinated pyrimidine differing from the normal DNA substrate, uracil, by a fluorinated number 5 carbon (chemically, 5-fluoro-2,4(1H,3H)-pyrimidinedione). 5-FU has activity as a second-line agent in advanced ovarian and cervical cancers and, in combination with cisplatin, is used as an adjunct to radiation therapy in women with locally advanced cervical cancer. Floxuridine (FUDR) is highly similar to its prodrug, 5-FU. The discussion of FUDR in this chapter will be limited to its special application as an IP-administered agent for salvage therapy for ovarian cancer. 5-FU is light sensitive and precipitates at low temperatures or, occasionally, with prolonged standing at room temperature. It has the molecular formula of C₄H₃FN₂O₂ and a molecular weight of 130.08.

Mechanism of Action

5-FU acts as a false pyrimidine or antimetabolite ultimately to inhibit the formation of the DNA-specific nucleoside base thymidine. There are at least 3 mechanisms of action: inhibition of thymidylate synthase by 5-fluoro-21-deoxyuridine-5'-monophosphate (FdUMP), the active metabolite of 5-FU; incorporation of 5-fluorouridine triphosphate (FUTP) into cellular RNA; and incorporation of FUTP into cellular DNA (331). 5-FU is a cell cycle phase-specific agent with cytotoxic effects seen maximally in S phase.

Drug Disposition

There is disagreement over whether 5-FU is eliminated by a 2-compartment or 3-compartment model (2,332,333). Fraile and associates (334) demonstrated that plasma levels of 5-FU after oral administration are quite erratic. Schaaf and colleagues (335) documented that the pharmacokinetic characteristics of 5-FU are nonlinear. Doubling of the dose was accompanied by a decrease in nonrenal clearance. The half-life from the high dose

was twice as long as that for the low dose of 5-FU. Their data were compatible with a product-inhibition model. Yoshida and coworkers (336) found positive correlations between the dose and serum steady-state levels (C_{ss}) and areas under the concentration-time curves (AUC). Patients who developed toxic reactions had greater C_{ss} s and AUCs. However, there were no correlations between serum levels and patient response to therapy.

5-FU and FUDR are extensively metabolized in the liver (hepatic metabolism can detoxify up to 80% of the total dose). However, there is no absolute documentation that patients with impaired liver function require dose reductions of 5-FU (337); however, patients should be monitored as they may be at increased risk of toxicity. As much as 15% of a dose may be found intact in the urine by 6 hours, with 90% of this excreted in the first hour. Depressed renal function does not generally require dosage adjustment for 5-FU.

5-FU distributes to all areas of body water by simple diffusion. Significant quantities of the drug may enter the central nervous system, and after 15 mg/kg given IV, CSF levels of 6 to 8×10^{-6} M are obtained after 30 minutes. These levels persist for several hours and slowly subside. Although distribution to brain tissue is less rapid, abnormal areas, such as those with neoplasms, may more readily take up the drug.

5-FU achieves high and persistent levels in effusions after IV administration. Hepatic administration through the portal vein or artery also achieves high concentrations in the liver parenchyma and produces relatively low systemic levels.

Santini and colleagues (338) showed that therapeutic monitoring of 5-FU levels in patients with head and neck cancer can be used to improve the therapeutic index of the drug (i.e., less toxicity with maximal efficacy).

Administration and Dosage

Doses of 5-FU to be given by the IV push route do not require further dilution from the commercial solution. Vein patency should be assured before giving a dose, with a 5- to 10-mL flush of normal saline or D₅W and another flush after the dose to rinse the remaining drug from the tubing. For short infusions (<24 hour), the rate of administration is not critical, and the dose should be given at a rate compatible with the particular vein selected. The patient should be continuously monitored to guard against extravasation. Most doses can be conveniently given over 1 to 2 minutes in this fashion.

Continuous infusions (over 4 to 5 days) may maximize efficacy of this cycle-specific drug and lessen hematologic toxicity (339–341). Infusions of the drug may be added to a convenient volume of D₅W or normal saline, and each reconstituted daily dose can be administered over 24 hours. Commonly, the daily dose of the drug is added to 1 L, although volume is not critical.

Regimens reported for the use of 5-FU include the use of a loading dose, weekly IV bolus, continuous infusions over 4 to 5 days or over 6 weeks, and oral dosing. 5-FU may be administered intravenously as a bolus, rapid injection on a monthly (425 to 450 mg/m² IV on days 1 to 5 every 28 days) or a weekly schedule (500 to 600 mg/m² every week for 6 weeks, every 8 weeks), or continuous IV infusion (24-hour infusion 2,400 to 2,600 mg/m² every week; 96-hour infusion 800 to 1000 mg/m²/day; or 120-hour infusion 1,000 mg/m²/day on days 1 to 5 every 21 to 28 days) (79). Oral doses of up to 15 to 20 mg/kg/day for 5 to 8 days have been used (342). However, the efficacy of oral 5-FU has not been confirmed at this time (see Capecitabine section above for a discussion of the oral prodrug of 5-FU).

The loading dose scheme calls for one course of 400 to 500 mg/m² (12 mg/kg; maximum of 800 mg) daily for 5 days every 28 days given as a single daily bolus injection or as a 4-day continuous infusion. This is followed by a weekly maintenance regimen. Horton and coresearchers (343) and Jacobs

and coworkers (344), however, strongly associated the use of the loading dose with significant morbidity and occasional fatalities, and suggested that it offers no greater antitumor efficacy over a weekly bolus injection of 15 mg/kg given IV.

Maintenance of 5-FU dosing regimens include the following: 200 to 250 mg/m² (6 mg/kg) every other day for 4 days, repeated in 4 weeks (if toxicity has resolved); or 500 to 600 mg/m² (15 mg/kg), given IV weekly as a continuous infusion or bolus injection (with and without the loading dose).

By continuous infusion, higher daily doses have been successfully used, and many investigators have reported lessened hematologic toxicity and enhanced efficacy. Most of a dose is eliminated by the liver and the remainder by the kidney. Therefore, marked dysfunction in either system probably requires a dose reduction.

There are 2 commonly used dosing regimens for 5-FU combined with leucovorin: 370 mg/m²/day of 5-FU for 5 days plus leucovorin given as a continuous infusion of 500 mg/m²/day, beginning 24 hours before the first dose of 5-FU and continuing for 12 hours after completion of therapy; or 5-FU given at doses of 500 to 1,000 mg/m² every 2 weeks, preceded by calcium leucovorin at a dose of 20 mg/m² given as a 10-minute infusion (345,346).

Phase III studies performed by the GOG, SWOG, and Radiation Therapy Oncology Group have documented the efficacy of cisplatin/5-FU chemotherapy as an adjunct to radiation therapy in women with high-risk cervical cancer (47,184,347). The regimen used in the SWOG study was cisplatin 70 mg/m² by 2-hour IV infusion on day 1 of radiation followed by 5-FU 1,000 mg/m²/day by 96-hour continuous infusion on days 1 to 4 every 3 weeks for 4 cycles, with the first and second cycles given concurrently with radiation therapy (184). The addition of concurrent cisplatin-based therapy to radiation therapy significantly improved progression-free and overall survival in this study; however, no definitive study has compared cisplatin versus cisplatin/5-FU as an adjunct to radiation therapy for cervical cancer, and the relative importance of 5-FU remains to be addressed.

Side Effects and Toxicities

The most pronounced and dose-limiting toxic effects of 5-FU are on the normal, rapidly proliferating tissues of the bone marrow and the lining of the gastrointestinal tract. Some nausea and vomiting can be expected. These adverse effects may respond relatively well to antiemetic treatment. Stomatitis, however, is usually an early sign of impending severe toxicity that may become evident after 5 to 8 days of therapy. Symptoms include soreness, erythema, or ulceration of the oral cavity or dysphagia. Other reported gastrointestinal symptoms are diarrhea, proctitis, and esophagitis.

Leukopenia, primarily granulocytopenia, and thrombocytopenia occur with a nadir at 9 to 14 days for the granulocytes and 7 to 14 days for platelets. Patients who are poor candidates for 5-FU therapy are those with a total leukocyte count of 2,000/mm³ or less, or platelet count of 100,000/mm³ or less, or those with poor nutritional status at the outset of therapy.

Some degree of alopecia is expected, although hair regrowth has occurred even when successive doses are given. Partial loss of nails and hyperpigmentation of the nail beds and other body areas (e.g., face, hands) have been reported. These may resemble the hyperpigmentation seen in Addison's disease. A maculopapular rash may occur on the extremities and sometimes the trunk. The rash is usually reversible. Sunlight may initiate or heighten many dermatologic reactions to 5-FU.

PPEs have been reported with very long continuous infusion 5-FU (over several weeks). This has been reported in 42% to 82% of patients in various series. The syndrome is progressive and disrupts treatment (348). This has encouraged the development of prodrugs of 5-FU, such as 5'-deoxy-5-fluorouridine,

capecitabine, BOF-A2, ftorafur, UFT, and S-1 (349,350). Although there is no indicated treatment for PPE, the incidence has been reduced to a few percentage points by limiting 5-FU continuous infusion durations to 21 days with at least 1 additional week off drug. Possible therapies that are yet to be evaluated in clinical trials include DMSO, systemic corticosteroids, and pyridoxine (vitamin B₆) (349,351).

Hyperpigmentation over the veins used for 5-FU administration has been observed (352). In one instance, the veins remained patent, but there was marked darkening of the skin immediately over the vein.

5-FU may also cause an acute cerebellar syndrome that can persist beyond the period of actual treatment (353,354). Neurotoxicity may be evidenced by headache, minor visual disturbances, cerebellar ataxia, or all 3. This is a rare complication. The neurotoxic metabolite is probably fluorocitrate.

Cardiotoxicity is a rare but potentially serious toxicity attributable to 5-FU. The incidence of cardiotoxicity may vary from 1.2% to 18.0% of patients (355) and includes cases of myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death, and electrocardiographic changes. The mechanism producing 5-FU-induced cardiotoxicity is unknown.

Special Precautions

5-FU should never be given to pregnant women. 5-FU may increase the cortisone requirement in patients who have had an adrenalectomy (e.g., for breast cancer), and consideration should be given to increased doses of cortisone for patients receiving 5-FU.

Because dihydropyrimidine dehydrogenase is the rate-limiting enzyme in the metabolism of 5-FU, patients with a familial deficiency of dihydropyrimidine dehydrogenase (familial pyrimidinemia) should not receive 5-FU. The administration of 5-FU to patients with this enzyme deficiency has led to severe toxicity and even death (356,357).

Accidental splashing of 5-FU on the skin or eyes of personnel should be treated with immediate irrigation with saline solution or water. There have been no long-term sequelae of these accidents (358).

Because of the alkaline nature of the drug, admixture with any acidic agents (amino acids, penicillin, multivitamins, insulin, tetracycline) represents a theoretic incompatibility.

Special Applications

FUDR, a closely related analog of 5-FU, has efficacy as a salvage agent when administered as an IP agent to stage III ovarian cancer patients with minimal residual disease (i.e., <1 cm) following second-look surgery. A SWOG study utilized IP FUDR (3 g/day for 3 days every 3 weeks for 6 courses) as a salvage regimen in this patient population and documented a median overall survival of 38 months (359). Additionally, 69% of study patients had not progressed 12 months after receiving IP FUDR. Because the majority of the IP FUDR dose is extracted during "first pass," it is relatively well tolerated, although grade 4, uncomplicated neutropenia was observed in 14% of patients (359). Because of the favorable 1-year progression-free survival in this study, a subsequent phase I to II trial was conducted by the SWOG (360). The researchers recommend that the regimen of IP FUDR + IP cisplatin (or IP FUDR with both platinum) be tested in a phase III trial in comparison to IP cisplatin (360).

Speyer and colleagues (361) investigated IP 5-FU in patients with ovarian and colon carcinomas. Using a Tenckhoff catheter, patients received repeated 36-hour courses of eight 2-L exchanges, each 4 hours long, or a 3- to 5-day course of single, daily 2-L instillations. 5-FU concentrations ranged from 10⁻⁶ M (130 µg/L) to 8 × 10⁻³ M (1 g/L).

The procedure was relatively well tolerated locally, although there were 2 instances of catheter-related bacterial peritonitis that were easily managed. Concentrations of 4×10^{-3} M for 36 hours caused mucositis, pancytopenia, and alopecia. The systemic toxicities were quite severe with the highest dose tested (8×10^{-3} M). Pharmacokinetic studies revealed first-order drug elimination, with an IP half-life of 72 to 112 minutes. Intraperitoneal drug levels were 300-fold greater than simultaneous plasma levels. Intraperitoneal 5-FU administration appears to produce high drug concentrations with minimal systemic toxicity. Objective responses were documented in 2 of 7 patients studied in this phase I investigation. The investigators recommended further IP 5-FU investigation at initial drug concentrations of 4×10^{-3} M (500 mg/L) for 36 hours (361).

Suhrland and Weisberger (362) used intracavitary 5-FU to manage malignant pleural effusions from carcinoma of the breast and lung tumors and to control malignant ascites from ovarian carcinoma. Approximately 38% of the patients responded to a single intracavitary dose of 2 to 3 g. For pericardial effusions, doses of 500 to 1,000 mg were used. Repeat dosing was not necessary. Patients with pleural effusions also tended to respond better than those with ascites. Although side effects were minimal in this study, some systemic toxicity was consistently produced.

Gemcitabine

Chemistry

Gemcitabine (Gemzar) is a relatively new chemotherapeutic agent that was approved by the FDA in 1995 for the treatment of patients with advanced pancreatic cancer based on an increase in survival and clinical benefit (improvement in pain and performance status). The combination of gemcitabine plus cisplatin also is FDA approved and is considered standard therapy for patients with advanced non-small cell lung cancer. Gemcitabine has demonstrated significant activity in advanced ovarian cancer patients and is active against refractory ovarian cancer and cervical cancer, as well as other solid tumors (363–367). Gemcitabine is a synthetic nucleoside analog with a structure that is highly similar to deoxycytidine and cytosine arabinoside (ara-C). Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β isomer). The empiric formula for gemcitabine is $C_8H_{11}F_2N_3O_4 \cdot HCl$ and the agent has a molecular weight of 299.66.

Mechanism of Action

Gemcitabine is a prodrug and undergoes multiple phosphorylations by deoxycytidine kinase at the intracellular level to form the active diphosphate and triphosphate metabolites. The triphosphate is incorporated into DNA as a fraudulent base pair. Following the insertion of gemcitabine, one additional deoxynucleotide is added to the end of the DNA chain before replication is terminated. This process is known as “masked chain termination” and prevents exonucleases from excising off the fraudulent base pair (368,369). The diphosphate inhibits ribonucleotide reductase and thereby depletes the deoxynucleotide pools that are necessary for DNA synthesis and repair (370). Inactivation of gemcitabine occurs when the drug is metabolized by cytidine deaminase (both intracellularly and extracellularly) to form difluorodeoxyuridine (371).

Drug Disposition

Following administration of gemcitabine 1,000 mg/m² by 30-minute IV infusion, the parent compound undergoes rapid clearance in a biphasic manner. The plasma half-life and clearance are dose, age, and gender dependent. Gemcitabine pharmacokinetics were evaluated in 353 patients with varied solid tumors using short infusions (<70 minutes) and long infusions

(70 to 285 minutes) at various total doses (500 to 3,600 mg/m²) (372). There is a three- to fourfold interpatient variability in pharmacokinetics. As noted above, gemcitabine is metabolized intracellularly by deoxycytidine kinase to form the active diphosphate and triphosphate metabolites. The drug is inactivated both intracellularly and extracellularly by cytidine deaminase to form difluorodeoxyuridine (dFdU). Of the administered gemcitabine dose, 99% is excreted in the urine either as the parent compound (<10%) or as dFdU (373,374).

Dutch researchers have performed a pharmacokinetic schedule-finding study of gemcitabine plus cisplatin. Gemcitabine 800 mg/m² was administered as a 30-minute infusion either 4 hours before, 24 hours before, 4 hours after, or 24 hours after administration of cisplatin 50 mg/m² by 1-hour IV infusion. Neither of the dosing schedules that used a 4-hour interval between drug administrations resulted in significant pharmacokinetic or pharmacologic differences. However, when gemcitabine was administered 24 hours before cisplatin, there was a twofold decrease in the plasma AUC of platinum. Furthermore, when the order of the drugs was reversed (i.e., cisplatin was administered 24 hours before gemcitabine), there was a 1.5-fold increase in the concentration-time product of the active triphosphate metabolite of gemcitabine within white blood cells. On the basis of these results, the investigators conducted a phase II study of the cisplatin/gemcitabine combination wherein cisplatin was administered 24 hours prior to gemcitabine (375).

Administration and Dosage

Gemcitabine should be diluted in 0.9% sodium chloride to a concentration of no greater than 40 mg/mL (higher drug concentrations may result in incomplete dissolution). Gemcitabine is generally administered as a 30-minute IV infusion at a dose of 1,000 mg/m²; infusion durations of greater than 60 minutes are associated with dose-limiting flu-like symptoms (376).

The standard dosing schedule used for treatment of pancreatic cancer is 1,000 mg/m² by 30-minute IV infusion once weekly for 7 weeks for cycle 1 followed by a 1-week rest and then 1,000 mg/m² once weekly for 3 weeks followed by a 1-week rest for subsequent cycles (377).

Multiple phase II studies of single-agent gemcitabine in refractory/recurrent ovarian cancer have used a dosing schedule of 800 to 1,250 mg/m² once weekly for 3 weeks followed by a week of rest; however, doses above 1,000 mg/m² may be associated with higher toxicity (364,366,378).

In vitro studies have shown synergism between gemcitabine and cisplatin in a variety of human cancer cell lines (379,380). It is believed that this synergism is primarily the result of increased platinum-DNA adduct formation (380). An increase in DNA-platinum adducts has also been demonstrated for the combination in the clinical arena (381). As noted (see Drug Disposition section above), the interval between cisplatin and gemcitabine administration can affect both pharmacokinetic and pharmacologic parameters (375). This combination appears to be especially promising for patients with advanced ovarian cancer. Several phase II studies have been conducted in previously untreated ovarian cancer patients using a dosing schedule of cisplatin (75 to 100 mg/m²) on day 1 followed by gemcitabine 1,250 mg/m² days 1 and 8 (363,382,383). Others have performed phase II studies of gemcitabine plus cisplatin for patients with relapsed ovarian cancer after prior platinum-based chemotherapy and have determined that cisplatin 30 mg/m² plus gemcitabine 600 to 750 mg/m² on days 1 and 8 every 21 days is an active and tolerable regimen that demonstrated activity in platinum-resistant patients (130,384).

A phase III study comparing 4 different carboplatin-based regimens with the standard regimen of carboplatin + paclitaxel for the first-line treatment of ovarian cancer showed very similar survival and progression-free survival for the

gemcitabine-containing arm, confirming the activity of gemcitabine but not demonstrating superiority over standard treatment.

Side Effects and Toxicities

Gemcitabine-induced toxicity is highly schedule dependent; small daily doses are associated with greater toxicity than large doses administered on a weekly basis (385). The dose, schedule, and duration of infusion of gemcitabine directly affect the toxicity profile (385). Infusion durations of more than 60 minutes are associated with increased myelosuppression and hepatic toxicity, whereas the administration of small daily doses results in dose-limiting flu-like symptoms (371,376). When gemcitabine is administered using the standard weekly dosing schedule, therapy is generally well tolerated and bone marrow suppression is the major dose-limiting toxicity.

Analysis of safety data from 22 completed clinical trials in which gemcitabine was administered on a weekly basis to 979 patients revealed that neutropenia was the most significant hematologic side effect. Six percent of patients experienced grade 4 neutropenia, and an additional 20% experienced grade 3 neutropenia. Grade 4 leukopenia was experienced by less than 1% of patients. Decreases in white blood cell counts were noncumulative, short-lived, and rarely resulted in complications. Only 6 of 979 patients (1.1%) developed severe infections, and no patient developed a life-threatening infection. Grades 3 and 4 anemia were experienced by 6.8% and 1.3% of patients, respectively, and only 2 of the 979 patients discontinued gemcitabine secondary to anemia. Grades 3 and 4 thrombocytopenia occurred in 4.1% and 1.1% of patients, respectively. Less than 1% of patients received platelet transfusions, and only 4 patients (0.4%) discontinued therapy on account of thrombocytopenia (385).

Gemcitabine is associated with a low incidence of hepatic toxicity. Grade 3 elevations in alkaline phosphatase, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) occurred in less than 8% of patients. Grade 4 elevations in these liver enzymes occurred in 2% or less of patients. Grade 3 or 4 increases in bilirubin occurred in 1.8% and 0.8% of patients, respectively. It is noteworthy that one-third of patients in this study population had documented liver metastases (385).

Clinically significant renal toxicity rarely occurs with gemcitabine therapy. However, rare cases of hemolytic uremic syndrome have been reported with gemcitabine therapy. The incidence is believed to be approximately 0.6% (385,386).

Other nonhematologic toxicities reported in more than 5% of patients were nausea/vomiting (64.3% overall, 17.1% grade 3, 1.2% grade 4), fever (37.3% overall, 0.7% severe), edema (>20% of patients), flu-like symptoms (18.9%, 0.9% severe), cutaneous reactions (24.8%, 0.2% severe), alopecia (14.1%, 0.4% severe), diarrhea (12.1%, 0.7% severe), somnolence (9.1%, 0.9% severe), infection (8.7%, 1.1% severe), mucositis (8.4%, 0.2% severe), constipation (7.8%, 0.7% severe), and dyspnea (7.7%, 1.2% severe). Nausea and vomiting rarely were dose limiting, and only 2 (0.2%) patients discontinued gemcitabine therapy because of nausea. Fever was a fairly frequent toxicity and sometimes occurred in the absence of flu-like symptoms or infection. Subcutaneous edema, including peripheral edema and facial edema, occurred in a significant number of patients. Edema was generally mild to moderate in nature; few patients (0.6%) discontinued gemcitabine because of this side effect, and the edema resolved after drug discontinuation. Flu-like symptoms consisted of headache, back pain, chills, myalgia, asthenia, and anorexia and were generally short lived. Paracetamol was reported to provide relief to some patients. Cutaneous reactions consisted of erythema in mild cases (15.5%) and dry desquamation, vesiculation, and/or pruritus in moderate cases (9.1%). Only one patient developed severe cutaneous toxicity characterized as moist desquamation and ulceration. Dyspnea (with or without bronchospasm) occurs in

less than 10% of patients following gemcitabine administration. This toxicity generally occurs within a few hours of treatment and resolves within 6 hours (385).

Fatal pulmonary toxicity (acute respiratory distress syndrome) has been reported as a rare side effect of gemcitabine therapy (387). Symptoms include progressive dyspnea, tachypnea, marked hypoxemia, and bilateral interstitial infiltrates consistent with pulmonary edema. Some patients have responded to the termination of gemcitabine therapy and treatment with corticosteroids and diuretics. Prior radiation therapy to the mediastinum may be a risk factor for gemcitabine-induced pulmonary edema (387,388).

Possible incompatibilities between gemcitabine solutions and other drug solutions have not been studied.

Ifosfamide

Chemistry

In combination with cisplatin, ifosfamide (IFEX, Holoxan) is a commonly used drug for the first-line treatment of patients with advanced cancer of the cervix, and in combination chemotherapy, it is a second-line treatment for patients with advanced cancer of the ovary (389,390). It also has activity in advanced or recurrent endometrial cancer (391). Chemically, ifosfamide is 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide, and is chemically related to the nitrogen mustards and a structural analog of cyclophosphamide. It differs only in the position of one of the 2 chloroethyl groups, which is transposed to the endocyclic (ring) nitrogen in ifosfamide. The molecular formula is $C_7H_{15}Cl_2N_2O_2P$, and the compound has a molecular weight of 261.1.

Mechanism of Action

Ifosfamide is a metabolically activated alkylating agent. Like cyclophosphamide, it must first undergo hydroxylation by microsomal (mixed-function oxidase) enzyme systems (392). The activation of ifosfamide occurs more slowly than that of cyclophosphamide, and there is quantitatively greater oxidation of the chloroethyl side chains with ifosfamide. This leads to a greater production of chloroacetaldehyde, a possible neurotoxin.

The activation process generates highly reactive metabolites, particularly 4-hydroxyifosfamide, which are capable of cellular uptake and, ultimately, covalent binding to protein and to DNA (393). Metabolites can spontaneously break down to yield the bladder irritant acrolein and the active alkylating moiety, ifosforamide mustard. Cross-linking of DNA strands proceeds from ifosforamide mustard, but acrolein binds nonspecifically and covalently to bladder epithelium. The DNA-cross-link distance is greater for ifosfamide (7 atoms) compared with cyclophosphamide (5 atoms). Furthermore, the aziridine forms more slowly and is less reactive since it lacks a positive charge (394). Chain scission of DNA and inhibition of thymidine uptake also occur with ifosfamide. The primary mechanism of alkylation is not cell cycle specific.

Drug Disposition

The pharmacokinetics of ifosfamide appears to be qualitatively similar to that of cyclophosphamide. Creaven and coworkers (395) found a plasma half-life of radiolabeled ifosfamide ($5,000 \text{ mg/m}^2$) of 13.8 hours, with 82% urinary (radioactivity) recovery.

The plasma decay pattern appears to be biexponential (2-compartment model) for large bolus doses and monoexponential (one-compartment model) with fractionated doses. In contrast to single-dose pharmacokinetics studies, Allen and associates (396) found that with sequential daily administration of $2,400 \text{ mg/m}^2/\text{day}$ for 3 days, there is monoexponential

plasma decay with a half-life of 6.9 hours and a metabolized urinary recovery fraction of 72.8%, in contrast to the biexponential decay (plasma half-life 15.2 hours) of a single-bolus dose of ifosfamide (5,000 mg/m²). This finding suggests that the metabolic disposition of the drug may be dose dependent. These half-lives are approximately twice those reported for cyclophosphamide. Of note, a longer ifosfamide half-life may be seen in obese patients who are more than 20% over ideal body weight. The renal clearance rate of ifosfamide is about twice that for cyclophosphamide: 21.3 versus 10.7 mL/min in bolus dosing and 18.7 versus 10.7 mL/min with fractionated doses. Only about half of an ifosfamide dose is metabolized compared with approximately 90% for cyclophosphamide. This reflects a substantial difference in the metabolic clearance capacity for the 2 analogs. Although more intact (inactive) ifosfamide than cyclophosphamide is renally excreted, urinary alkylating activity persists longer with ifosfamide.

Creaven and coworkers (395) demonstrated that because unchanged ifosfamide, but not metabolites, penetrates the blood-brain barrier, alkylating activity in the CSF may occur but is probably negligible.

Administration and Dosage

Ifosfamide is reconstituted by the addition of sterile water to the vial, which should be shaken to dissolve. Ifosfamide may be further diluted to a concentration of 0.6 to 29.0 mg/mL in 5% dextrose or 0.9% sodium chloride. It is administered intravenously, usually by a short infusion. Ifosfamide may also be administered by slow IV push in a 75-mL minimal volume of sterile saline solution but not water and infused over at least 30 minutes or by continuous infusion over 5 days. Large single doses of ifosfamide produce much more toxicity than fractionated schedules, which are therefore preferred in solid-tumor treatment regimens. Adequate hydration of the patient before and for 72 hours after ifosfamide therapy is recommended to reduce the incidence of drug-induced hemorrhagic cystitis. The use of a concurrent prophylactic agent for hemorrhagic cystitis, such as mesna (Mesnex), is required to prevent severe hematuria from high-dose ifosfamide. At least 2 L of fluid each day is recommended to produce a copious urine output.

Continuous infusions of ifosfamide over 24 hours have also been given every 3 weeks (397). Mesna can be given concurrently in the same infusion container or as a 4-hour intermittent IV bolus (398). However, renal toxicities may be increased with the single, large infusions. Extravasation of the drug should not cause tissue necrosis, but one such case has been described (399).

The FDA-approved dose for testicular cancer is 1,200 mg/m²/day for 5 consecutive days every 21 days. Other dosage schedules include 2,000 mg/m² IV continuous infusion on days 1 to 3 every 21 days as part of the MAID regimen (mesna, Adriamycin, ifosfamide, dacarbazine) for soft-tissue sarcoma; 1,000 mg/m² on days 1 and 2 every 28 days as part of the ICE regimen (ifosfamide, carboplatin, etoposide) for non-Hodgkin's lymphoma; and 1,000 mg/m² on days 1 to 3 every 21 to 28 days as part of the TIC regimen (paclitaxel, ifosfamide, carboplatin) for head and neck cancer (79).

A phase II study evaluated ifosfamide (1,500 mg/m² IV over 1 hour, days 1 to 3) with mesna in combination with paclitaxel (175 mg/m², IV over 3 hours on day 1) and cisplatin (75 mg/m² IV over 2 hours on day 2) as first-line therapy in advanced, suboptimally debulked epithelial ovarian cancer patients (400). This regimen was associated with an 85% objective response rate and a median overall survival of 52.8 months in 22 patients with stage III or IV disease. A regimen of paclitaxel (175 mg/m²), ifosfamide (5,000 mg/m²), and cisplatin (75 mg/m² or 50 mg/m² in irradiated patients) every 21 days in 45 recurrent or persistent cervical cancer patients was associated with a 67% objective response rate (401).

Morgan and colleagues (402) evaluated several IV push and infusion dose schedules in non-small cell lung cancer: 700 to 900 mg/m²/day by IV push for 5 days repeated every 3 weeks; 700 to 1,000 mg/m²/day for 5 days repeated every 3 weeks plus 1 g/day of oral ascorbic acid; 4 g/m² slow infusion repeated every 3 weeks; and 900 mg/m² by IV push weekly. There appeared to be less hematuria produced with the sequential 5-day schedule with concomitant ascorbic acid.

Rodriguez and colleagues (403) described a 47% response rate in leukemia patients with continuous infusions of ifosfamide at 1,200 mg/m²/day given for 5 days. Significant genitourinary toxicity was not encountered, and myelosuppression predominated as the dose-limiting toxicity. In combination with other cytotoxic drugs, such as doxorubicin or lomustine (CCNU), a single IV push dose of 1,000 mg/m² (not to exceed 12,500 g total) has been recommended.

Side Effects and Toxicities

Creaven and associates (395) reviewed the clinical toxicity of ifosfamide given as a large bolus injection (200 to 10,000 mg/m²) and in a fractionated 3-day (2,400 mg/m²/day) schedule. Urinary tract toxicity is the dose-limiting factor with both schedules. The clinical hallmark is hemorrhagic cystitis, which is caused by excretion of active alkylating metabolites into the urinary bladder. Vigorous hydration with oral and IV fluids and concomitant mesna are needed to prevent serious ifosfamide-induced bladder damage. Hydration may also overcome the antidiuretic effects of this drug. Nelson and colleagues (398) used IV furosemide (20 to 40 mg) to maintain adequate urine flow in a phase I study of ifosfamide. Diuretic responses usually occurred within 1 hour.

Symptoms of dysuria and urinary frequency appear to parallel those of hematuria. The onset of symptoms is 1 to 2 days after injection, with an average duration of 9 days (range, 1 to 41 days) (404). Dose-related ifosfamide-induced nephrotoxicity was detected by elevation of BUN, producing subsequent dose-related uremia in 66% of patients receiving 150 mg/kg. Other lesions seen at autopsy (4 of 7 patients) included evidence of acute tubular necrosis and pyelonephritis. At low daily doses, granular cylindruria was seen in all patients, denoting marked tubular damage. The cylindruria cleared within 10 days of drug discontinuance (404). DeFronzo and co-researchers (405) also described glomerular dysfunction and a Fanconi-type picture in a patient treated with ifosfamide. Prior cisplatin therapy may also increase ifosfamide-induced nephrotoxicity (406,407).

Nausea and vomiting appear to be common and are more severe after a rapid injection of large ifosfamide doses. Emesis typically begins within a few hours of administration and persists for an average of 3 days (range, 1 to 28 days) (404).

Hematologic toxicity from ifosfamide usually involves only a mild to moderate degree of leukopenia in most patients. In a review by Creaven and coworkers (395), significant thrombocytopenia was not encountered for any of the dose schedules used.

Lethargy and confusion are seen with high doses of ifosfamide and may be caused by the chloroacetaldehyde metabolite. Nelson and associates (398) observed that this lasted from 1 to 8 hours, was spontaneously reversible, and was related to the passage of intact drug into the central nervous system (CNS). Seizures, ataxia, stupor, and weakness have been reported after ifosfamide. These effects may be increased by concomitant neurotoxic drugs, such as certain antiemetics, tranquilizers, narcotics, and antihistamines. There is a single case report of nonconvulsive status epilepticus associated with ifosfamide therapy. The patient responded to discontinuation of the ifosfamide and phenytoin therapy (408). Although alkylating metabolites appear to penetrate the blood-brain barrier, the levels achieved are too low to be useful in the treatment of CNS tumors (395).

Alopecia is usually seen with ifosfamide, especially when large bolus doses are used. In a study by Van Dyk et al. (404), the average onset of maximal hair loss was 19 days (range, 11 to 32 days) after the start of treatment.

Hepatic enzyme elevations have been described in some patients. The elevations in alkaline phosphatase and serum transaminase are transient and typically resolve rapidly without sequelae.

Special Precautions

The patient must be kept well hydrated during ifosfamide therapy to reduce the potential for hemorrhagic cystitis. The use of mesna given IV or orally is required to prevent hemorrhagic cystitis. Table 14.5 outlines the recommended mesna schedule for ifosfamide uroprotection.

Patients who have received previous or concurrent therapy with radiation or cytotoxic drugs may require significant ifosfamide dosage reductions. Dose reductions should also be considered for patients with impaired renal function and/or serum albumin concentrations below 3.5 g/dL.

Drug Interactions

Several drug interactions are possible with ifosfamide. Because the compound undergoes hepatic activation by microsomal enzymes, induction is potentially possible by pretreatment with various enzyme-inducing drugs, such as phenobarbital, phenytoin, and chloral hydrate.

Nephrotoxic drugs like cisplatin may significantly increase ifosfamide renal damage (406). Other drug interactions reported for cyclophosphamide that may also occur with ifosfamide include reactions with metabolic alteration of H₂-antihistamines, such as cimetidine.

Irinotecan

Chemistry

Irinotecan (CPT-11, Camptosar), a TOPO-I inhibitor, is a water-soluble semisynthetic derivative of camptothecin, a natural product extracted from the stem wood of the *Camptotheca acuminata* tree, that has significant antitumor activity. It was approved by the FDA in 1998 for the treatment of patients with progressive metastatic colon or rectal cancer following 5-FU therapy. Early clinical development of camptothecin was halted because of severe, unpredictable hemorrhagic cystitis, vomiting, and myelosuppression. Subsequently, irinotecan was formulated as a prodrug to have greater water solubility, increased antitumor activity, and less toxicity than the parent compound. Its chemical name is (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidino)carbonyloxy]-1Hpyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H) dione hydrochloride trihydrate. This drug

has a molecular weight of 677.19 and the empirical formula is C₃₃H₃₈N₄O₆ · HCl · 3H₂O.

Mechanism of Action

Irinotecan's cytotoxicity is believed to be related to the inhibition of TOPO-I, an enzyme necessary for DNA replication (298). Irinotecan is activated to the active metabolite SN-38 by the liver (409). Irinotecan and SN-38 bind to the transient TOPO-I-DNA complex, stabilize the complex, and thereby promote DNA single-strand breaks. These strand breaks prevent DNA replication and result in cell death (298,409). Current research suggests that the cytotoxicity of irinotecan is due to DNA damage produced during DNA synthesis. Mammalian cells cannot repair these double-strand breaks.

Drug Disposition

Pharmacokinetic studies performed by Rothenberg et al. (410) have determined that when irinotecan is administered as a 90-minute IV infusion at dose ranges of 50 to 180 mg/m², the plasma terminal-phase half-life for irinotecan (total) was 7.9 ± 2.8 hours, 6.3 ± 2.2 hours for irinotecan (lactone), and 11.5 ± 3.8 hours for SN-38 (the active metabolite). The time of peak plasma concentration for irinotecan was at infusion end, whereas the time of peak concentration for total SN-38 varied from 30 to 90 minutes after completion of the infusion. Plasma clearance was unrelated to dose, with a mean clearance of 15.3 ± 3.5 L/h/m² for the total and 45.6 ± 10.8 L/h/m² for the lactone. At the 150-mg/m² dose, the following pharmacokinetic parameters were observed: peak plasma concentration, 1.97 µg/mL for total irinotecan; 0.83 µg/mL for the lactone form; and 36.7 ng/mL for total SN-38; and concentration-time product (AUC) 8.44 µg · h/mL for total irinotecan, 2.81 µg · h/mL for the lactone form, and 409.8 ng · h/mL for total SN-38. Renal excretion was not a major route of drug elimination.

Abigeres et al. (411) determined in their pharmacokinetic study of irinotecan (100 to 700 mg/m² by 30-minute IV infusion) that the plasma disposition of irinotecan was biphasic or triphasic. The mean plasma terminal-phase half-life, volume of distribution, and total body clearance of irinotecan were 14.2 ± 0.9 hours, 157 ± 8 L/m², and 15 ± 1 L/m²/h, respectively. Both the irinotecan and SN-38 concentration-time product (AUC) increased linearly with dose. At the 350-mg/m² dose level, the irinotecan and SN-38 AUCs were 34.0 ± 4.1 µg · h/mL and 451 ± 100 ng · h/mL, respectively. The plasma terminal-phase half-life of SN-38 was 13.8 ± 1.4 hours.

Administration and Dosage

The appropriate dose of irinotecan should be diluted with 500 mL of dextrose (5%) to a final concentration of 0.12 to 1.1 mg/mL and administered IV over 90 minutes (410). Alternatively, French investigators have administered irinotecan by diluting the appropriate amount of drug in 250 mL of 0.9% sodium chloride solution and delivering the drug IV over 30 minutes (411).

In the United States, the recommended dose for irinotecan therapy in colon cancer patients is 125 mg/m² weekly by 90-minute infusion for 4 weeks followed by a 2-week rest. In Europe, the recommended dose is 300 to 350 mg/m² by 90-minute infusion every 21 days. The U.S. schedule has been used in 3 phase II clinical trials, wherein irinotecan displayed modest activity in cervical cancer patients (412–414). When administered as a single dose every 3 weeks, a 240 mg/m² dose is recommended (410,415). French investigators have determined that a 600 mg/m² 30-minute IV infusion every 3 weeks can be administered if drug-induced diarrhea is aggressively managed by high-dose loperamide (e.g., up to 16 mg/day); however, these investigators recommended a dose level of 350 mg/m² every 3 weeks until further experience is gained with higher dose levels (411).

Table 14.5 Dosing Schedules for Mesna Combined with Ifosfamide

Route of Mesna Administration	Dose (mg/kg) as a Percentage of Ifosfamide Dose at Times before and after Ifosfamide		
	15 min before	4 hr after	8 hr after
Intravenous	20%	20%	20%
Oral ^a	Not recommended; use IV route	0%	0%

^aFor highly reliable patients with total emetic control, mesna solution can be diluted 1:1 to 1:10 in carbonated cola drinks or in chilled fruit juices (e.g., apple, grape, tomato, and orange juice) and administered orally.

Side Effects and Toxicities

Diarrhea and neutropenia are the major dose-limiting toxicities associated with irinotecan (410,411,415). Other moderate to severe toxicities associated with irinotecan therapy include anemia, dehydration (secondary to diarrhea), nausea, vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, elevations in liver transaminases, and alopecia.

The diarrhea associated with irinotecan appears to be due to 2 separate mechanisms. The diarrhea that may occur during irinotecan infusion is highly responsive to atropine therapy and, therefore, appears to be related to cholinergic activity. However, the subacute diarrhea that develops 2 to 3 weeks after irinotecan therapy is refractory to anticholinergic agents. The most effective treatment for the subacute diarrhea is institution of therapy with antimotility agents (i.e., loperamide or diphenoxylate hydrochloride with atropine sulfate) at the first signs of increased intestinal motility (e.g., loose bowels). If left untreated, subacute diarrhea can rapidly progress to grade 4 toxicity. This life-threatening diarrhea is refractory to antidiarrheal therapy and generally lasts for 5 to 7 days. Patients with grade 4 diarrhea should be hospitalized and receive supportive care with IV fluids and electrolyte replacement (410).

Special Precautions

As described above (see Side Effects and Toxicities section), irinotecan can induce grade 4 diarrhea that is refractory to antidiarrheal medication. Patients receiving irinotecan must be monitored carefully for early symptoms of increased intestinal motility and should receive antimotility therapy (e.g., up to 16 mg/day loperamide) as soon as initial symptoms of diarrhea appear. A low level of glucuronidation in the biliary system has been associated with the development of severe diarrhea in some patients (416). It has been shown that uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1) is responsible for conjugating SN-38 to form the glucuronide and that patients with low UGT1A1 activity are prone to increased toxicity from irinotecan (417). Patients with certain genetic polymorphisms in UGT1A1 have a reduced capacity for glucuronidation and are more likely to suffer serious toxicity (418).

Special Applications

The TOPO-I inhibitor irinotecan also has shown activity against advanced cervical cancer. Cottu and colleagues (419) reported response rates in patients with relapsed cervical cancer ranging from 20% to 22%. The GOG reported a response rate of 13.3% (6 of 45) in patients with advanced cervical cancer with no prior chemotherapy (413). No responses were reported in second-line (after resistance to cisplatin) treatment in a phase II study of 16 patients (412). However, Verschraegen et al. (414) reported a 21% response rate in the same patient population ($n = 42$). Reviews by Eisenhauer and Vermorken (420) and Verschraegen et al. (421) reported response rates ranging from 13% to 24%. The combination of irinotecan (60 mg/m² 90 min IV on days 1, 8, and 15) followed by cisplatin (60 mg/m² on day 8) administered every 3 weeks, demonstrated activity in a phase II trial of first-line treatment of cervical cancer, with 1-year disease-free and overall survival rates of 26.7% and 65.1%, respectively (422).

Liposomal Encapsulated Doxorubicin

Chemistry

Liposomal doxorubicin (Doxil, Caelyx) is FDA approved for the treatment of patients with metastatic, refractory ovarian cancer and AIDS-related Kaposi's sarcoma. Doxorubicin HCl, which is the established name for (8S,10S)-10-[(3-amino-2,3,6-trideoxy-

α -L-xylo-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride, has a molecular weight of 579.99, and the molecular formula is $C_{27}H_{29}NO_{11} \cdot HCl$. The liposomal carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2 distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Greater than 90% of the drug is encapsulated in the liposomes. The liposomal encapsulation of doxorubicin dramatically alters the pharmacokinetic and toxicity profiles of the drug.

Mechanism of Action

The mechanism of action of doxorubicin is discussed previously (see Doxorubicin section). Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The liposomes of the encapsulated form of doxorubicin are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time (423).

Drug Disposition

Liposomal doxorubicin is associated with a much longer plasma half-life, slower plasma clearance, and reduced volume of distribution than free doxorubicin. In a pharmacokinetics study performed in 6 patients with solid tumors, the area under the plasma disappearance curve was 1.0 mg/L hour versus 609 mg/L hour when 25 mg/m² of doxorubicin was administered as free drug or as a pegylated liposomal form, respectively. The initial half-life was 0.07 versus 3.2 hours, and the terminal half-life was 8.7 versus 45.2 hours for the free and liposomal forms of doxorubicin, respectively. Additionally, the steady-state volume of distribution was 254 L versus 4.1 L for the free and liposomal forms, respectively (424). Liposomal encapsulation of doxorubicin has also been shown to result in fourfold to 16-fold increases in tumor-tissue drug concentrations compared with the free form.

Administration and Dosage

Liposomal doxorubicin must be diluted in 250 mL of 5% dextrose prior to administration. Because liposomal doxorubicin contains no preservative or bacteriostatic agent, aseptic technique must be strictly observed. Liposomal doxorubicin may be administered as an IV infusion over 30 to 60 minutes. In that liposomal doxorubicin is not a vesicant, extravasation of the drug is not a critical concern. For ovarian cancer patients, liposomal doxorubicin should be administered at a dose of 50 mg/m² (every 4 weeks) at an initial rate of 1 mg/min to reduce the risk of infusion reactions. The rate may be increased to a 60-minute infusion if no adverse events are noted. The recommended dose in AIDS-related Kaposi's sarcoma patients is 20 mg/m² over 30 minutes, once every 3 weeks, for as long as the patient responds and tolerates treatment.

Side Effects and Toxicities

Unlike the parent drug, liposomal doxorubicin is not a vesicant and is associated with minimal cardiotoxicity, alopecia, and nausea/vomiting. However, the liposomal encapsulation results in acute infusion reactions and an increased rate of PPE and stomatitis (425). PPE is a dose-limiting toxicity that can occur in 26% of patients who receive 50 mg/m² every 4 weeks (426). Stomatitis is a second dose-limiting toxicity associated with liposomal doxorubicin. Current methods to prevent PPE and stomatitis include dose reduction and discontinuation (grade 1—redose; if patient has experienced previous grade 3 or 4 toxicity, delay the treatment by 2 weeks until resolution to grades 0 to 1 and

reduce dose by 25% before returning to the original dose level; grades 2 to 4—delay up to 2 weeks until resolved, if no resolution to grades 0 to 1, discontinue; grades 3 to 4—after delay and resolution to grades 0 to 1, decrease dose by 25%, if no resolution, discontinue). To help relieve pain from PPE, topical wound care, elevation, and cold compresses may be used as supportive care (351). Topical DMSO has been used to treat skin extravasations (99% DMSO 4 times daily up to 14 days), but has yet to be evaluated in a randomized trial (349). Other possible therapies that are yet to be evaluated in clinical trials include systemic corticosteroids and pyridoxine (vitamin B₆) (351).

Infusion-related reactions occur in less than 10% of patients treated with liposomal doxorubicin and are most common during the first course of treatment. Symptoms may include flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest and throat, and hypotension. Alopecia has been observed in only 15% of ovarian cancer patients treated with liposomal doxorubicin.

Melphalan

Chemistry

Melphalan (Alkeran, L-phenylalanine mustard, L-PAM) is a phenylalanine derivative of nitrogen mustard that acts as a bifunctional alkylating agent. Melphalan is FDA approved for the chemotherapy of patients with multiple myeloma. The agent's molecular formula is C₁₃H₁₈Cl₂N₂O₂ and its molecular weight is 305.2. It is known chemically as 4-[bis(2-chloroethyl) amino]-L-phenylalanine. Melphalan is water insoluble and previously was only commercially available in a 2-mg tablet form. However, a parenteral formulation was approved by the FDA in 1993. Melphalan for injection is supplied as a freeze-dried powder in single-use vials containing 50 mg melphalan and 20 mg povidone. A vial of sterile diluent (10 mL) is also supplied.

Mechanism of Action

Melphalan is an alkylating agent of the bischloroethylamine type. Its cytotoxicity appears to be related to the extent of its interstrand cross-linking with tumor-cell DNA, probably by binding at the N⁷ position of guanine (427). The cross-helical base pairing causes strain and possible rupture of the double-stranded DNA backbone.

Melphalan is relatively stable in media containing high concentrations of chloride ions and at acidic pH (427). It has a relatively short *in vitro* half-life in plasma of approximately 2 hours, owing to the rapid hydroxylation of the chloroethyl groups of the molecule. Melphalan may form a reactive immonium ion that can alkylate or hydroxylate the monohydroxy and dihydroxy metabolites. Monohydroxy melphalan possesses only 2% of the cytotoxicity of the parent compound, and the dihydroxy derivative is inactive (428).

Melphalan is usually transported into cells by 2 amino acid-transporting systems: the sodium-independent system that transfers leucine and a monovalent cation-dependent system similar to that which transfers alanine, serine, or cysteine (429). Melphalan efflux from cells appears to be sodium independent, to be stimulated by amino acids in the extracellular medium, and to occur by a simple diffusion mechanism.

Drug Disposition

Melphalan has extremely variable systemic availability after oral administration. In the average patient, approximately one-third of an administered dose of melphalan can be recovered from plasma after a bolus oral dose. The range of systemic availability after oral dosing varies from 0% to greater than 90%. The terminal-phase plasma half-life of orally administered melphalan is approximately 90 minutes, and the 24-hour urinary excretion

rate averages 11% (430). Melphalan penetration into cerebrospinal fluid is low. Plasma protein binding ranges from 60% to 90%, and approximately 30% is irreversibly bound to plasma proteins.

Studies of melphalan metabolism, using an isolated perfused rat liver model and *in vitro* rat microsomal enzyme preparations, have documented insignificant hepatic biotransformation (431).

Two groups of investigators have reported that the systemic availability of melphalan is increased if the drug is administered in the fasting state. The presence of a large meal appears to enhance melphalan degradation at the alkaline pH found in the upper small bowel before systemic absorption (432,433).

Patients with multiple myeloma receiving IV melphalan achieved longer durations of survival than those receiving the oral formulation. Furthermore, a significantly lower dose of IV drug was associated with life-threatening leukopenia and infectious complications compared with the oral formulation (433).

Administration and Dosage

The usual IV dose is 16 mg/m² (15- to 20-minute infusion), administered at 2-week intervals for 4 doses, then at 4-week intervals. The oral agent dose is 6 mg/day for 2 to 3 weeks, followed by up to 4 weeks without treatment. As a single agent, one-time IV doses of 1 mg/kg repeated at 4- to 6-week intervals are generally well tolerated. Although the manufacturer reports equal effects from IV or oral doses, bioavailability differences and the potential for lessened hepatic clearance of IV doses suggest IV dosing at reduced levels. In a surgical adjuvant setting for ovarian carcinoma, melphalan has been used in large cyclic doses of 1 mg/kg given IV over 8 hours and repeated in 4 weeks (434). The apparently equivalent therapeutic results with IV and oral dosing are surprising in light of the reported poor oral absorption of the compound.

Side Effects and Toxicities

Compared with other standard alkylating agents, melphalan is relatively well tolerated after oral administration. Except for dose-limiting bone marrow suppression (i.e., neutropenia, thrombocytopenia, anemia), other acute side effects are uncommon and include nausea and vomiting and, rarely, skin rash and pulmonary toxicity (435). Melphalan is characterized by its potential to cause cumulative bone marrow damage, as expressed by profound and prolonged depression of neutrophils and platelets. There is a slow reduction in peripheral leukocyte and platelet counts to their nadirs at 28 to 35 days after drug administration followed by a 14- to 21-day recovery period.

Acute nonlymphocytic leukemia has been reported in patients with multiple myeloma and ovarian cancer after prolonged melphalan therapy. In one Swedish study of 474 patients with ovarian carcinoma, there were 4 cases of acute nonlymphocytic leukemia among 12 patients who received 800 mg or more of melphalan (436). An evaluation of the relationship between alkylating agents and leukemic disorders in 3,363 one-year survivors of ovarian cancer revealed that the 10-year cumulative risk of acquiring leukemia was 11.2% after treatment with melphalan and 5.4% after cyclophosphamide treatment (437). The risk of developing leukemia after melphalan and cyclophosphamide treatment was significantly higher than in matched patient groups who received no chemotherapy. These data suggest that to reduce the leukemia risk, the total dose of melphalan should not exceed 600 mg.

Special Applications

One major impediment to the success of cancer chemotherapy is the rapid development of drug resistance as manifested clinically by short objective responses and subsequent, progressive

tumor growth despite aggressive chemotherapy. Several mechanisms have been postulated to explain this relatively universal phenomenon.

Melphalan therapy has been used in autologous bone marrow transplantation. A series of studies have been reported for high-dose (120 to 225 mg/m²) IV-administered melphalan against adult melanoma, breast, and colon cancers (438,439). Although the resulting high response rates appear to be promising, most have been partial, and survival advantages have not yet been established. In general, these high doses of melphalan have been tolerated relatively well, with diarrhea and stomatitis becoming severe and dose-limiting at doses greater than 200 mg/m².

Because ovarian cancer remains confined to the IP space for most of its natural history, there has been increasing interest in the IP administration of cytotoxic drugs to patients with minimal residual IP disease (i.e., plaques <1 cm in diameter) after aggressive cytoreductive surgery or primary chemotherapy. Melphalan exhibits a high degree of *in vitro* cytotoxicity compared with other standard chemotherapeutic agents when tested against fresh human ovarian cancer tumors at drug concentrations achievable by IP administration (440). In addition to its high degree of cytotoxicity, melphalan's high molecular weight ensures a relatively low clearance from the peritoneal space.

In a phase I dose-finding study, Howell and coworkers (441) showed that an IP melphalan dose of 70 mg/kg was tolerated, with only moderate leukopenia (median nadir 2,000 cells/ μ L) and thrombocytopenia (median nadir 69,000 platelets/ μ L) and no evidence of peritoneal irritation. The peak peritoneal concentration averaged 93-fold greater than the plasma concentration, and total drug exposure for the peritoneal cavity averaged 63-fold greater than that for the plasma.

Methotrexate

Chemistry

Methotrexate is an active drug in the first-line treatment of gestational choriocarcinoma, chorioadenoma destruens, and hydatidiform mole. It is used in the prophylaxis and treatment of meningeal leukemia, and is used in combination with other agents for the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides, advanced non-Hodgkin's lymphoma, lung cancer, and metastatic squamous-cell cancer of the cervix. Methotrexate is a cell cycle-specific antifolate analog, which differs from folic acid in 2 substitutions: an amino group for a hydroxyl in the pteridine portion of the molecule and a methyl group on the amino nitrogen between the pteridine nucleus and the benzoyl group of 4-amino-10-methyl folic acid. Chemically, methotrexate is N-[4-[(2,4-diamino-6-pteridinyl)methyl]benzoyl]-L-glutamic acid. It is a weak acid, with a molecular weight of 454.45 and a molecular formula of C₂₀H₂₂N₈O₅. It is only slightly soluble in water and alcohol. Sodium methotrexate is water soluble and is used in injectable preparations.

Mechanism of Action

Free intracellular methotrexate tightly binds to dihydrofolate reductase, blocking the reduction of dihydrofolate to tetrahydrofolic acid, the active form of folic acid. As a result, thymidylate synthetase and various steps in *de novo* purine synthesis that require 1-carbon transfer reactions are halted. This in turn arrests DNA, RNA, and protein synthesis.

Amino acid syntheses blocked by methotrexate include those requiring 1-carbon transfer, such as the conversion of glycine to serine and homocysteine to methionine. Experimental studies have shown that thymidylate synthetase is inhibited at methotrexate concentrations of 10⁻⁸ M or less, but inhibition of purine synthesis requires concentrations of 10⁻⁷ M or greater (442).

Methotrexate undergoes a variable degree of polyglutamation intracellularly. The polyglutamated forms of the drug are positively charged and do not readily pass through cell membranes. Methotrexate polyglutamates form an intracellular pool of active drug that is retained for long periods, sometimes months, after a single dose (443). The ability of tumor cells to add t-glutamyl residues to methotrexate may be a key determinant of antitumor activity.

The effects of methotrexate are rapidly reversible as free methotrexate leaves the cells. The normal intracellular levels of dihydrofolate are very low (10⁻⁸ M) but increase greatly after methotrexate administration.

Resistance to methotrexate may develop as a result of elevated dihydrofolate reductase activity or defective transport of methotrexate into malignant cells. Increased dihydrofolate reductase enzyme levels may also result from amplification of the dihydrofolate reductase gene, a process associated with homogeneously staining regions of chromosomes and an unstable inheritance mediated by double minutes or extra chromosomal DNA fragments (444). Certain quinazolines have been shown to be effective inhibitors of thymidylate synthetase and may be useful clinically in overcoming this type of resistance (445). *In vitro* studies and clinical experimentation with high-dose therapy indicate that a major mechanism of resistance is probably secondary to decreased cellular uptake.

Methotrexate is classified as a cell cycle phase-specific antimetabolite with activity mostly in S phase. Experimentally, methotrexate synchronizes tumor cells in S phase about 36 to 72 hours after administration (446).

The enhanced toxic effect on tumors compared with normal tissue from high-dose methotrexate with leucovorin rescue may be a result of bypassing normal carrier-mediated cell membrane transport of methotrexate. Leucovorin and its metabolite, 5-methyltetrahydrofolate, share a common influx transport site with methotrexate. There appear to be at least 2 active transport carrier systems involved in the influx and efflux of methotrexate and folates (447). If normal cells are rescued with calcium leucovorin, methotrexate can then exert a relatively greater toxic effect on the tumor cells. Selective rescue of normal cells may be mediated by a slower rate of DNA synthesis relative to the tumor cell or to tissue-specific differences in transmembrane transport.

Drug Disposition

Orally administered methotrexate is rapidly but incompletely absorbed from the gastrointestinal tract. It reaches peak blood levels in approximately 1 hour. Approximately 50% to 60% of the drug in the blood is bound to plasma proteins. Methotrexate is widely distributed to body tissues. In conventional doses, methotrexate is excreted unchanged in the urine. In high doses, it is partially metabolized to 7-hydromethotrexate, which is only slightly soluble in acidic solutions. Approximately 1% to 11% of a dose is excreted as the 7-hydroxy metabolite, and this may comprise as much as 35% of the drug level in the terminal elimination phase. Only about one-third of an oral dose is absorbed, but intramuscular absorption is almost 100% (448).

The hepatic extraction coefficient for methotrexate appears to be very low, and intraarterial hepatic doses show metabolism and pharmacokinetics similar to those of IV doses (449). Methotrexate is both filtered at the glomerulus and actively secreted by the renal tubule. Drugs that interfere with renal excretion of weak acids, such as probenecid, sulfinpyrazone, and salicylates, may reduce the rate of methotrexate excretion. Probenecid has been used successfully in one study to produce a prolonged elevation of plasma methotrexate levels from otherwise low doses of methotrexate (450).

Plasma decay of methotrexate levels have been reported to be biphasic and possibly triphasic. Huffman and associates (451)

reported half-lives after a 30 mg/m² dose to be triphasic: 0.750 ± 0.11, 3.49 ± 0.55, and 26.99 ± 4.44 hours, respectively. Stoller and colleagues (452) reported a biphasic plasma decay for high-dose therapy of 2.06 ± 0.16 and 10.4 ± 1.8 hours. Wang and coresearchers (453) reported age-dependent biphasic elimination of high-dose methotrexate.

Patients with pleural effusions may accumulate methotrexate that slowly distributes from this compartment back into the plasma to increase systemic exposure and the risk of toxicity (454). Effusions should be drained before administration of methotrexate.

Administration and Dosage

Methotrexate may be given by the oral, intramuscular, IV (IV infusion or push), intraarterial, or intrathecal routes. For treatment of neoplastic disease, oral administration of low-dose methotrexate is preferred, owing to the rapid absorption of the tablet form of the agent. Methotrexate has been given by numerous dosing schedules. The usual starting doses are adjusted based on clinical response and hematologic monitoring. In general, methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a 5-day course. Courses are usually repeated 3 to 5 times as required, with rest periods of 1 or more weeks between courses until toxicities subside (455). Leucovorin is indicated following treatment with higher doses of methotrexate to diminish toxicity.

If the IV formulation is administered, the dose should be reduced by 50% for patients with renal insufficiency (BUN ≥30 mg/L). Similar dose reductions should be made for the oral form, although no specific guidelines are available. Methotrexate administration is contraindicated in patients with a creatinine clearance less than 40 mL/min and/or a serum creatinine greater than 2 mg/dL.

Side Effects and Toxicities

Hematologic effects of methotrexate include leukopenia, thrombocytopenia, and anemia. They occur rapidly and depend on the dose and schedule used. The nadir of hemoglobin depression occurs after 6 to 13 days, and of reticulocyte at 2 to 7 days, with rebound between 9 and 19 days. Leukocyte nadir occurs within 4 to 7 days, followed by partial recovery and then, in rare instances, a second decrease in the leukocyte counts occurs during days 12 to 21. The platelet nadir is reached in 5 to 12 days. Hypogammaglobulinemia may also occur after methotrexate administration.

Nausea, vomiting, and anorexia are usually the earliest gastrointestinal symptoms. Gingivitis, glossitis, pharyngitis, stomatitis, and ulcerations with bleeding of the mucosal membranes of the mouth or other portions of the gastrointestinal tract may occur. If ulcerative stomatitis or diarrhea occurs, methotrexate therapy must be interrupted to prevent severe hemorrhagic enteritis or intestinal perforation.

Hepatotoxicity is more common in patients receiving high-dose therapy and in those receiving frequent small doses. Hepatocellular injury is indicated in liver function tests by a rise in serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), usually within the first 12 hours. Prothrombin times may rise with a decrease in plasma factor VII activity, and indirect hyperbilirubinemia may develop. All of these usually return to normal within 1 week. Hepatocytes appear to be protected by fractionated high-dose methotrexate treatments with leucovorin rescue if treatments are administered at intervals of less than 1 week. This may be due to leucovorin activity remaining from prior doses. Various pathologic hepatic changes can occur, including atrophy, necrosis, fatty changes, fibrosis, and cirrhosis. Liver biopsy is the only reliable means of assessing the degree of methotrexate hepatotoxicity.

Dermatologic side effects include erythematous rashes, pruritus, urticaria, folliculitis, vasculitis, photosensitivity, depigmentation, or hyperpigmentation. Alopecia may occur, with several months being required for regrowth. CNS effects include dizziness, malaise, and blurred vision. Encephalopathy also has been reported. Intrathecal administration has been followed by increased CSF pressure, convulsions, paresis, and a syndrome resembling the Guillain-Barré syndrome (384). Deaths have been reported after intrathecal therapy. Renal failure may occur in patients receiving methotrexate, especially in high doses. This risk may be decreased by alkalization of the urine to increase methotrexate solubility and by giving large quantities of fluid. Other reactions rarely reported include chills and fever, osteoporosis, and pulmonary reactions, mainly fibrosis (456).

Drug Interactions

Potential drug interactions have been postulated to occur with other protein-bound drugs, such as salicylates, sulfonamides, phenytoin, and *p*-aminobenzoic acid. These drugs displace methotrexate from its protein-binding site in the blood, causing an increase in the levels of the free drug. However, the overall degree of binding is probably not high enough for major displacement interactions.

Antibiotics used in gut sterilization may also alter methotrexate pharmacokinetics in humans, eliminating the slow phase of excretion (457). Salicylates and probenecid may also compete with methotrexate for renal tubular secretion and increase its serum half-life.

Ethyl alcohol may increase the possibility of methotrexate-induced hepatotoxicity. Oral anticoagulants, such as warfarin, may be greatly potentiated by methotrexate. Methotrexate may alter the liver metabolism of these drugs.

There are several drug interactions described for methotrexate with other chemotherapeutic agents. For example, a clinically significant interaction between methotrexate and L-asparaginase involves the administration of methotrexate 3 to 24 hours before L-asparaginase. The methotrexate treatment is believed to block protein synthesis and reduce asparaginase toxicities, allowing larger doses to be given. Some sequential methotrexate combinations may produce enhanced therapeutic activity. For example, methotrexate given 4 to 9 hours before 5-FU may produce enhanced antitumor activity in breast cancer, but with a commensurate increase in toxic effects (201,458). The mechanism of this interaction involves a significant increase in 5-FU for at least 3 hours (458). The reverse sequence decreases therapeutic activity (459).

Methotrexate activity is enhanced, and thus toxicity increased, when it is used with aspirin, penicillins, nonsteroidal anti-inflammatory agents, cephalosporins, or phenytoin. These agents inhibit the renal excretion of methotrexate (79).

Special Applications

Very high doses of methotrexate have been administered for a variety of tumors. Although leucovorin rescue reduces toxicity, it is still not clear whether high-dose therapy is superior to more conventional dosing without rescue. Specific dosing schemes vary, but a high dose of methotrexate is usually administered IV and followed by calcium leucovorin 24 to 36 hours after initiation of therapy to prevent toxicity. Table 14.6 presents specific dosing recommendations.

The dose range of methotrexate with leucovorin rescue is 100 mg/m² to 10 g/m² given every 1 to 3 weeks. The lower end of this dosing spectrum has been administered in 4 divided oral doses over a 24-hour period. Most frequently, the dose is given by IV infusion in 1 to 2 L of fluid as a rapid infusion or over 6 to 24 hours. Higher peak methotrexate levels occur with more rapid IV infusions, and this may be theoretically more efficacious. There does not appear to be a clinical difference in

Table 14.6 Determination of Leucovorin Dose for High-Dose Methotrexate (50–250 mg/kg over 6 hours) Regimens

Plasma Methotrexate Concentration at 48 hr (M)	Leucovorin Plasma Administration	
	mg/m ² of Leucovorin Every 8 hr	No. of Doses of Leucovorin
$<5 \times 10^{-7}$	15	7
5×10^{-7}	15	8
1×10^{-6}	100	8
2×10^{-6}	100	8

Note: Plasma methotrexate concentration at 96 hours should be determined also. If the plasma concentration at 96 hours is $\geq 5 \times 10^{-6}$ M, the previously used leucovorin regimen should be continued until the plasma methotrexate concentration is $\leq 5 \times 10^{-7}$ M. All patients should also be prehydrated for 12 hours to establish an alkaline diuresis using 1.5 L/m² of fluid containing 10 mEq of bicarbonate and 20 mEq of KCl (pH of urine should be 7.0).

toxicity between rapid and prolonged infusions. Only the 500- and 1,000-mg vials with no preservative should be used for this purpose. Further dilution of methotrexate is necessary and can be accomplished with normal saline or D₅W.

High-dose methotrexate has been associated with reversible nephrotoxicity. At high concentrations, methotrexate may precipitate in the renal tubule, causing tubular dilatation and damage. The pK_a of methotrexate is 5.4. When the urine pH is near this value, methotrexate exists predominantly in its insoluble form and is likely to precipitate. Renal toxicity may be prevented by increasing urine alkalinity and flow. Sodium bicarbonate (3 g every 3 hours for 12 hours before therapy) is usually sufficient to induce alkaline urine in adults. The sodium bicarbonate should be continued with frequent urine pH checks during the therapy and for 48 hours after the dose has been delivered. Methotrexate serum levels are useful in predicting toxic reactions and appropriately adjusting rescue doses of leucovorin (460,461). High-dose methotrexate with rescue is complicated and potentially extremely toxic. Only experienced teams using carefully designed protocols should attempt this treatment. Immediate methotrexate levels should be readily available. Fatal renal or hematologic reactions have occurred at major treatment centers despite the prophylactic precautions described (462).

Mitomycin

Chemistry

Mitomycin (Mutamycin, mitomycin C) is a purple antibiotic isolated from *Streptomyces caespitosus* that is indicated for disseminated adenocarcinoma of the stomach or pancreas in combination with other agents and as palliative treatment. It has also been proven to be useful in combination chemotherapy as a third-line agent in the treatment of advanced cervical cancer. Its chemical name is [1aR]-6-amino-8-[[[(aminocarbonyl)oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methylazirino[2',3':3,4]-pyrrolo[1,2-a]indole-4,7-dione, and it has a molecular weight of 334. Mitomycin is heat stable, is soluble in water and other organic solvents, and has a unique absorption peak at 365 nm (463). In solution, it is slowly inactivated by visible but not ultraviolet light. It is very unstable in acidic and highly basic conditions. The aziridine and carbamate groups on mitomycin are necessary for alkylating activity but not for antibacterial activity. The compound is activated by reduction of the quinone moiety, which releases a methanol residue from the molecule. This allows the aziridine ring to open, exposing an electrophilic carbon at C₁ (alkylating site). The second

(cross-linking) site for alkylation is exposed at C₁₀ after an enzymatic or chemically mediated loss of the carbamate side chain.

Mechanism of Action

Mitomycin is activated *in vivo* to an alkylating agent that cross-links complementary DNA strands, halting DNA synthesis. DNA is the major site of mitomycin activity, although at extremely high concentrations, RNA synthesis may also be affected. The active metabolites of mitomycin resulting from reduction of the quinone moiety yield an opened aziridine ring exposing the primary alkylating site at C₁. A second alkylating site at C₁₀ is exposed with the enzymatic loss of the carbamate side chain (464). The molecular site of DNA binding has been identified at the N₂ and O₆ positions of adjacent guanines in the minor groove of DNA (465).

Activation of the drug can be mediated by chemical reducing agents, by microsomal enzymes, or even by brief exposure to an acidic pH. The extent of DNA binding appears to be related to the guanine and cytosine content of the particular DNA. Cytotoxicity probably results directly from DNA synthesis inhibition secondary to alkylation.

Oxygen free radicals may also contribute to the cytotoxicity of mitomycin by producing DNA strand breaks (466). Oxygen free radicals are produced by cyclic redox reactions of the quinone moiety. Mitomycin's cytotoxic action is not cell cycle phase-specific, but cytotoxic effects are maximized if cells are treated in late G₁ and early S phase. In addition to the direct cytotoxic effects of the drug, mitomycin also causes chromosomal aberrations (mutagenic activity), and in experimental systems, it is a potent carcinogen and teratogen.

Kennedy and coworkers (467) described selective activation of mitomycin by hypoxic cells, suggesting some drug selectivity for hypoxic tumors. Resistance to mitomycin involves an increase in specific cytosolic proteins (possibly a glutathione transferase) and collateral resistance with anthracyclines and dactinomycin (468,469). The latter type of multidrug resistance is mediated by P-glycoprotein expression, with resultant enhanced drug efflux, as observed in mitomycin C-resistant L-1210 cells (470).

Drug Disposition

Mitomycin is cleared rapidly from the vascular compartment. Peak serum concentrations of about 1 µg/mL are typically achieved after IV bolus doses of 10 mg/m² (471). Less than 10% of the dose is excreted into the urine, and this is complete within a few hours after administration. Mitomycin also has been detected in the bile and feces, although animal studies demonstrate that the highest drug levels occur in the kidneys. Detectable levels were also found in muscle, lung, intestine, stomach, and eye, but not in the brain, spleen, or liver (463).

The primary means of mitomycin elimination is by liver metabolism, but the specific enzymes responsible are unknown. However, the enzymes responsible for metabolism do not appear to involve the P450 mixed-function oxide family. *In vitro* studies demonstrate drug inactivation on contact with tissue preparations from the spleen, liver, kidney, brain, and heart. This inactivation is further augmented by anaerobic conditions (463).

There is no detectable change in mitomycin pharmacokinetics in patients with altered hepatic function or when other drugs, including furosemide, are given concurrently (471,472). Schilcher and colleagues (473) showed that the pharmacokinetics of mitomycin does not change after the administration of high doses.

Mitomycin distribution into bile and ascites fluids has been quantitated in patients receiving standard IV doses. The maximum biliary level of 0.5 µg/mL was achieved after 2 hours and was five- to eightfold higher than simultaneous plasma levels during the elimination phase (474). Mitomycin also rapidly

penetrates into ascites fluid and reaches maximal concentrations of 0.05 $\mu\text{g/mL}$ 1 hour after administration. This distribution represents approximately 40% of the total plasma exposure. The drug also appears to slightly concentrate in cervical tissues after IV administration (475).

With intraarterial administration, the hepatic extraction of mitomycin averages only 23% (476). The calculated relative advantage for hepatic arterial infusions is only 2.5- to 3.6-fold greater than for other methods.

Administration and Dosage

Sterile water (10 mL) should be added to each 5-mg vial of mitomycin and shaken gently to dissolve. Mitomycin should be administered IV to avoid extravasation of the drug. If extravasation occurs, severe local tissue necrosis may occur (477). The drug is usually given by a slow IV push, with continuous patient monitoring to lessen the chance of extravasation. Short infusions in 100 to 150 mL of D₅W or normal saline have also been used. Vein patency should be checked before the administration of any dose using 5 to 10 mL of fluid that does not contain the drug. The same procedure should follow the dose. This flushes any remaining drug from the tubing and the venipuncture site.

The recommended dose of mitomycin used as a single agent is 20 mg/m^2 given IV every 6 to 8 weeks. In combination with other myelosuppressive drugs, mitomycin doses are typically limited to 10 mg/m^2 every 6 to 8 weeks. Bolus doses greater than 20 mg/m^2 produce severe toxicity without greatly enhancing efficacy.

Repeat dosing of mitomycin should be based on adequate marrow recovery, including leukocytes, platelets, and erythrocytes. Leukocyte count should return to 4,000/ mm^3 and platelet count to 100,000/ mm^3 .

An ambulatory continuous infusion of mitomycin has been administered at 0.75 $\text{mg/m}^2/\text{day}$ for consecutive 50-day dosing (478). A dosing regimen of 3 $\text{mg/m}^2/\text{day}$ for 5 days every 4 to 6 weeks has also been used (478). These regimens are believed to deliver greater dose intensity by reducing myelosuppression. Intraarterial perfusion doses of 20 mg/m^2 have been given every 6 to 8 weeks (479).

Side Effects and Toxicities

Bone marrow suppression involving platelets, leukocytes, and erythrocytes is the most serious toxicity, and it can continue for 3 to 8 weeks after drug administration is halted (463). Myelosuppression, particularly anemia, can be cumulative. This has been minimized by keeping total lifetime doses under 50 to 60 mg/m^2 .

Gastrointestinal disturbances in the form of nausea, vomiting, and anorexia occasionally develop. These reactions are usually not severe and have an onset within 1 to 2 hours after administration. They may persist for several hours. Stomatitis may also occur, but it is generally not severe.

Renal toxicity detected by increasing serum BUN and creatinine levels with glomerular dysfunction is occasionally seen. This does not appear to be dose- or treatment-duration related, and it is usually not severe. However, mitomycin can also induce a microangiopathic hemolytic anemia with progressive renal failure (hemolytic-uremic syndrome) and cardiopulmonary decompensation. This disease is fatal within 3 to 4 weeks of diagnosis, although the onset is typically delayed for months after mitomycin administration (480). The incidence of this toxic effect may approach 10% among patients given large cumulative doses (480). In one series, renal complications from mitomycin developed in 1.6% of 63 patients receiving a total dose of 50 mg/m^2 or less, 11% of 37 patients receiving 50 to 69 mg/m^2 , and 28% of 18 patients receiving total doses greater than 70 mg/m^2 (481). This suggests that a threshold for inducing microangiopathic hemolytic anemia may be a cumulative dose of about 50 mg/m^2 of mitomycin. Signs of the disease

include thrombocytopenia, circulating schistocytes, and acute renal failure. Histopathologic examinations of the kidneys reveal fibrin thrombi in arterioles, tubular atrophy, and widespread glomerular necrosis.

Veno-occlusive disease of the liver has been reported after high-dose mitomycin therapy and autologous bone marrow transplantation (482). Signs include progressive hepatic dysfunction, abdominal pain, and ascites. Although this rarely has been observed with low-dose therapy, it appears to be much more frequent after high-dose regimens.

Alopecia may occur after mitomycin therapy, but it is usually not severe. Rarely, purple bands in the nail beds correspond to sequential doses of the drug. Lethargy or weakness may occur and can last from several days to 3 weeks. Fatigue and some drowsiness or confusion has also been observed. Dose-related skin reactions and fever with drug administration are occasionally seen.

Severe soft-tissue ulcers may also be expected if the drug escapes the vein during administration. Mitomycin extravasation injuries can result in chronic ulcers that can expand over months (477). Particularly distressing aspects of some mitomycin extravasations include the delayed (3 to 4 months) and sometimes distal occurrence of soft-tissue ulceration after uneventful injections in a peripheral vein (483,484). In animals, the only effective antidote to mitomycin skin reactions was topical DMSO (99% DMSO). Mitomycin extravasations may be empirically treated with topical application of 1.5 mL of DMSO every 6 hours for 14 days (485).

Interstitial pneumonia thought to be secondary to mitomycin has been reported in a small number of patients. These patients showed rapid improvement after treatment with corticosteroids (486).

Special Precautions

Myelosuppression may be cumulative with successive doses of mitomycin and may necessitate dose reductions. Careful monitoring of blood counts is critical. Serious local ulceration may occur if the drug is delivered outside the vein. Extravasation of mitomycin must be avoided.

Clinically significant antitumor drug synergy in humans has yet to be described for mitomycin, although it is probably at least additive in several drug combinations, including the FAM regimen (5-FU, doxorubicin, mitomycin) used in gastrointestinal cancer, the MOB regimen [mitomycin, vincristine (Oncovin), bleomycin] used in carcinoma of the uterine cervix, and megestrol acetate in patients with advanced breast cancer.

Special Applications

Mitomycin and IP hyperthermia were combined to prophylactically treat patients with gastric cancer (487). Mitomycin (8 to 100 $\mu\text{g/mL}$) was administered continuously in bags containing 2,000 mL of heated (40°C to 45°C) saline solution. The total perfusion was 8 to 12 L over 50 to 60 minutes, comprising a mitomycin C dose of 64 to 100 mg. Low peak plasma levels (0.1 $\mu\text{g/mL}$) were produced, and approximately 39% of the administered dose was retained intraperitoneally. The half-lives of mitomycin C in the perfusate are 10 to 17 minutes (α) and 70 to 120 minutes (β) (488). Serum protein levels decreased significantly during and after the procedure, indicating that serum protein reaccumulates in the peritoneal space.

Mitomycin (5 to 10 mg) has also been given every 28 days combined with cisplatin (100 mg/m^2) using the IP route. Mitomycin was always given 1 week after cisplatin, and the dose was diluted in 2 L of normal saline. In 11 patients with malignant peritoneal mesothelioma, 5 of 8 previously untreated patients had reduced fluid reaccumulation lasting from 2 to 32 months (median, 5 months) (292). The major toxic reaction was pain, and catheter failure was related to the IP mitomycin.

Oxaliplatin

Chemistry

Oxaliplatin (Eloxatin, diaminocyclohexane platinum, DACH platinum) is a third-generation platinum with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of *cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N,N'*][oxalato(2-)-*O,O'*]platinum, and it has a molecular weight of 397.3. Oxaliplatin is an organo-platinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and with an oxalate ligand as a leaving group. Oxaliplatin is slightly soluble in water (6 mg/mL), slightly soluble in methanol, and practically insoluble in ethanol and acetone. It is FDA approved for second-line treatment in metastatic colorectal cancer in combination with fluoropyrimidines.

Mechanism of Action

Oxaliplatin binds to DNA in a manner similar to cisplatin, in that it binds to repeating deoxyguanosines d(GpG) in a single DNA strand. It reacts with DNA to produce intrastrand cross-links (>90%) at adenine-guanine d(ApC) sites and to produce intrastrand cross-links (<5%) with guanosines of opposing DNA strands (dG)₂ (79,189). This results in inhibition of DNA synthesis, function, and transcription. Oxaliplatin reacts more rapidly with DNA to form these interlinks and intralinks (e.g., within 15 minutes) than the other platinum agents (12 hours for cisplatin and over 24 hours for carboplatin) (189). Furthermore, unlike the other platinum-DNA adducts, mismatch repair enzymes are unable to recognize the adducts formed by oxaliplatin because of their bulkier size (79).

Drug Disposition

In a summary of pharmacokinetic studies, plasma platinum C_{max} values have been shown to be in the range of 2.59 to 3.22 $\mu\text{g/mL}$, and mean AUC_{0-48h} in the range of 50.4 to 71.5 $\mu\text{g/mL} \cdot \text{hour}$ after an oxaliplatin dose of 130 mg/m^2 (2-hour infusion) (489). Inpatient and outpatient variability was moderate to low (23% and 6%, respectively) (490). In 1-hour infusion studies, mean plasma platinum C_{max} and AUC_{0-24h} increased in a dose-dependent fashion up to 180 mg/m^2 . The pharmacokinetics of platinum in ultrafiltrate after administration of oxaliplatin are triphasic and characterized by short α (0.28 hour) and β (16.3 hours) distribution phases, which are followed by a long terminal γ phase (273 hours) (489). Oxaliplatin is primarily cleared from plasma by renal excretion (53.8%) and covalent tissue binding. Clearance is not affected by age, gender, or hepatic impairment (489).

Administration and Dosage

Oxaliplatin is reconstituted by adding 10 mL sterile water for each 50-mg vial, or dextrose (5%). The solution must be further diluted in 250 to 500 mL of 5% dextrose prior to administration. The infusion line should be flushed with D₅W prior to administration of any concomitant medication (490). Premedication with antiemetics is recommended.

The recommended dose for metastatic colorectal cancer is as follows: on day 1 of every 2-week cycle, oxaliplatin (85 mg/m^2) is generally administered intravenously with leucovorin (200 mg/m^2) over 120 minutes at the same time in 2 separate bags using a Y-line, followed by 5-FU (400 mg/m^2 IV bolus), followed by 5-FU (600 mg/m^2) in 500 mL D₅W as a 22-hour continuous infusion. On day 2, the patient should receive leucovorin (200 mg/m^2) over 120 minutes at the same time in 2 separate bags using a Y-line, followed by 5-FU (400 mg/m^2 IV bolus), followed by 5-FU (600 mg/m^2) in 500 mL D₅W as a 22-hour continuous infusion.

In phase II trials for gynecologic cancers, the recommended dose of oxaliplatin is 130 mg/m^2 IV over 2 hours every 21 days (491,492).

Side Effects and Toxicities

Oxaliplatin produces dose-limiting peripheral neuropathy and gastrointestinal and hematologic adverse events. Neurotoxic symptoms usually resolve within a week of stopping therapy; however, symptom intensity is cumulative with repeated courses of oxaliplatin (189,490,493). Other common adverse events include mild leukopenia and mild to moderate thrombocytopenia. Nausea and vomiting are common, and antiemetic prophylaxis is required with oxaliplatin therapy.

Unlike other platinum-containing agents, oxaliplatin is not associated with nephrotoxicity. Alopecia has not been reported with oxaliplatin.

Special Applications

Oxaliplatin is an agent with substantial activity in platinum-sensitive ovarian cancer patients previously treated with cisplatin. Bougnoix and colleagues (494) noted 2 complete and 8 partial responses in 24 patients who were platinum sensitive (41.7% response rate). Similar findings were seen in a phase II study, which also saw a 42% response rate in platinum-sensitive patients (495). Chollet and colleagues (496) studied similar populations of patients and noted 6 responses in 13 platinum-sensitive patients (46%) and a 17% response rate (3 of 18 patients) in platinum-resistant patients. Phase II studies have seen only minimal activity in platinum-resistant patients (<6% response rate) (491,495).

Paclitaxel

Chemistry

Paclitaxel (Taxol) is one of the most commonly used drugs in oncology, with FDA approval for primary or salvage therapy for epithelial ovarian cancer, as salvage therapy for metastatic breast cancer, in second-line treatment of AIDS-related Kaposi's sarcoma, and in the treatment of non-small cell lung cancer. It is also active against a variety of other solid tumors, including cervical and endometrial cancer (427,428). It is a diterpene plant product derived from the bark of the Pacific yew, *Taxus baccata*. It has a molecular weight of 853.9, is insoluble in water, and has an empiric formula of $C_{47}H_{51}NO_{14}$. Its chemical name is 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one-4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Mechanism of Action

Paclitaxel acts as a mitotic spindle poison. In a manner contrary to known mitotic spindle inhibitors, such as colchicine and podophyllotoxin, paclitaxel promotes assembly of microtubules and stabilizes them, preventing depolymerization. This inability to depolymerize microtubules prevents cellular replication (177).

Drug Disposition

Early pharmacokinetic studies using standard doses and a 24-hour infusion suggested that paclitaxel pharmacokinetics were linear; however, with short infusions and/or high dose levels, paclitaxel's nonlinear pharmacokinetics becomes readily apparent (239). The nonlinearity is due to saturable distribution, metabolism, and elimination. Terminal elimination half-life is largely dependent on the dose and administration schedule. At a dose level of 175 mg/m^2 with a 3-hour infusion, mean pharmacokinetic parameters of paclitaxel include the following: plasma $t_{1/2\alpha}$, 16 minutes; plasma $t_{1/2\beta}$, 140 minutes; plasma $t_{1/2\gamma}$, 18.75 hours; plasma clearance, 12.69 L/h/m²; plasma AUC, 16.81 $\mu\text{mol/L} \cdot \text{hour}$; 48-hour urinary excretion, <10% of dose; and 48-hour fecal excretion, 70% of dose (239).

Clearance is rapid and not due to urinary excretion; the major route of paclitaxel elimination is believed to be via hepatic

metabolism and subsequent biliary excretion (497). Approximately 70% to 80% of the drug is eliminated by fecal excretion.

Administration and Dosage

All patients undergoing paclitaxel therapy should receive premedication to prevent severe hypersensitivity reactions. A recommended regimen is dexamethasone (either 20 mg orally the night before treatment and the morning of treatment, or 20 mg IV 30 minutes before paclitaxel delivery) plus diphenhydramine (50 mg) and famotidine (20 mg) IV 30 minutes before chemotherapy (498). For the majority of patients, administration of dexamethasone 20 mg IV 30 to 60 minutes before paclitaxel is sufficient and has been proven to be effective in preventing hypersensitivity reactions.

Paclitaxel is commercially available as an injection concentrate in 30-mg (5 mL), 100-mg (16.7 mL), and 300-mg (50 mL) multidose vials. Before infusion, paclitaxel must be diluted with 0.9% sodium chloride, 5% dextrose, 5% dextrose and 0.9% sodium chloride injection, or 5% dextrose in Ringer's injection to a final concentration of 0.3 to 1.2 mg/mL. The solution is stable for up to 27 hours at room temperature. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 μm to remove particulates that are present in paclitaxel solutions. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excess particulate matter formation should be discarded. Because of the possibility of leaching of phthalate plasticizers with paclitaxel solutions, only nonpolyvinylchloride (such as polyethylene or polyolefin) IV administration sets should be used.

As a result of an unacceptable level of severe hypersensitivity reactions in early phase I studies (most likely related to the Cremaphor EL vehicle), a 24-hour infusion schedule and a premedication regimen with corticosteroids and histamine H_1 - and H_2 -antagonists were used in all phase II and III clinical trials conducted in the United States from 1987 to 1992. Later clinical studies established that a 3-hour paclitaxel infusion schedule can be administered safely without a significant increase in major hypersensitivity reactions and that the shortened infusion schedule is associated with significantly less grade 4 neutropenia than the 24-hour infusion (i.e., 71% vs. 18% for the 24- and 3-hour infusions, respectively) (499). Follow-up studies have determined that a 1-hour infusion schedule also is feasible; however, infusion durations less than 1 hour are associated with a prohibitively high rate of hypersensitivity reactions (500).

There were early concerns that the shorter infusion schedules might be associated with a decline in efficacy. However, results from GOG-158, a phase III, randomized study in women with optimal disease, advanced ovarian cancer, revealed that paclitaxel 175 mg/m^2 by 3-hour infusion combined with carboplatin (targeted AUC of 7.5) (arm II) had similar activity with less toxicity than paclitaxel 135 mg/m^2 by 24-hour infusion plus cisplatin 75 mg/m^2 (arm I) (501). Median progression-free survival and overall survival were 19.4 and 48.7 months, respectively, for arm I (paclitaxel-cisplatin) compared with 20.7 and 57.4 months, respectively, for arm II (paclitaxel-carboplatin). Because of its ease of administration and lower toxicity profile (cisplatin plus short-infusion paclitaxel is associated with dose-limiting neurotoxicity), the recommended primary chemotherapy regimen for advanced ovarian cancer is paclitaxel 175 mg/m^2 by 3-hour infusion plus carboplatin (targeted AUC of 6.0 to 7.5) every 21 days for 6 cycles (501). Although this generally is a well-tolerated regimen, neurosensory toxicity and prolonged thrombocytopenia can prove to be dose limiting. The FDA-approved regimen for first-line treatment of ovarian cancer is paclitaxel 135 mg/m^2 over 24 hours plus cisplatin 75 mg/m^2 every 21 days for 6 cycles or paclitaxel 175 mg/m^2 over 3 hours plus cisplatin 75 mg/m^2 .

The FDA-approved recommended regimen for salvage therapy for patients with platinum-refractory ovarian cancer is paclitaxel 135 or 175 mg/m^2 administered IV over 3 hours every 3 weeks, but the optimal regimen has not clearly been established. Paclitaxel has been administered by various other schedules during investigational studies in patients with solid tumors, including 135 to 250 mg/m^2 as a 24-hour continuous infusion every 3 weeks; 212 to 225 mg/m^2 as a 6-hour infusion every 3 weeks; 30 mg/m^2 as a 1-hour infusion daily for 5 days every 3 weeks; 30 mg/m^2 as a 6-hour infusion daily for 5 days every 3 weeks; 120 to 140 mg/m^2 as a 96-hour infusion every 3 weeks; and 150 mg/m^2 as a 120-hour infusion every 3 weeks (177). Most recently, IP therapy for optimally debulked advanced ovarian cancer demonstrated a significant survival advantage with a regimen of IV paclitaxel on day 1, IP cisplatin on day 2, and IP paclitaxel on day 8 (see Intraperitoneal Drug Pharmacokinetics and Cisplatin sections of this chapter for more details on this IP regimen) (4,154,155,502).

Weekly schedules of paclitaxel have been explored extensively, particularly in combination with carboplatin, although there are few data comparing them with 3-weekly regimens. They are generally reported as being well-tolerated in relapsed disease, with some responses reported in patients previously exposed to the 3-weekly schedule (503,504). A randomized study comparing weekly versus 3-weekly paclitaxel has been conducted in breast cancer. Five hundred and seventy-seven patients were randomized and an additional 158 patients were included in the sample. The combined sample showed a statistically significant improvement in response rate, time to progression and overall survival (505), with neurotoxicity as the dose-limiting toxicity.

Special Precautions

Before the institution of standard prophylactic medications, the incidence of major hypersensitivity reactions associated with paclitaxel therapy approached 25% to 30%. With premedication, the incidence of severe hypersensitivity reactions has decreased to less than 2%. The majority of paclitaxel-induced hypersensitivity reactions can be categorized as grade 1, with symptoms of dyspnea with bronchospasm, urticaria, and hypotension. Major sensitivity reactions usually occur within the first 10 minutes after the first or second dose of paclitaxel (177). Minor symptoms of flushing and rashes are not predictive of the future development of severe manifestations (177,499). According to National Cancer Institute guidelines for paclitaxel administration, emergency equipment must be available and medical personnel should be in attendance during paclitaxel infusion, especially during the first 15 minutes of the first and second courses. Vital signs should be periodically monitored during the first several hours of drug infusion. The paclitaxel infusion should be discontinued immediately if symptoms of a major hypersensitivity reaction occur (including respiratory distress, hypotension, generalized urticaria, and angioedema). Severe hypersensitivity reactions may be treated with IV epinephrine, IV diphenhydramine, IV fluids, and nebulized β -agonists. Steroid therapy may be helpful in the resolution of recurrent symptoms (506). There is strong evidence that patients who develop major hypersensitivity reactions may be successfully retreated with slow, low-dose infusions of paclitaxel after premedication with multiple high doses of corticosteroids and antihistamines (507).

Drug Interactions

Paclitaxel therapy appears to modify the hematologic toxicity associated with platinum agents. Rowinsky et al. (508) conducted a phase I study of sequential escalating doses of paclitaxel and cisplatin therapy and determined that myelosuppression was more severe when paclitaxel was administered immediately after cisplatin therapy than when given prior to cisplatin.

Concomitant medications that contain substrates or inhibitors of hepatic enzymes, principally cytochrome P450 isoenzymes CYP_{2C8} and CYP_{3A4}, may increase paclitaxel clearance, and caution should be exercised when administering paclitaxel. In a study by Chang et al. (509), the pharmacokinetics of paclitaxel was significantly altered by the concomitant use of anticonvulsants (i.e., phenytoin, carbamazepine, and phenobarbital), and the maximum tolerated doses of paclitaxel in malignant glioma patients were 360 mg/m² for those on anticonvulsant therapy versus 240 mg/m² for those not receiving anticonvulsants. There was also a significant difference in paclitaxel metabolite and toxicity profiles between the 2 groups. Central neurotoxicity, rather than neutropenia, was the dose-limiting toxicity in patients on anticonvulsant therapy who received paclitaxel at a dose greater than 350 mg/m².

Special Applications

Paclitaxel is a particularly promising agent for IP administration in that this route of drug delivery results in a more than 3-log increased exposure of the peritoneal cavity relative to systemic circulation. Additionally, potentially cytotoxic levels of paclitaxel remain in the peritoneal cavity for 5 to 7 days following IP administration; therefore, weekly IP treatment results in continuous drug exposure (510). A phase II study in women with ovarian, fallopian, or peritoneal cancer and small-volume residual disease following primary chemotherapy showed that IP paclitaxel had significant activity as evidenced by a 61% surgically defined complete response rate (511). Three large phase III trials in the GOG and the Southwest Oncology Group (GOG-104/SWOG-8501, GOG-114, and GOG-172) comparing various combination chemotherapeutic regimens administered IV or IP documented significant survival advantages for the IP treatment arms (3–5). Most recently, in GOG-172, an IP regimen (IV paclitaxel, 135 mg/m² over 24 hours on day 1, IP cisplatin 100 mg/m² on day 2, and IP paclitaxel 60 mg/m² on day 8, every 21 days) was associated with a 25% reduction in the risk of death compared to the IV administered regimen (IV paclitaxel plus cisplatin) ($p = 0.03$) (4). The day 1 paclitaxel may alternatively be given over 3 hours to reduce the myelosuppressive activity of paclitaxel and to eliminate the need for a hospital stay (154).

Paclitaxel has demonstrated activity against both endometrial and cervical cancers (512). Woo and colleagues (513) reported a 43% response rate to paclitaxel (95% CI: 6% to 80%) in 7 patients with advanced, progressive, or recurrent endometrial cancer following platinum analog treatment. A GOG study noted a 14.3% complete and 21.4% partial response rate in 28 evaluable patients with endometrial cancer not previously treated with chemotherapy (514). Leukopenia was the most prominent side effect noted. A response rate of 37% (95% CI: 16% to 62%) was reported in 19 patients pretreated with cisplatin, doxorubicin, and cyclophosphamide (515). A GOG phase II trial of paclitaxel (3-hour infusion of 200 mg/m² every 21 days or 175 mg/m² for patients with prior pelvic radiation therapy) found a 27.3% response rate (95% CI: 15% to 42.8%) in 44 persistent or recurrent endometrial cancer patients who failed prior chemotherapy (516).

A GOG phase II trial of single-agent paclitaxel in advanced cervical cancer demonstrated a response rate of 31% (427). Trials of combination cisplatin-paclitaxel (IV paclitaxel 175 mg/m² by 3-hour infusion followed by cisplatin 75 mg/m²) in metastatic and recurrent cervical cancer showed moderate activity (47% response rate; 95% CI: 30% to 65%) (517). A similar response rate (45%) was seen in another phase II trial of first-line therapy of advanced cervical cancer (IV paclitaxel 135 mg/m² by 24-hour infusion followed by cisplatin 75 mg/m² every 28 days) (518).

Pemetrexed

Chemistry

Pemetrexed (Alimta) is an antifolate antineoplastic agent with the chemical name of L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It has a molecular weight of 597.49, and its molecular formula is C₂₀H₁₉N₅Na₂O₆ · 7H₂O. Pemetrexed is FDA approved for combination therapy with cisplatin for malignant pleural mesothelioma, and for single-agent therapy for non-small cell lung cancer.

Mechanism of Action

Pemetrexed inhibits the folate-dependent enzymes thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). The inhibition of GARFT, for example, is directly associated with a decrease in the rate of tumor cells (519). Although methotrexate was an early but potent inhibitor of DHFR, the antifolate activity of pemetrexed is quite different. The K_m for pemetrexed is one hundredth that of methotrexate for folylpolyglutamate synthetase (FPGS), making it possible to rapidly and completely block TS activity; whereas methotrexate acts in a more gradual and cumulative process, only impacting cellular proliferation at the point where more than 95% of the enzyme is inhibited (519). Additional details regarding the unique mechanism of action of pemetrexed, including features of membrane transport, its maintained activity in loss of transport activity, and its comparison with other antifolates (e.g., 5-FU, methotrexate, raltitrexed) are discussed in more detail elsewhere (519).

Drug Disposition

Pemetrexed is primarily excreted in the urine and is only minimally metabolized. The elimination half-life is approximately 3.5 hours among patients with normal renal function. Pemetrexed exposure increases with decreasing renal function. Pemetrexed is 81% bound to plasma proteins, and binding is not affected by renal function.

Administration and Dosage

Pemetrexed is administered IV at 500 mg/m² over 10 minutes on day 1 of every 21-day cycle. When used in combination therapy, cisplatin (75 mg/m² over 2 hours) should begin 30 minutes after the pemetrexed administration. The premedication regimen with pemetrexed includes corticosteroids (dexamethasone) to reduce skin rash reactions and folate-containing vitamin supplementation (daily for at least 7 days prior to pemetrexed administration) to reduce some toxicities.

Side Effects and Toxicities

The most commonly occurring side effects associated with pemetrexed treatment include hematologic toxicity, fever and infection, stomatitis, pharyngitis, and rash. Although many toxicities appeared significantly lower among patients receiving folate supplementation (e.g., neutropenia, nausea, vomiting, fever, infection), hypertension (11% vs. 3%), chest pain (8% vs. 6%), and thrombosis/embolism (6% vs. 3%) were higher among those receiving supplementation. Rare cases of colitis have been reported in postmarketing studies.

Topotecan

Chemistry

Topotecan (Hycamtin, topotecan hydrochloride) was approved by the FDA in 1996 for the treatment of ovarian cancer patients after failure of primary chemotherapy. It is also indicated in the

treatment of small-cell lung cancer after failure of first-line chemotherapy. Topotecan is a semisynthetic analog of camptothecin. The parent compound is derived from the bark of an ornamental tree native to Asia, *Camptotheca acuminata*. Sodium camptothecin was studied in clinical trials in the late 1960s through the early 1970s. However, clinical development of this agent was halted despite evidence of a variety of tumor responses because of severe and unpredictable toxicities (e.g., myelosuppression and hemorrhagic cystitis) (520). Topotecan and other camptothecin analogs (e.g., irinotecan) have been formulated in an effort to overcome unacceptable toxicities and to increase cytotoxicity and water solubility. Topotecan incorporates a stable basic side chain at the 9-position of the A-ring of 10-hydroxycamptothecin, which increases aqueous solubility. The molecular weight is 457.9 (the HCl salt) and the formula is $C_{23}H_{23}N_3O_5 \cdot HCl$ (the free base has a molecular weight of 421.5). The chemical name of topotecan is (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7] indolizino [1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride.

Mechanism of Action

In a manner similar to camptothecin, topotecan's cytotoxicity results from the inhibition of TOPO-I, an enzyme that induces reversible single-strand breaks during DNA replication. Camptothecin analogs bind with and stabilize the transient TOPO-I-DNA complex, preventing religation of the single-strand breakage. The interaction of the ternary topotecan-TOPO-I-DNA complex with replication enzymes results in double-strand DNA breaks and cellular death. Topotecan exists in a pH-dependent equilibrium as both a closed lactone ring and a hydroxy acid; the hydroxy acid is formed by hydrolysis of the lactone ring. The active lactone form predominates at a pH below 7.0, and at a pH of 6.0, greater than 80% of topotecan exists in the lactone form. Slow reaction kinetics studies have shown that the hydroxy acid is inactive, and only the closed lactone bonds with the TOPO-I-DNA complex (409).

Drug Disposition

After IV administration, plasma pharmacokinetics shows that the lactone form, which is active as an inhibitor of TOPO-I, is rapidly converted to the hydroxy acid form. At the end of a brief infusion, approximately half of the dose administered exits as hydroxy acid (415). One hour after administration, less than 30% of the dose remains in the lactone form. Topotecan does not inhibit TOPO-II.

Both forms of topotecan are subject to rapid biphasic elimination. In a summary of pharmacokinetics studies, the mean half-life of topotecan lactone was only 3.0 hours (range, 1.2 to 4.9 hours) (409). Binding to plasma proteins is approximately 35%. Renal excretion appears to account for 40% to 70% of drug clearance (79,189).

When topotecan was administered as a weekly 24-hour IV infusion of 1 to 2 mg/m², the plasma steady-state concentration and the AUC increased linearly with dose. The lactone to total drug concentration ratio was constant, which suggests that the total drug concentration may be used as a measure of active lactone exposure with weekly, long infusions (521). Additionally, comparison of day 1 pharmacokinetics values with blood counts showed that both the topotecan AUC and lactone AUC were predictive of the level of neutrophil reduction on days 15, 22, and 29 using the sigmoid E_{max} model (521). This led the investigators to suggest that topotecan-induced myelosuppression is noncumulative and that elimination probably remains unchanged with repeat dosing in individual patients. Other studies have also found a correlation between the topotecan AUC and level of neutropenia (415,522).

Limited sampling models for topotecan pharmacokinetics have been proposed that may facilitate tailoring of topotecan drug doses in individual patients and large pharmacodynamic studies of topotecan (523,524). Plasma concentrations of the

lactone and hydroxy acid forms of topotecan at 2 hours, after a 30-minute infusion, reliably predicted the lactone form AUC, the hydroxy acid AUC, the total topotecan AUC, and the clearance rate.

Administration and Dosage

Each 4-mg vial of topotecan should be reconstituted with 4 mL of sterile water. The resulting solution can be further diluted with either 0.9% sodium chloride or 5% dextrose. Because the active lactone form of topotecan is subject to a pH-dependent hydrolysis to the inactive hydroxy acid, consideration should be given to maintenance of an acidic pH during drug infusion. When the topotecan lactone is dissolved in 5% dextrose, only approximately 10% is converted to the hydroxy acid (415). Because the product does not contain an antibacterial preservative, it should be used immediately once constituted.

Parenteral topotecan has been administered by IV infusions varying in length from 30 minutes to 21 days (409). As discussed below, the dosing schedule has a profound effect on the maximum tolerated dose (MTD).

An oral formulation has been evaluated in murine tumor models and in phase I to II trials. It has been associated with excellent bioavailability and similar efficacy compared with parenteral topotecan in 4 of the 5 murine tumor models tested (525). In early phase human trials, oral topotecan was well tolerated and active in second-line therapy of ovarian cancer and small-cell lung cancer, and was associated with less neutropenia than the IV formulation (526–528).

The standard FDA-approved dosing regimen is 1.5 mg/m²/day × 5 days by 30-minute IV infusion every 21 days, for a minimum of 4 courses owing to delayed tumor response, as tolerated (in the absence of tumor progression). However, this dosing schedule is associated with a greater than 80% incidence of grade IV neutropenia. Many oncologists, therefore, use a dose of 1.25 mg/m²/day for 5 days and/or administer prophylactic G-CSF.

In phase I studies, the MTD of topotecan was highly dependent on the length of infusion schedules; longer infusions were generally associated with lower MTDs. The estimated MTD of topotecan when administered as a 30-minute, 72-hour, and 120-hour continuous infusion is 22.5 mg/m², 1.6 mg/m²/day (4.8 mg/m² total), and 0.68 mg/m²/day (3.4 mg/m² total), respectively. As a continuous 21-day infusion administered every 28 days, the MTD of topotecan appears to be 0.5 mg/m²/day (10.5 mg/m²/cycle) (409,529,530). A weekly dosing schedule has been developed that appears to maintain antitumor activity without causing severe myelosuppression (531,532).

Side Effects and Toxicities

Toxicity data are available from a phase III, randomized study of topotecan 1.5 mg/m²/day for 5 days every 21 days versus paclitaxel 175 mg/m² IV over 3 hours every 21 days in ovarian cancer patients with progressive or recurrent disease following primary platinum-based chemotherapy (533). Neutropenia was the predominant toxicity in this study: 79% of patients experienced grade 4 neutropenia, 25% of patients experienced febrile neutropenia, and 5% of patients developed sepsis [2 patients (2%) died of sepsis]. The onset of grade 4 neutropenia, which responded to G-CSF therapy, occurred on days 9 through 15 of a chemotherapy cycle. Thrombocytopenia also occurred frequently: 50% of patients experienced grades 3 to 4 thrombocytopenia (25% experienced grade 4). Grade 4 anemia occurred in 3.6% of patients.

The most common nonhematologic toxicities were cumulative, dose-related alopecia (76%) and nausea/vomiting (10% grades 3 to 4), which was amenable to antiemetic therapy. Other frequent toxicities were fatigue (41%), constipation (43%), diarrhea (40%), abdominal pain (27%), fever in the absence of neutropenia (29%), stomatitis (24%), dyspnea (24%), and asthenia (22%) (533).

Although the results of the study described in the above paragraphs led to the FDA approval of topotecan as salvage therapy for patients with ovarian cancer, with a recommended dose level of 1.5 mg/m²/day for 5 days, it is important to note that the patients in this European study only received one prior platinum-based chemotherapeutic regimen, and that most received cisplatin (not carboplatin), and none had received prior paclitaxel. In general, topotecan-induced myelosuppression is more severe in patients who have previously received carboplatin and/or multiple prior chemotherapeutic regimens. For this reason, many clinicians use an initial topotecan dose of 1.25 mg/m²/day and/or administer prophylactic G-CSF.

Special Precautions

Because topotecan has a high rate of renal excretion and a modest hepatic clearance, a clinical study was conducted to evaluate the impact of renal and hepatic dysfunction on toxicity in patients undergoing treatment with topotecan on a daily $\times$ 5 dosing schedule (534,535). Pharmacokinetic analyses showed clear correlations between creatinine clearance and plasma clearance of both topotecan and topotecan lactone ($r^2 = 0.65$, $p < 0.0001$). Although the standard dose for patients with good renal function is 1.5 mg/m²/day $\times$ 5 days, this study determined that the recommended starting dose for patients with moderate hepatic dysfunction (creatinine clearance of 20 to 39 mL/min) was 0.75 mg/m². The investigators urged extreme caution with topotecan administration in patients with more profound renal insufficiency and recommend further dose reductions for heavily pretreated patients (534). Hepatic insufficiency did not appear to exacerbate hematologic toxicity (534). Nonhematologic toxicity appeared to be unaffected by either renal or hepatic insufficiency.

Drug Interactions

Drug sequence of the paclitaxel/topotecan combination had no apparent impact on hematologic toxicities or pharmacologic behavior (536). However, drug sequence of the cisplatin/topotecan combination did have a significant impact on toxicity and topotecan pharmacokinetics. Prior administration of cisplatin significantly reduced the clearance of topotecan (possibly as a result of subclinical nephrotoxicity) and increased hematologic toxicity (508). In GOG-182, carboplatin was administered on day 3 of a daily $\times$ 3 topotecan administration schedule, because administration of carboplatin on day 1 was associated with excessive neutropenia and thrombocytopenia (537).

There has been interest in sequential administration of topotecan (TOPO-I inhibitor) with TOPO-II inhibitors (e.g., doxorubicin, etoposide). The rationale is that administration of a TOPO-I inhibitor would induce upregulation of TOPO-II in tumor cells and thus enhance cytotoxicity. One clinical/translational study of topotecan (0.17 to 1.05 mg/m²/day as a 72-hour continuous infusion on days 1 to 3) followed by etoposide (75 or 100 mg/m²/day as a 2-hour infusion daily on days 8 to 10) failed to show reliable downregulation of TOPO-I and upregulation of TOPO-II following administration of topotecan (538). Although significant clinical activity was observed in this phase I study in patients with various solid tumors, the investigators concluded that the toxicity and translational research results did not support a significant synergistic advantage of this combination. Another study of the TOPO-I and TOPO-II inhibitor combination therapy (IV topotecan 0.5 mg/m² per day for 5 days and oral etoposide 50 mg twice daily for 7 days of every 21-day cycle, with dose escalation of topotecan 0.75 and 1.0 mg/m²) found the combination to be safe and effective in small-cell lung cancer patients; however, the incidence of grades 3 to 4 neutropenia was 25%, and 2 patients died from neutropenic sepsis (539).

TOPO-I is a biochemical mediator of radiosensitization in cultured mammalian cells by camptothecin derivatives (540). There are *in vitro* and *in vivo* data suggesting that topotecan

may have activity as a radiation-sensitizing agent (541). However, this apparent synergistic relationship remains to be explored in clinical trials.

Special Applications

Phase I trials of IP topotecan have demonstrated the feasibility of IP administration and a favorable toxicity profile (542,543). Pharmacokinetic studies revealed that the pharmacologic advantage associated with IP administration of topotecan (expressed as the ratio of the peritoneal to plasma AUC) was 31.2 (543). In a Netherlands study, patients were treated with escalating doses (5 to 30 mg/m² every 21 days). The dose-limiting toxicity was acute hypotension, chills, and fever at the 30-mg/m² dose level (542). The University of California, San Diego study treated patients with escalating doses from 2 to 4 mg/m² every 21 days. The MTD of IP topotecan was determined to be 4 mg/m² every 21 days, and the recommended dose for further phase II study was 3 mg/m². The dose-limiting toxicity was neutropenia. Other toxicities included anemia, vomiting, fever, and abdominal pain (543).

Vinblastine Sulfate

Chemistry

Vinblastine (Velban) is used in the treatment of germ-cell tumors of the ovary (544) and has demonstrated activity in early clinical trials of cervical, endometrial, and ovarian cancers (544,545). In combination with other agents, it has also demonstrated activity in early trials of ovarian cancer (546). Vinblastine is the sulfate salt of an alkaloid isolated from *Vinca rosea* (periwinkle). It is structurally related to vincristine, another alkaloid isolated from the same plant. Vinblastine sulfate is a white to off-white crystalline powder that is freely soluble in water, soluble in methane, and slightly soluble in ethanol. Its empiric formula is C₄₆H₅₈N₄O₉ · H₂SO₄, and it has a molecular weight of 909.07.

Mechanism of Action

Vinblastine binds to tubulin and inhibits microtubule assembly. This inhibition prevents mitotic spindle formation and results in an accumulation of cells in metaphase (547).

Vinblastine is considered cell cycle phase specific for mitosis; however, the cytotoxic effect probably occurs in S phase and is expressed only in M phase. At high doses, direct effects may be expressed in S and G₁ phases. Vinblastine is assumed to have stathmokinetic (cell cycle arrest) effects similar to vincristine.

Drug Disposition

After IV administration, vinblastine is rapidly cleared from the plasma and concentrated in various tissues. The apparent volume of distribution for the central compartment is quite large (3 to 4 times the blood volume). Vincristine and vindesine approximate total body water in their distributions. There is a triphasic vinblastine elimination pattern, with average half-lives of 3.7 minutes, 1.6 hours, and 24.8 hours, respectively (548). The drug also localizes in platelet and leukocyte fractions of whole blood (549). A radiolabeled drug study showed that urinary elimination accounts for approximately 33% of the total vinblastine radioactivity, with 21% appearing in the stool, both after 72 hours (549). A large portion of the radiolabel was retained in the body: 73% remained at 6 days after dosing. Apparently, insufficient amounts of the drug pass the blood-brain barrier to produce an effective concentration in the central nervous system. Vinblastine is partially metabolized in the liver. Most of the drug is, therefore, ultimately excreted intact in the bile or the urine. Toxicity may be increased if there is obstructive liver disease, and doses should be greatly reduced.

Administration and Dosage

The solution for administration is usually prepared by adding 10 mL of sodium chloride solution (which may be preserved with phenols or benzyl alcohol) to the 10-mg vial. The use of other solutions is not generally recommended. The resultant solution has a concentration of 1 mg/mL and a pH of 3.5 to 5.0. Solutions prepared with preserved sodium chloride injection may be stored in the refrigerator (protected from light) for 28 days without significant loss of potency.

Vinblastine is usually given by the IV push technique, with the total dose being delivered over approximately 1 minute. This is usually accomplished by slowly pushing the dose through the injection site of a running IV infusion. Alternatively, the drug may be given directly into the vein. If this method is followed, the double-needle technique should be used: do not use the same needle to withdraw the dose from the vial that is used for the direct injection into the vein. Vinblastine is very irritating and should not be given intramuscularly or subcutaneously. Vein patency should be checked before drug administration by flushing with a small quantity of normal saline or D₅W. After the dose has been given, the site should be flushed again to assure that all of the drug has been delivered into the vein.

Vinblastine has been given by several dosing schemes. The dose depends on the protocol being followed, condition of the patient, other drugs or irradiation being used, and individual patient response. Usually, the drug is given no more frequently than once every week. In general, the dosage range is 3.8 to 18.5 mg/m² when used in combination with other agents. Patients are customarily started at a low dose and worked up in 1.8- to 1.9-mg/m² increments, depending on the degree of resulting leukopenia (e.g., the dose should not be increased beyond the dose at which the white cell count reaches 3,000 cells/mm³) (548). The dosage ranges for the indicated use of vinblastine are 6 mg/m² IV on days 1 and 15 as part of the doxorubicin-bleomycin-vinblastine-dacarbazine regimen (Hodgkin's disease) and 0.15 mg/kg IV on days 1 and 2 as part of the cisplatin-vinblastine-bleomycin regimen (testicular cancer) (79). In gynecologic malignancies, vinblastine is only rarely used for ovarian and trophoblastic disease.

Side Effects and Toxicities

The major toxic effect of vinblastine is a dose-related bone marrow depression. This is more frequent and severe than with the close structural analog, vincristine. Dose-related leukopenia occurs with a nadir of 4 to 10 days and with recovery occurring over another 7 to 14 days. Because of the relatively predictable nadir, it may be possible to administer vinblastine cautiously as often as every 7 to 10 days. Thrombocytopenia typically occurs; however, with standard dosing regimens, serious platelet depressions are infrequent. Erythrocytes are usually only slightly depressed.

Nausea and vomiting occur rarely with vinblastine therapy and are at least partially responsive to antiemetics. Severe stomatitis is occasionally observed. Gastrointestinal symptoms, which may be related to neurotoxicity, include constipation, adynamic ileus, and abdominal pain, especially if high doses (>20 mg) are used. These side effects are rarely seen with doses of less than 10 mg. Prophylactic stool softeners may prevent constipation. Generalized muscle and tumor pain are commonly experienced by patients receiving vinblastine, especially in high doses (550).

Neurotoxicity associated with vinblastine occurs less frequently than with vincristine and usually occurs in patients on prolonged therapy or in those receiving high individual doses. Symptoms include paresthesias, peripheral neuropathy, depression, headache, malaise, jaw pain, urinary retention, tachycardia, orthostatic hypotension, or convulsions. Extravasations of vinblastine may result in local soft-tissue necrosis. Treatment with subcutaneously administered hyaluronidase is recommended (278).

Other side effects include a reversible and mild alopecia, rashes, and photosensitivity reactions. Transient hepatitis has also been reported on the continuous-infusion regimen.

There have been several reports of a Raynaud's phenomenon associated with vinblastine or bleomycin in treating testicular cancer. The reaction consists of a delayed presentation of a cold feeling in the hands with physical evidence of cyanosis (551). Ginsberg and coworkers (552) demonstrated a case of vinblastine-associated syndrome of inappropriate antidiuretic hormone (ADH) secretion, which was previously thought to occur only with vincristine.

The drug is well documented as a teratogen in humans, and as with most anticancer drugs, usage in pregnancy is strongly contraindicated (553).

Special Precautions

Avoid extravasation of vinblastine. If extravasation occurs, stop the administration of the remaining drug immediately. Dorr and Alberts (554) favor injection of a corticosteroid into the infiltration site with sodium chloride to dilute the drug. Only minor tissue damage has occurred when vinblastine extravasation was treated with 50 to 500 mg of hydrocortisone sodium succinate. This is followed by cold compresses to minimize spread of the reaction.

Liver disease may alter the elimination of vinblastine and necessitate a dosage reduction. Neurotoxicity may be more frequent in patients with underlying neurologic problems or those who are weak or cachectic at the start of treatment.

Vinblastine solution is topically irritating and has caused corneal irritation when inadvertently splashed in the eyes. Protective precautions should be used by all persons working with the drug.

Vinorelbine

Chemistry

Vinorelbine (Navelbine) is a third-generation semisynthetic vinca alkaloid that has been commercially available in the United States since 1994 for treatment of non-small cell lung cancer. Vinorelbine also appears to have significant activity in breast cancer patients (555,556) and moderate activity in patients with cervical or ovarian cancer (557,558), as well as other tumor types (559). It has a molecular formula of C₄₅H₅₄N₄O₈ · 2C₄H₆O₆ and a molecular weight of 1079.12. Vinorelbine's structure differs from that of the parent compounds, vincristine and vinblastine, in that it contains a nine-member (rather than 8-member) catharanthine ring (560). Its chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincalcoloblastine[R-(R*,R*)-2,3-dihydroxybutanedioate-(1:2)(salt)].

Mechanism of Action

Like other vinca alkaloids, vinorelbine is classified as a "spindle poison" since it interacts with tubulin, with resulting inhibition of microtubule assembly and cellular division during mitosis (561). Vinorelbine blocks cell cycle progression specifically in G₂ and M phases (189).

Drug Disposition

The pharmacokinetics of vinorelbine shows large interpatient variability and is best described by a triphasic model. Following IV administration of a 30-mg/m² dose, a peak plasma level of 1,000 ng/mL is achieved, but the plasma level declines to 100 ng/mL within 2 hours. Vinorelbine rapidly binds to platelets (78% of total dose) and plasma proteins (13.5%), and only 1.7% is available as free drug (561). The drug readily diffuses into other tissues and has a large volume of distribution (75.61 L/kg). The terminal half-life is approximately 45 hours (562).

The primary means of vinorelbine clearance appears to be hepatic metabolism. Approximately 18% and 46% is recovered

in the urine and feces, respectively; however, recovery was incomplete in pharmacokinetic studies (563,564).

Administration and Dosage

Vinorelbine is a vesicant and requires careful administration. The drug should be diluted in a syringe or IV bag to a concentration of 1.5 to 3.0 mg/mL (syringe) or 0.5 to 2 mg/mL (IV bag). When using a syringe or IV bag, vinorelbine should be diluted with dextrose (5%) or sodium chloride (0.9%). When using an IV bag, it may also be diluted with sodium chloride (0.45%), Ringer's injection, or lactated Ringer's injection. Diluted vinorelbine should be administered over 6 to 10 minutes into a side port of a free-flowing IV line closest to the IV bag. Following vinorelbine administration, the vein should be flushed with at least 75 to 125 mL of IV solution. Longer IV infusions (e.g., 20 minutes) are associated with a higher incidence of phlebitis (565).

Vinorelbine solution is incompatible with fluorouracil, mitomycin, and thiotepea. It is also incompatible with several antibiotics (including a number of cephalosporins, amphotericin B, ampicillin, piperacillin, and trimethoprim-sulfamethoxazole), acyclovir, furosemide, ganciclovir, methylprednisolone, and sodium bicarbonate (566).

Vinorelbine is generally administered at a dose of 30 mg/m² every week. This dosing schedule has been used in combination chemotherapeutic regimens; however, the recommended dosing schedule in combination with cisplatin (100 mg/m² every 4 weeks) is weekly administration of vinorelbine at a dose of 25 mg/m². Attempts to increase vinorelbine dose intensity using a daily $\times$ 3 every 21 days dosing schedule with or without G-CSF have not been successful (567,568). However, Weiss et al. (569) reported that continuous infusion of vinorelbine at doses of 8 to 10 mg/m²/day with concurrent administration of G-CSF results in a twofold increase in vinorelbine dose intensity without increasing toxicity.

Side Effects and Toxicities

The primary dose-limiting toxicity of vinorelbine is myelosuppression, chiefly granulocytopenia (36% of patients, <500 cells/mm³). A safety summary of data from North American clinical trials reported that when vinorelbine was administered at a dose of 30 mg/m²/week to patients with breast cancer and non-small cell lung cancer, 64% of patients experienced grades 3 to 4 granulocytopenia, 50% experienced grades 3 to 4 leukopenia, and 9% developed grades 3 to 4 anemia. Despite the high incidence of granulocytopenia, most events were uncomplicated and only 7% of patients required hospitalization for fever and/or infection. The death rate due to sepsis was 1% to 2%. Myelosuppression was noncumulative, and the incidence of grades 3 and 4 granulocytopenia declined during later cycles of vinorelbine therapy. The granulocyte nadir typically occurred on day 14 of treatment, with recovery of the granulocyte count within 7 days (570).

Vinorelbine therapy is frequently associated with transient increases in liver enzymes, especially alkaline phosphatase. Virtually all patients experience a rise in alkaline phosphatase, with approximately 25% developing grade 3 toxicity and an additional 2% experiencing grade 4 elevations. Increases in AST and ALT also occur in more than half of all patients. However, most patients with liver enzyme increases remain asymptomatic and do not require dose modification of vinorelbine. Total bilirubin also can be elevated: 10% of patients experience some degree of increased bilirubin, with 2% experiencing grade 4 elevation. Because of the high incidence of liver and bone metastases in the study population (breast cancer and non-small cell lung cancer patients), the proportion of these toxicities that is directly attributable to vinorelbine therapy is unknown (570).

Other common toxicities associated with vinorelbine when administered as a single agent at a dose of 30 mg/m²/week by a 20-minute IV infusion include nausea (38% overall, 2% severe), vomiting (17% overall, 2% severe), constipation (31%, 3%

severe), asthenia (29%, 5% severe), injection-site reactions (26%, 2% severe), anorexia (15%, 1% severe), diarrhea (15%, 1% severe), stomatitis (14%, 0% severe), pain (13%, 2% severe), paresthesia (13%, $<1\%$ severe), fever (11%, 1% severe), and alopecia (10%, $<1\%$ severe) (570). Vinorelbine-induced nausea and vomiting are generally mild and are readily controlled with standard antiemetic medication (570). Injection-site reactions include erythema, warmth, pain, and phlebitis. Repeated administration of vinorelbine can result in discoloration of the vein. As discussed above, shortening the injection duration to 6 to 10 minutes significantly reduces the incidence of injection-site reactions (565).

Injection-site pain and pain of unspecified etiology has been reported with administration of vinorelbine as a single agent (570). Additionally, acute tumor pain has been reported in several cancer patients who received treatment with vinorelbine plus a platinum-containing agent (either carboplatin or cisplatin) (571,572).

Pulmonary toxicity is an infrequent side effect of vinorelbine. Approximately 5% of patients experience dyspnea. Some cases of dyspnea are characterized by rapid onset during administration and resolve with bronchodilator therapy. Other cases occur usually within 1 hour of vinorelbine infusion and are characterized by life-threatening progressive dyspnea and the development of interstitial infiltrates (570,573). The coadministration of mitomycin may increase the pulmonary toxicity of vinorelbine (573).

Rare side effects of vinorelbine include pancreatitis, PPE (with prolonged infusions), paralytic ileus, and syndrome of inappropriate ADH secretion (574–577).

Special Precautions

Vinorelbine extravasation can result in severe local irritation, tissue necrosis, and phlebitis. If extravasation occurs, the injection should be halted immediately and any remaining portion of the dose should be injected into a different vein. Specific antidotes for vinorelbine extravasation have not been studied; however, vinblastine extravasation reactions may be ameliorated with the use of corticosteroid injections followed by cold compresses (554).

Drug Interactions

In that vinca alkaloids are metabolized by the cytochrome P450 3A system, coadministration of strong P450 inhibitors, such as erythromycin and ketoconazole, could potentially reduce vinorelbine clearance and increase toxicity (578,579). Doxorubicin and etoposide also are metabolized by the P450 system, and coadministration of these drugs with vinorelbine could potentially affect vinorelbine metabolism (578).

Mitomycin is known to exacerbate vinca alkaloid-induced pulmonary toxicity (580), and the combination of high-dose vinorelbine (50 mg/m² on days 1 and 21) plus mitomycin (15 mg/m² on day 1) has been associated with life-threatening acute pulmonary toxicity characterized by rapid onset of severe, progressive dyspnea and the development of bilateral interstitial infiltrates (573).

The combination of paclitaxel and vinorelbine has been associated with severe neurotoxicity including grade 4 motor neuropathy, irreversible ototoxicity, and vocal cord paresis (581,582). In one report of clinical experience in 5 patients with preexisting, mild to moderate, paclitaxel-induced sensory neuropathy, the combination of vinorelbine 25 to 30 mg/m² followed by paclitaxel 150 mg/m² by 3-hour infusion every 2 weeks resulted in severe, slowly reversing motor neuropathy in all 5 patients. Four of the 5 patients required the use of a wheelchair (581).

Special Applications

On a well-tolerated weekly dose schedule for vinorelbine, Bajetta and colleagues (583) noted 4 partial responses and one complete response in 31 patients (24 platinum-resistant, 4 platinum-sensitive, 5 with undetermined sensitivity) for an overall

response rate of 15% (95% CI of 5.1, 37.9%). A phase II trial (vinorelbine 30 mg/m² weekly infusion) in persistent or recurrent ovarian cancer found a 29% objective response rate; granulocytopenia was a dose-limiting but manageable toxicity (557). This is consistent with previous findings of a 21% response rate in the population of heavily pretreated and platinum-resistant ovarian cancer patients (583).

Molecularly Targeted Agents

Estrogen Receptor/Progesterone Receptor-targeted Agents

Anastrozole

Chemistry

Anastrozole (Arimidex) is FDA approved in 3 settings to treat postmenopausal breast cancer: 1) For the adjuvant treatment of postmenopausal patients with estrogen receptor positive (ER+) early breast cancers; 2) For the first-line treatment of postmenopausal women with ER+ or hormone receptor unknown locally advanced or metastatic breast cancer; and 3) For second-line treatment following tamoxifen therapy. It is one of many available aromatase inhibitors (AI) but is unique in that it is a nonsteroidal AI. Anastrozole is rarely associated with response in ER-negative disease. Anastrozole has been shown to have fewer side effects and a significant survival advantage compared to megestrol acetate in the treatment of postmenopausal patients with breast cancer (584). Chemically, it is 1,3-benzenediacetonitrile, α , α , α' , α' -tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). It has a molecular formula of C₁₇H₁₉N₅ and a molecular weight of 293.4.

Mechanism of Action

Anastrozole is a nonsteroidal AI that prevents the peripheral conversion of androgens (androstenedione and testosterone) to estrogens (estrone, estrone sulfate, and estradiol) (79). Anastrozole has a significant effect on serum estradiol; as low as 1 mg/day has caused estradiol levels to be undetectable (585). In patients receiving 5 and 10 mg of anastrozole, there was no effect on adrenal corticosteroids or aldosterone.

Drug Disposition

Following oral administration, anastrozole is well absorbed into the systemic circulation and not affected by food ingestion. Pharmacokinetics is linear and not affected by repeated dosing. Steady state concentration levels are achieved after approximately 7 days of treatment.

Administration and Dosage

Anastrozole is administered orally at a dose of 1 mg/day. For advanced disease, treatment should continue until disease progression.

Side Effects and Toxicities

When compared in a controlled clinical study to megestrol acetate, the principal side effect of anastrozole was diarrhea (occurred in 8.4% vs. 2.8% of patients treated with megestrol acetate). In general, it is very well tolerated, with the most frequent side effects (any grade) being asthenia (18%), nausea (18%), headache (14%), hot flashes (13.2%), and pain (10%).

Special Precautions

Anastrozole is contraindicated in pregnancy and premenopausal women as well as those who have shown a hypersensitivity to the drug or its excipients. In women with preexisting ischemic

heart disease, an increased incidence of ischemic cardiovascular events has been seen. It can also cause a decrease in bone mineral density and an elevation in serum cholesterol.

Drug Interactions

Coadministration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentrations by 27%. Estrogen-containing regimens should not be coadministered as they may diminish its pharmacologic action. The drug does not appear to alter the effect of warfarin or inhibit cytochrome P450.

Special Applications

According to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Uterine Neoplasms (586), anastrozole (as well as other AIs) is listed as a possible “substitute” for progestational agents or tamoxifen in treating “asymptomatic or low-grade metastases.” It is hypothesized that anastrozole may play a role on a molecular level in the endometrium. Most endometrial carcinomas are associated with endometrial hyperplasia and are estrogen receptor (ER) and progesterone receptor (PR) positive. In addition to ER/PR status, there is a progressive increase in the expression of the protein pS2 from normal to hyperplastic to well-differentiated carcinoma (587). Aromatase inhibition may alter the course of disease by preventing the endometrium from being exposed to estrogen. This may in turn alter the expression of the pS2 protein as there is a strong association between ER/PR expression and expression of pS2 protein (587). Aromatase activity has been demonstrated in both ER/PR-positive and ER/PR-negative endometrial carcinomas (588). Although much research is still needed, phase I and II trials have demonstrated safety and minimal activity in an unselected population of recurrent endometrial carcinoma patients (589,590). There is some evidence that it may have benefit in the treatment of endometrial hyperplasia as well as endometrial stromal sarcomas (591).

Finally, the NCCN Clinical Practice Guidelines in Oncology for Ovarian Cancer (592) reported mentions anastrozole as well as other “hormonal therapies” (593) as “potentially active.” Case reports have also noted responses in recurrent and metastatic ovarian sex cord stromal cancers such as granulosa cell tumors (594).

Letrozole

Chemistry

Letrozole (Femara) is a nonsteroidal AI that is FDA approved for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer as well as the first- and second-line treatment of advanced or metastatic breast cancer (hormone receptor positive or hormone receptor unknown). Letrozole is also used for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy. The chemical name of letrozole is 4,4'-(1H-9 1,2,4-Triazol-1-ylmethylene) dibenzonitrile, and the empirical formula is C₁₇H₁₁N₅.

Mechanism of Action

Similar to other AIs, letrozole inhibits the conversion of androgens to estrogens via the aromatase enzyme. Letrozole treatment does not increase serum follicle stimulating hormone (FSH) and as a selective gonadal steroidogenesis inhibitor, does not impact adrenal mineralocorticoid or glucocorticoid synthesis.

Drug Disposition

Letrozole is not affected by food intake, and is rapidly and completely absorbed through the gastrointestinal tract. The terminal

elimination half-life is 2 days. The major excretion route is via the kidneys. Steady-state plasma concentration is reached in 2 to 6 weeks of daily 2.5 mg dosing. These concentrations are up to 2 times higher than after a single dose. Steady state levels can be maintained for long periods of time without continuous accumulation of letrozole.

Administration and Dosage

Letrozole is administered orally at 2.5 mg per day. Letrozole can be taken at any time during the day regardless of food intake. Treatment is indicated until disease progression.

Side Effects and Toxicities

Letrozole has a more favorable toxicity profile compared to tamoxifen, with greater or equivalent efficacy in breast cancer patients (595). The most common side effects (>20%) include hot flashes and arthralgia. Bone pain, flushing, sweating, asthenia, edema, back pain, nausea, hypercholesterolemia, and dyspnea each occur in less than 20% of patients.

Special Precautions

Letrozole may cause a decrease in bone mineral density to a much greater degree than tamoxifen. Increases in serum cholesterol, as well as hepatic impairment, have also been observed with Letrozole. Since it causes fatigue, dizziness and somnolence, caution should be advised when driving or using machinery. Letrozole is contraindicated in pregnancy.

Drug Interactions

Coadministration of letrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentrations by 38%. Estrogen-containing regimens should not be coadministered as they may diminish its pharmacologic action. The drug does not appear to alter the effect of warfarin or inhibit cytochrome P450.

Special Applications

Like anastrozole, the NCCN Clinical Practice Guidelines in Oncology for Ovarian Cancer (592) mention letrozole along with other “hormonal therapies” (593) as “potentially active (596,597). Finally, the NCCN Clinical Practice Guidelines in Oncology for Uterine Neoplasms (586) lists letrozole (as well as other AIs) as a possible “substitute” for progestational agents or tamoxifen in treating “asymptomatic or low-grade metastases” from endometrioid endometrial cancers.

Medroxyprogesterone

Chemistry

The chemical name of the progestational agent medroxyprogesterone acetate (Provera) is Pregn-4-ene-3,20-dione,17-(acetyloxy)-6-methyl-, (6 α)-. Its empirical formula is C₂₄H₃₄O₄, with a molecular weight of 386.53. Medroxyprogesterone acetate (MPA) therapy is indicated for the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. MPA is also indicated with estrogen therapy for therapeutic use in women to reduce the incidence of endometrial hyperplasia. MPA is not approved as a therapeutic approach to any solid tumor.

Drug Disposition

MPA is absorbed through the gastrointestinal tract and is primarily metabolized by the liver. Maximum concentrations are reached within 2 to 4 hours after oral administration. Food intake enhances the bioavailability of MPA (C_{max} by up to 70%

and AUC up to 33% increase) but does not affect its half-life (12 to 16 hours).

Administration and Dosage

MPA is administered at 5 or 10 mg/day for endometrial hyperplasia for 12 to 14 consecutive days every month. For abnormal uterine bleeding or amenorrhea, MPA is generally administered for a shorter duration (e.g., 5 to 10 consecutive days). Patients experience withdrawal bleeding for 3 to 5 days following the treatment cycle. Medroxyprogesterone acetate is recommended to be used with 0.625 mg conjugated estrogens in women with a uterus to avoid the risk of endometrial cancer. Women without a uterus may receive estrogen without a progestin. In addition to the tablet form for oral intake, there is an intramuscular (IM) depot formulation that may permit alternative treatment regimens. The IM formulation of MPA was compared to oral megestrol acetate for the treatment of menopausal symptoms in breast cancer patients. In this short-term study, the IM formulation provided superior benefit to patients and may be an alternative to long-term oral progestin therapy (598).

Side Effects and Toxicities

Medroxyprogesterone acetate, similar to other progestins (e.g., megestrol acetate), may cause abnormal uterine bleeding, breast tenderness, or nausea. The Women’s Health Initiative (WHI) study found that estrogen plus progesterone was associated with an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (599). A memory study embedded within the WHI found that this combination may also be associated with an increased risk of developing dementia in women over the age of 65 (600). A black box warning now included on the MPA package insert recommends that estrogen/progesterone be used at the lowest possible dose for shortest duration possible for the specific treatment goals of the patient.

Special Precautions

MPA is almost exclusively metabolized in the liver, with the glucuronide conjugate metabolites being excreted in the urine. Thus, MPA should be used with extreme caution in renal insufficiency or hepatic impairment. MPA is contraindicated in women with undiagnosed genital bleeding, breast cancer, suspected estrogen- or progesterone- dependent neoplasia, active venous or arterial thrombosis, missed abortion, pregnancy, or known hypersensitivity to MPA.

Drug Interactions

No formal pharmacokinetic drug interaction studies of MPA have been performed.

Special Applications

There is some evidence that MPA can be used for endometrial hyperplasia or stage I endometrial cancer as an alternative to surgery to preserve fertility (601,602). Medroxyprogesterone acetate has also demonstrated activity when used with other agents in advanced or recurrent endometrial cancer (603,604). Along with AIs and tamoxifen, MPA and other progestational agents are listed as an option in treating recurrent or advanced endometrial cancer by the NCCN (586). The NCCN does not list MPA as an active agent in epithelial ovarian cancer.

Megestrol Acetate

Chemistry

The chemical name of megestrol acetate (Megace) is 17 α -acetyloxy-6-methylpregna-4,6-diene-3,20-dione. Similar to

MPA, it has the empirical formula $C_{24}H_{34}O_4$, and has a molecular weight of 384.51. Megestrol acetate is an FDA-approved progestin that is used for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). The precise mechanism by which megestrol acetate produces its antineoplastic effects against endometrial carcinoma is unknown. However, there is evidence to suggest a local effect as a result of the marked changes brought about by the direct instillation of progestational agents into the endometrial cavity. The antineoplastic action of megestrol acetate on carcinoma of the breast is better understood. Progestational agents like megestrol acetate modify the action of other steroid hormones and exert a direct cytotoxic effect on tumor cells. Pharmacologic doses of megestrol acetate not only decrease the number of hormone-dependent human breast cancer cells but also is capable of modifying and abolishing the stimulatory effects of estrogen on these cells. It has been suggested that progestins may inhibit cell growth in one of 2 ways: by interfering with either the stability, availability, or turnover of the estrogen receptor complex in its interaction with genes or in conjunction with the progestin receptor complex, or by interacting directly with the genome to turn off specific estrogen-responsive genes.

Drug Disposition

Megestrol acetate is primarily excreted in the urine, and oral absorption rates are variable. Duration to peak concentration ranges from 1.0 to 3.0 hours, and the plasma elimination half-life ranges from 13.0 to 104.9 hours. Steady state plasma concentrations have not yet been established.

Administration and Dosage

Megestrol acetate is supplied in 20 mg and 40 mg tablets for oral intake. Although the recommended dosage for breast cancer is 160 mg/day (40 mg q.i.d.), and for endometrial carcinoma it is 40 to 320 mg/day in divided doses, there are a wide variety of dose and schedules implemented therapeutically for precancerous conditions (e.g., Atypical Endometrial Hyperplasia [AEH]).

Side Effects and Toxicities

The side effect profiles of the progestational agents such as megestrol acetate or MPA are similar. However, weight gain is a common side effect with megestrol acetate. Thrombophlebitis and pulmonary embolism have been reported with megestrol acetate. Other toxicities include heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, glucose intolerance, alopecia, hypertension, carpal tunnel syndrome, mood changes, hot flashes, malaise, asthenia, lethargy, sweating, and rash. In general, severe toxicities with progestational agents are rare.

Special Precautions

Megestrol acetate should be used with caution in patients with a history of thromboembolic disease. Exacerbation of preexisting diabetes with increased insulin requirements has also been reported in association with the use of megestrol acetate.

Drug Interactions

Drug interactions with megestrol acetate have not been evaluated.

Special Applications

In general, progestational agents are currently used in the treatment of endometrial hyperplasia at a variety of doses and schedules. The GOG is currently investigating megestrol

acetate in trial GOG-0224 [A Randomized, Controlled Phase II Evaluation Of Megestrol (Megace®) in Different Dose and Sequence in the Treatment of Endometrial Intraepithelial Neoplasia (EIN) from a Referred Cohort of Atypical Endometrial Hyperplasia or EIN)]. GOG-0224 is designed to provide objective data toward a standard treatment regimen for the care of women with EIN or AEH in addition to understanding the actual mechanism of action of progestational agents in the endometrium.

Megestrol acetate 80 mg BID $\times$ 3 weeks, alternating with tamoxifen 20 mg BID $\times$ 3 weeks orally, has been shown by the GOG to be the most active regimen in treating advanced endometrial carcinoma (605). Among 56 eligible patients, 15 patients responded (12 complete, 3 partial), for an overall response rate of 27% (90% CI: 17% to 38%). In 8 of 15 (53%) responders, response duration exceeded 20 months. The response rate was 38% in patients with histologic grade 1 tumors ($n = 16$), 24% in those with grade 2 disease ($n = 17$), and 22% among patients with grade 3 disease ($n = 23$). Women less than or equal to 60 years ($n = 16$) appeared to have a better response rate than those >60 years ($n = 40$), 44% versus 20%. The response rate in patients with extra pelvic disease ($n = 42$) was 31% compared to 14% in those with strictly pelvic and/or vaginal disease ($n = 14$). The median progression-free survival (PFS) was 2.7 months, and the median overall survival was 14.0 months. Two patients experienced a grade 4 thromboembolic event. Additional toxicities included one of each: grade 3 gastrointestinal, grade 3 neurologic, and grade 3 genitourinary. The NCCN lists megestrol acetate as an active drug in both endometrial carcinoma (586) and epithelial ovarian cancer (606).

Tamoxifen Citrate

Chemistry

Tamoxifen citrate (Nolvadex) is a nonsteroidal agent with antiestrogenic properties. It is indicated for the treatment of metastatic breast cancer in men and women. In premenopausal women, it is an alternative to oophorectomy or ovarian irradiation. ER+ tumors are more likely to respond. Tamoxifen is also indicated as adjuvant treatment in node-positive and -negative breast cancers. Thirdly, it is indicated in women with ductal carcinoma *in situ* (DCIS) to reduce the risk of invasive carcinoma. Finally, it is approved to reduce the incidence of breast cancer among high-risk women. Tamoxifen competes with estrogen for binding sites, which explains its increased effectiveness in ER+ tumors. Chemically, tamoxifen is (Z)-2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1), and has a molecular weight of 563.62.

Mechanism of Action

Tamoxifen, like raloxifene and toremifene, is a nonsteroidal selective estrogen receptor modulator (SERM). All 3 agents are competitive inhibitors of estrogen binding to ER, and all have mixed agonist and antagonist activity, depending on the target tissue. These mixed activities have led to the redesignation of this class of compounds from “anti-estrogens” to SERMs.

SERMs provide some protection against menopausal bone loss, presumably due to their partial agonist activity. However, the increase in bone density is substantially less than that seen with estrogen. SERMs lowers the serum total and low-density lipoprotein (LDL)-cholesterol concentrations (by 12% and 19%, respectively, in one report), although they do not increase serum HDL-cholesterol. Tamoxifen’s antagonist effect is particularly prominent with respect to breast cancer. Finally, tamoxifen is an estrogen agonist in the endometrium.

Most receptors of the steroid family, with the exception of the ER, are classically viewed as “translocating receptors.” That is, they move from a principally cytoplasmic distribution in the

absence of hormone to a predominantly nuclear localization in hormone-stimulated cells. However, the ER appears to be predominantly nuclear both in the presence and absence of hormone. The ER operates as a ligand-dependent transcription factor; attachment of estrogen hormone to the ER's ligand-binding domain results in either direct binding of the ER to estrogen response elements (EREs) in the promoter of target genes or to a protein-protein interaction with coactivators at their respective promoter sites (607). Subsequently, the hormone-receptor complex is able to bind to estrogen-specific response elements that activate or repress expression of genes whose protein products are responsible for the physiologic actions of the hormone. Estrogen exerts its effect through 2 receptors, ER α and ER β . The exact function of ER α and ER β is under study, but they appear to have different biological functions, as indicated by their distinct expression patterns.

Drug Disposition

Peak plasma concentrations (average 40 ng/mL) take place approximately 5 hours after dosing. The decline in plasma concentrations is biphasic, with a terminal elimination half-life of about 6 days. Steady-state concentrations for tamoxifen are achieved in approximately 4 weeks after initiation of therapy. Tamoxifen is extensively metabolized, with N-desmethyl tamoxifen being the major metabolite. Approximately 65% of the administered dose is eliminated in the feces within 2 weeks (608).

Administration and Dosage

Tamoxifen is available in 10- and 20-mg tablets for oral administration. The recommended dosage is 20 to 40 mg/day; when the higher daily dose is prescribed, it should be divided into 2 doses of 20 mg (morning and evening).

Side Effects and Toxicities

Tamoxifen causes estrogenic changes of the vaginal and cervical squamous epithelium and increases the incidence of cervical and endometrial polyps (609). It is associated with an increased risk of uterine malignancies (endometrial adenocarcinoma and uterine sarcoma). Other serious adverse events associated with tamoxifen treatment include stroke, deep vein thrombosis, and pulmonary embolism. A discussion weighing the benefits versus the risks should take place prior to treatment with tamoxifen; however, the benefits have been determined to outweigh the risks in women who take tamoxifen to reduce the risk of breast cancer recurrence. The National Adjuvant Breast and Bowel Project (NSABP P-1) found a higher incidence of the following side effects for tamoxifen versus placebo, respectively: vaginal discharge (54.7 vs. 34%); cold sweats (21.4% vs. 14.8%); hot flashes (77.7% vs. 65.1%); night sweats (66.8% vs. 54.9%); and genital itching (47.1% vs. 38.3%) (610). Serious adverse events reported more frequently among women taking tamoxifen compared to placebo in the NSABP P-1 trial included uterine malignancy, uterine sarcoma, stroke, and pulmonary embolism.

Special Precautions

Tamoxifen is contraindicated in patients with known hypersensitivity to the drug or any of its ingredients. In the treatment of DCIS, tamoxifen is contraindicated in women who require concomitant anticoagulant therapy or in women with a history of deep-vein thrombosis or pulmonary embolus. As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with tamoxifen. Tamoxifen has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of

more severe liver abnormalities including fatty liver, cholestasis, hepatitis, and hepatic necrosis. Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen.

Drug Interactions

When tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur.

Special Applications

Some ovarian cancers express hormonal receptors, a factor supporting the investigation of tamoxifen in the treatment of ovarian malignancies (611). It has demonstrated activity in patients with platinum-refractory ovarian cancer, with response rates ranging from 13% to 17% (with some complete responses), and with durations ranging from 4.4 months to more than 5 years (611–614). In the series by Hatch and colleagues (611), patients with ovarian cancer who had complete or partial responses on tamoxifen were more likely to have an ER+ tumor (89% ER+) than those who had stable disease or progression on tamoxifen (59% had elevated ER). The favorable toxicity profile of tamoxifen makes it an ideal agent to consider in patients with refractory ovarian cancer. In addition to activity in ovarian cancer, the NCCN also lists tamoxifen as an active agent in endometrial cancer (586).

Leuprolide Acetate

Chemistry

Leuprolide acetate (Lupron) is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH), also known as Luteinizing-hormone-releasing hormone (LHRH). The analog possesses greater potency than the natural hormone. It indicated in the palliative treatment of advanced prostate cancer. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamideacetate. GnRH agonists are synthetically modeled after the natural GnRH decapeptide, with specific amino acid substitutions typically in positions 6 and 10. Other than leuprolide acetate, other agonists include: (a) Buserelin (Suprefact, Supreacor); (b) Nafarelin (Synarel) (only a single substitution at position 6); (c) Histrelin (Supprelin LA, Vantas); (d) Goserelin (Zoladex); and (e) Deslorelin (Suprelorin, Ovuplant). These medications can be administered intranasally, by injection, or by implant. Injectables have been formulated for daily, monthly, and quarterly use, and implants can last from 1 to 12 months.

Mechanism of Action

GnRH agonists do not quickly dissociate from the GnRH receptor. As a result, initially there is an increase in FSH and LH secretion (so-called “flare effect”). However after approximately 10 days a profound hypogonadal effect (i.e., decrease in FSH and LH) is achieved through receptor down-regulation by internalization of receptors. Generally, this induced and reversible hypogonadism is the therapeutic goal.

Drug Disposition

Following a single injection of 7.5 mg of leuprolide acetate (depot Lupron), the mean plasma leuprolide concentration is almost 20 ng/mL at 4 hours and 0.36 ng/mL at 4 weeks. The mean steady-state volume of distribution of leuprolide following IV bolus administration to healthy male volunteers was 27 L.

In vitro binding to human plasma proteins ranged from 43% to 49%. In healthy male volunteers, a 1-mg bolus of leuprolide administered IV revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a 2-compartment model. Following administration of depot Lupron 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent or one of its major metabolites in the urine.

Administration and Dosage

The recommended dose of depot Lupron has traditionally been 7.5 mg monthly. Other recently approved doses and schedules include 22.5 mg every 3 months, 30 mg every 4 months, and 45 mg every 6 months.

Side Effects and Toxicity

Side effects of GnRH agonists are signs and symptoms of hypogonadism, including hot flashes, headaches, and osteoporosis.

Special Precautions

Leuprolide acetate is contraindicated in individuals with known hypersensitivity to GnRH agonists or any of the excipients in Lupron. Reports of anaphylactic reactions to GnRH agonist analogs have been reported in the medical literature. Leuprolide acetate and other GnRH analogs may cause fetal harm when administered to a pregnant woman. GnRH analogs are contraindicated in women who are or may become pregnant. Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Increased risk of developing myocardial infarction, sudden cardiac death, and stroke has been reported in association with use of GnRH agonists in men.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with GnRH agonists. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by Cytochrome P-450 enzymes as noted in specific studies, and the drug is only approximately 46% bound to plasma proteins, drug interactions are not expected.

Special Applications

In gynecologic cancers, leuprolide acetate is listed as an active agent in endometrial cancer by the NCCN (586), although the results of clinical trials have been mixed (615,616).

Approximately 80% of human ovarian and endometrial cancers and 50% of breast cancers express GnRH and its receptor as part of an autocrine regulatory system (617). The classical GnRH receptor signal-transduction mechanisms, known to operate in the pituitary, are not involved in the mediation of antiproliferative effects of GnRH analogs in these cancer cells. The GnRH receptor rather interacts with the mitogenic signal transduction of growth-factor receptors and related oncogene products associated with tyrosine kinase activity via activation of a phosphotyrosine phosphatase, resulting in downregulation of cancer cell proliferation. In addition, GnRH activates nucleus factor kappaB (NFkappaB) and protects the cancer cells from apoptosis. Furthermore, GnRH induces activation of the c-Jun N-terminal kinase/activator protein-1 (JNK/AP-1) pathway independent of the known AP-1 activators, protein kinase (PKC), or mitogen activated protein kinase (MAPK/ERK) (618).

Antiangiogenesis Agents

Angiogenesis is the process by which new blood vessels are sprouted from preexisting ones. Endothelial cells must migrate,

proliferate, and assemble into tubes during this process. In normal tissues, blood vessel growth is tightly controlled by numerous angiogenesis-stimulating factors and angiogenesis-inhibiting factors. Vascular endothelial growth factor (VEGF), angiopoietin, and platelet-derived endothelial-cell growth factor (PD-ECGF) are 3 of the most extensively studied growth factors that appear to function primarily as angiogenesis-stimulating factors. Other growth factors and cytokines, such as basic fibroblast growth factor (bFGF), have multiple functions in addition to angiogenesis stimulation (619). Naturally occurring factors that suppress angiogenesis include angiostatin, endostatin, interferon- α , interferon- β , interferon- γ , interleukin-1, interleukin-12, platelet factor-4, thrombospondin-1, 1,2-methoxyestradiol, tissue inhibitor metalloproteinases (TIMPs), and, at high concentrations, tumor necrosis factor- α (620,621).

In the early 1970s, Folkman (622) pioneered the study of tumor angiogenesis with his observation that the growth of tumor nodules to a diameter of greater than 1 to 2 mm required neovascularization of the tumor. He hypothesized that pharmacologic suppression of tumor angiogenesis could induce tumor dormancy. Further research has shown that formation of new blood vessels within tumor nodules results in an exponential increase in tumor cell growth, the transition from hyperplasia to malignancy parallels the induction of neovascularization, and tumor angiogenesis is a prerequisite for metastatic spread (619,623–625). Additionally, blood vessel density of tumors has been shown to be a potentially important prognostic factor in multiple human neoplasms, including cancers of the ovary, cervix, and endometrium (626–630).

Obviously, this is a very brief discussion of tumor angiogenesis. The reader is referred to several reviews on angiogenesis inhibition and its potential for cancer treatment (620,631–636). Several angiogenetic agents have received FDA approval for various indications and may also have potential activity in the treatment of gynecologic cancers. However, only bevacizumab has shown clear clinical benefit. The NCCN lists it as an active agent in recurrent cervical, ovarian, and endometrial cancers (586). In addition, 2 recently reported phase III trials (637,638) have led to regulatory approval of bevacizumab in the front-line treatment of ovarian cancer in many parts of the world, although it has not yet been submitted to the FDA.

Bevacizumab

Chemistry

Bevacizumab (Avastin) is a recombinant humanized monoclonal IgG1 antibody that is designed to inhibit angiogenesis through targeting the human vascular endothelial growth factor (VEGF). Bevacizumab is FDA approved for treatment for first- or second-line metastatic colorectal cancer in combination with 5-FU-based chemotherapy; for first-line treatment of unresectable, locally advanced, recurrent or metastatic nonsquamous non-small cell lung cancer (NSCLC) with carboplatin and paclitaxel; for treatment of glioblastoma with progressive disease following front-line therapy; and for treatment of metastatic renal cell carcinoma with interferon- α . Ovarian, endometrial, and cervical cancers have been shown to express VEGF-A (639–642). Early trials showed promising results in refractory ovarian cancer and heavily pretreated cervical cancer patients (643–645). In addition to the 2 large randomized trials demonstrating efficacy in frontline ovarian cancer mentioned above, a study in platinum-sensitive disease in combination with carboplatin and gemcitabine also met its primary endpoint of improving time to progression (646) (HR, 0.484; 95% CI, 0.388 to 0.605; log-rank $p < 0.0001$).

Mechanism of Action

The immediate mechanism of action of bevacizumab is to bind and inactivate VEGF, thereby inhibiting endothelial cell activation

and proliferation. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Though the inhibition of tumor angiogenesis was originally thought to simply deny a tumor nutrients and oxygen, VEGF inhibition has also been shown to induce so-called vascular normalization, a restoration of normal structure, function, and flow to the disorganized, leaky vessels characteristic of malignant tumors, which improves the delivery of oxygen, nutrients, and cytotoxic chemotherapy to the tumor. Because VEGF also plays an important role in normal physiologic processes—such as fetal development, stabilization of damaged endothelia, and wound healing—VEGF inhibition carries a unique toxicity profile that involves normal tissues, tumor tissues, and the interface of them both. Despite uncertainty regarding these toxicities, the need for novel antitumor agents was an overriding force for the clinical investigation of bevacizumab.

Drug Disposition

According to the package insert, “The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of bevacizumab weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11 to 50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8. The clearance of bevacizumab varied depending on body weight, gender, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. There has been no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with bevacizumab as compared to females and patients with low tumor burden. The relationship between bevacizumab exposure and clinical outcomes has not been explored.”

Administration and Dosage

Bevacizumab is usually administered in gynecologic cancers at 15 mg/kg IV once every 21 days until disease progression or unacceptable toxicity. However, ICON7 (638) also showed activity of 7.5 mg/kg IV once every 21 days, and 28-day regimens generally use 10 mg/kg IV once every 14 days.

Side Effects and Toxicities

The most common serious (grade 3 to 4) side effects of bevacizumab treatment include asthenia, pain, hypertension, diarrhea, and leucopenia. Bevacizumab has been associated with gastrointestinal perforation (647), wound healing complications, and hemorrhage. Hemorrhage was specifically pronounced among patients with recent hemoptysis; therefore, these patients should not receive bevacizumab. Patients receiving bevacizumab therapy have also demonstrated an increase in hypertension, proteinuria, and congestive heart failure. It is recommended that bevacizumab therapy be delayed at least 28 days following any major surgical procedure. The safety of bevacizumab in patients with cardiovascular disease is limited. The management of

bevacizumab-associated toxicities in ovarian cancer have been recently reviewed by Randall and Monk (648).

Special Precautions

The warnings and precautions include the following:

- Nongastrointestinal fistula formation: Discontinue bevacizumab if fistula formation occurs.
- Arterial thromboembolic events (ATE) (e.g., myocardial infarction, cerebral infarction): Discontinue bevacizumab for severe ATEs.
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend bevacizumab if not medically controlled. Discontinue bevacizumab for hypertensive crisis or hypertensive encephalopathy.
- Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue bevacizumab.
- Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Temporarily suspend bevacizumab for moderate proteinuria.
- Infusion reactions: Stop for severe infusion reactions.
- Ovarian failure: Inform females of reproductive potential of the risk of ovarian failure with bevacizumab.

Drug Interactions

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without bevacizumab. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38. In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with bevacizumab. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after 4 cycles of treatment (at day 63) than those at day 0, while patients receiving paclitaxel/carboplatin without bevacizumab had a greater paclitaxel exposure at day 63 than at day 0.

Finally, there was no difference in the mean exposure of interferon alfa administered in combination with bevacizumab when compared to interferon alfa alone.

Special Applications

Bevacizumab has clear clinical activity in ovarian, endometrial, and cervical cancers. However, anti-angiogenesis agents have also been noted to control symptomatic effusions such as malignant ascites (649) and pleural effusions (650). In fact, one case report noted the use of bevacizumab in a woman with refractory ovarian granulosa-cell carcinoma and symptomatic ascites (651).

MODULATING AGENTS/ SUPPORTIVE CARE DRUGS USED IN THE TREATMENT OF GYNECOLOGIC CANCERS

Defining approaches to improve the therapeutic index of cancer chemotherapy, such that tumor-cell kill is enhanced while toxicity to normal cells is minimized, remains a fundamental goal of cancer treatment. A major limiting factor in successful cancer therapy is the ability of the tumor to develop resistance to the drugs used for treatment. A second fundamental problem faced by the oncologist treating patients with chemotherapy is the acute and chronic toxic effects of the drugs to the normal tissues.

One approach that holds promise for the improvement of the therapeutic index is the concept of modulation, or the use of drugs with little or no cytotoxic activity to modulate the efficacy of standard anticancer drugs. Modulating agents can be divided into 3 main classes based on their ability to: (a) protect host tissue from the toxic effects of the cancer drugs; (b) potentiate anticancer drugs; and (c) reverse acquired drug resistance. In this section, we discuss agents with chemoprotective abilities used with chemotherapy in the treatment of gynecologic cancers. Agents such as erythropoiesis-stimulating agents and myeloid growth factors are discussed elsewhere. Amifostine (652) and dexrazoxane (653) are not commonly used agents in gynecologic oncology and are thus not considered.

Chemoprotective Agents

Leucovorin

Chemistry

Leucovorin, a chemically reduced derivative of folic acid, is also known as citrovorum factor or folinic acid. It was the original chemoprotective agent employed to overcome high-dose methotrexate-induced bone marrow toxicity (654,655). Leucovorin calcium tablets contain either 5 mg or 25 mg leucovorin as the calcium salt of N-[4-[(2-amino-5-formyl-1, 4, 5, 6, 7, 8-hexahydro-4-oxo-6-pteridiny]methyl] amino]benzoyl]-L-glutamic acid.

Mechanism of Action

Leucovorin can serve as a substitute for the endogenous reduced-folate cofactor (N^5 , N^{10} -methylene tetrahydrofolate) that is diminished by methotrexate. Thus, leucovorin can “rescue” cells by replenishing intracellular reduced-folate pools and preventing methotrexate toxicity via blockade of thymidine synthesis. Leucovorin acts in a dose- and time-dependent fashion and must be given within 48 hours of methotrexate in order to elicit its rescue effects.

Leucovorin is also a successful modulatory agent used clinically to potentiate the antitumor activity of 5-FU (656). Leucovorin can enhance the DNA toxicity induced by 5-FU through the formation of a stable tertiary complex of 5,10-methylene tetrahydrofolate, thymidylate synthase, and fluorodeoxyuridine monophosphate. Compared with 5-FU alone, this combination has been shown to produce higher response rates and, in some cases, longer survival for patients with metastatic gastrointestinal malignancies (657). The combination of 5-FU and leucovorin currently is being tested extensively in other malignancies, including metastatic breast cancer (658). A complete review of leucovorin as a modulating agent is beyond the scope of this chapter, and the reader is referred to a number of excellent reviews on this topic (656,659).

Drug Disposition

Both IV and intramuscular leucovorin produce rapid increases in serum concentrations of biologically active folates; these rises are sustained over time and are still detectable at 24 hours after drug administration. The bioavailability of IV and intramuscular doses are comparable based on area under the serum concentration-time curve, although for intramuscular administration, the peak concentration was lower and the time to peak concentration is longer. The initial rise in serum folate associated with IV and intramuscular dosing is represented as 5-formyltetrahydrofolate; this falls concomitantly with the appearance of 5-methyltetrahydrofolate. Oral leucovorin is 92% bioavailable compared with IV administration and produces a predictably different pattern of circulating folates, 5-methyltetrahydrofolate being the predominant form. Terminal

elimination half-life, apparent volume of distribution, and clearance of total folate were not significantly different among the 3 treatments.

Administration and Dosage

Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdoses of folic acid antagonists.

Leucovorin calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible. Leucovorin is also indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer. In advanced colorectal cancer, either of the following 2 regimens is recommended:

1. Leucovorin administered at 200 mg/m² by slow IV injection over a minimum of 3 minutes, followed by 5-fluorouracil at 370 mg/m² by IV injection.
2. Leucovorin administered at 20 mg/m² by IV injection followed by 5-fluorouracil at 425 mg/m² by IV injection. 5-Fluorouracil and leucovorin should be administered separately to avoid the formation of a precipitate. Treatment is repeated daily for 5 days. This 5-day treatment course may be repeated at 4-week (28-day) intervals for 2 courses and then repeated at 4- to 5-week (28 to 35 day) intervals provided that the patient has completely recovered from the toxic effects of the prior treatment course. In subsequent treatment courses, the dosage of 5-fluorouracil should be adjusted based on patient tolerance of the prior treatment course. The daily dosage of 5-fluorouracil should be reduced by 20% for patients who experienced moderate hematologic or gastrointestinal toxicity in the prior treatment course, and by 30% for patients who experienced severe toxicity.

Leucovorin calcium tablets are indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdoses of folic acid antagonists. Because absorption is saturable, oral administration of daily doses greater than 25 mg is not recommended.

Side Effects and Toxicity

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin *per se*.

Special Precautions

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on other established toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Drug Interactions

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin, and primidone, and increase the frequency of seizures in susceptible children.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate. Leucovorin may enhance the toxicity of fluorouracil.

Special Applications

In gynecologic cancer, leucovorin is primarily used with high-dose methotrexate for gestational trophoblastic disease (660–662).

Mesna

Mesna (Mesnex) is used clinically as a specific chemoprotective agent against bladder toxicity resulting from oxazophosphorine-based alkylating agents, such as cyclophosphamide and ifosfamide. It is sodium-2-mercaptoethane sulfonate, with the molecular formula $C_2H_5NaO_3S_2$ and a molecular weight of 164.18.

Mechanism of Action

Mesna inactivates the protein-reactive aldehyde, acrolein metabolite of ifosfamide and cyclophosphamide, which accumulates in the urinary bladder and results in dose-limiting urotoxicity (325). Plasma conversion of mesna to its inactive disulfide metabolite, dimesna, allows for the pretreatment and simultaneous administration of mesna as a urinary protector for ifosfamide and cyclophosphamide (high dose). Following renal filtration and secretion, dimesna is converted back to the active parent compound by glutathione reductase, which is subsequently delivered to the bladder. The mesna free sulfhydryl groups in the urinary bladder can directly complex to and thus neutralize acrolein, in addition to potentially blocking acrolein formation in the urinary tract (663). The metabolic characteristic of mesna should preclude any potential protection to tumors. Indeed, there is no clinical evidence that mesna coadministration with ifosfamide results in decreased antitumor activity. However, mesna has been shown to prevent the cytotoxicity of platinum agents when given simultaneously with them in *in vitro* models. As such, careful scheduling of mesna is warranted for clinical trials using ifosfamide in combination with platinum compounds. Additionally, mesna should not be given simultaneously with cisplatin.

Drug Disposition

Proper scheduling of mesna has been based on pharmacokinetic analysis, which showed that mesna and dimesna have relatively short half-lives of approximately 1 hour and that peak urinary thiol accumulation following IV or oral mesna occurs at 1 and 3 hours, respectively (664). Because the half-life of mesna is much shorter than that of acrolein, it must be administered beyond the completion of ifosfamide.

Administration and Dosage

Mesna is available for IV bolus injection (100 mg/mL) or for oral use, available as 400-mg tablets. For IV administration, it should be diluted to obtain a final concentration of 20 mg/mL. The diluted solution is stable for 24 hours at room temperature. The approved schedule for IV administration of mesna is as a bolus dose (20% of the ifosfamide dose) prior to ifosfamide and 2 additional doses 4 and 8 hours after ifosfamide treatment (390). A combination of IV and oral mesna has been used to simplify outpatient ifosfamide therapy. The oral dose of mesna is given equal to 40% of the ifosfamide dosage in 2 doses at 2 and 6 hours after ifosfamide administration, based on a 50% urinary bioavailability of oral mesna. Oral doses of 3 g/m² have been well tolerated in patients; however, nausea was observed in healthy volunteers receiving oral doses greater than 2 g/m². Goren (665) reviewed the dosing schedules and incidence of hematuria in 47 clinical studies in which oral mesna was administered to 1,986 patients who received more than 6,475 courses of ifosfamide. Compilation of the data showed that a variety of doses and schedules of oral and IV mesna were effective at preventing hemorrhagic cystitis in patients treated with a number of different ifosfamide regimens. Although an optimal dose and schedule of mesna has not been established, adequate protection

against ifosfamide-induced cystitis can be achieved using an initial IV dose of mesna that is equal to 20% of the ifosfamide dose, followed by 2 oral doses of mesna, each equal to 40% of the ifosfamide dose.

Side Effects and Toxicities

The most common side effects of mesna include headache, injection site reactions, flushing, dizziness, nausea, vomiting, flu-like symptoms, and coughing. Patients may develop hematuria (up to 6%) when administered ifosfamide plus mesna; a urine sample should be evaluated for hematuria each day prior to ifosfamide therapy.

Special Precautions

Health care providers should advise patients taking mesna to drink at least a quart of liquid a day. Patients should be informed to report if their urine has turned a pink or red color, if they vomit within 2 hours of taking oral mesna, or if they miss a dose of oral mesna.

Drug Interactions

No clinical drug studies have been conducted.

Special Applications

The superiority of mesna as a chemoprotectant against ifosfamide- and cyclophosphamide-induced bladder toxicity has been demonstrated in a number of clinical trials (390). In a comparative study of patients treated with ifosfamide at a dose of 2 g/m²/day for 5 days, only 20% of the patients treated with mesna (400 mg/m²) exhibited hematuria compared with 60% of those treated with N-acetylcysteine (NAC, 1.5 g/m²) (665). Similar results were reported by Munshi et al. (605), wherein 4.2% of patients treated with mesna developed hematuria compared with 27.9% of NAC patients. In a phase II trial of ifosfamide and mesna in patients with platinum/paclitaxel-refractory ovarian cancer, there were no documented episodes of hemorrhagic cystitis, but one patient experienced treatment-related microscopic hematuria (389).

Subcutaneous administration of mesna is also being explored as an alternative to IV and oral dosing (666). Patients with gynecologic cancers receiving ifosfamide were treated with an initial IV dose of mesna at 20% of the ifosfamide dose. A subcutaneous infusion of mesna was given approximately 30 minutes after the completion of the ifosfamide infusion. A total dose of mesna equal to 40% of the ifosfamide dose was infused at a rate of 4 mL/hr over 8 hours. The subcutaneous infusion of mesna was well tolerated, and no episodes of gross hematuria were observed.

Oprelvekin

Chemistry

Oprelvekin (Neumega) is FDA approved for the prevention of severe thrombocytopenia and to reduce the need for platelet transfusions in patients with nonmyeloid malignancies. The active ingredient is produced from *Escherichia coli* (*E. coli*) by recombinant DNA technology. This protein has a molecular mass of 19,000 daltons and is similar to native interleukin eleven (IL-11) with the exception of its lack of the amino-terminal proline residue.

Mechanism of Action

Interleukin eleven is a thrombopoietic growth factor that induces megakaryocyte maturation, resulting in increased platelet production. Platelets that develop as a result of oprelvekin therapy are morphologically and functionally similar to those produced normally.

Dosage and Administration

Oprelvekin is administered subcutaneously (to the abdomen, thigh, hip, or upper arm) at a dose of 50 $\mu\text{g/kg}$ daily. Patients with renal impairment (creatinine clearance less than 30 mL/min) should receive half the normal dose (e.g., 25 $\mu\text{g/kg}$ daily). Oprelvekin should be initiated within 24 hours of the completion of chemotherapy until the patient's platelet count is at least 50,000/ μL . Treatment generally lasts between 10 and 21 days, and is not recommended beyond 21 days.

Side Effects and Toxicities

Allergic reactions may occur with oprelvekin, and patients should be counseled to be aware of potential allergic symptoms. Treatment with oprelvekin may also cause severe fluid retention. Fluid balance should be monitored during treatment. Other serious adverse effects associated with oprelvekin treatment include cardiovascular events and anemia.

Special Precautions

In the postmarketing setting, oprelvekin has caused allergic or hypersensitivity reactions.

Drug Interactions

Most patients in trials evaluating oprelvekin were treated concomitantly with filgrastim (G-CSF) with no adverse effect of oprelvekin on the activity of G-CSF. No information is available on the clinical use of sargramostim (GM-CSF) with oprelvekin in human subjects.

Special Applications

The primary use of oprelvekin in gynecologic cancer is in the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy. Efficacy has been demonstrated in patients who have experienced severe thrombocytopenia following the previous chemotherapy cycle. Oprelvekin should only be used when the value of chemotherapy dose intensity is clear since dose reduction is another effective strategy of reducing thrombocytopenia in subsequent chemotherapy cycles.

Inhibitors of poly(ADP-ribose) polymerase

Introduction

Poly(ADP-ribose)polymerase-1 (PARP-1) is an enzyme that has several biological roles, one of the most important being its role in the repair of DNA single-strand breaks. There are 17 isoforms of PARP. PARP-2 has a similar function to PARP-1. Tankyrases, involved in telomerase activity, are also PARP isoforms. The functions of many of the isoforms are incompletely understood. All of the PARP inhibitors in development have been designed as inhibitors of PARP-1, although they cross-react to varying degrees with other PARP family members (667).

PARP-1 is activated by DNA single-strand breaks. It uses NAD as a substrate and forms polymers of ADP-ribose attached to histone proteins. These are negatively charged and displace the histone proteins from the DNA backbone, permitting access for specific repair enzymes (668). PARP-1 inhibitors therefore inhibit single-strand break repair and thus have potential applications in cancer therapy. Firstly, they may potentiate the activity of drugs that act by causing DNA damage, and secondly, they have activity as single agents in tumors with specific DNA repair defects.

No PARP inhibitors are currently licensed at the time of writing. However, at least nine have been studied in clinical trials

and several are advanced in clinical development and are showing significant activity in ovarian cancers arising in *BRCA1* and *BRCA2* mutation carriers.

Chemistry

All the PARP inhibitors currently in clinical development mimic the nicotinamide moiety of NAD. A common structural feature retains the 3-carboxamide substituent of the benzamide portion of the molecule in the *sin* configuration, which is optimal for binding to the active site (669). Compounds currently in clinical development include olaparib, veliparib, rucaparib, and BMN 673. Another compound, iniparib, showed early promise in a randomized phase II trial in triple negative breast cancer (670). However, this result was not confirmed in a subsequent phase III study (671). Although this compound seems to have some activity, both anecdotally in *BRCA*-related pancreatic cancer (672) and on subset analysis in combination in triple negatives breast cancer (673), it seems that it is probably not acting as a PARP inhibitor (674,675) and is therefore not included in the following discussion.

Mechanism of Action

There are 2 potential mechanisms of action of PARP inhibitors. They may be used in combination with DNA damaging agents (drugs or radiotherapy) to potentiate their effects or they may be used as single agents in patients whose tumors are deficient in the ability to undertake homologous recombination repair.

In experimental systems, PARP inhibitors have been shown in particular to potentiate monofunctional alkylating agents and topoisomerase I inhibitors (676). Also, they are effective at potentiating radiotherapy (677).

The role of PARP inhibitors that has generated the most interest is in their single-agent activity in familial breast and ovarian cancers. Two simultaneous publications from independent research groups showed that cell lines with a homozygous deletion of *BRCA1* (678) or *BRCA2* (678,679) were exquisitely sensitive to PARP inhibitors. The IC₅₀s for the lines with a homozygous deletion were hundreds to thousands of times lower than the IC₅₀s for the heterozygote or wild-type. Since *BRCA1*- and *BRCA2*-related cancers arising in mutation carriers have lost the function of both alleles of the relevant gene, while their normal tissues are heterozygous, this suggests that PARP inhibitors should show therapeutic activity in this setting.

The selective toxicity towards the *BRCA*-nonfunctional tumors is due to a phenomenon known as selective lethality, whereby 2 individual biochemical lesions will not be individually toxic, but the combination is lethal to the cell. The *BRCA1* and *BRCA2* proteins are both involved in a form of DNA double strand break repair known as homologous recombination repair (HR). DNA double-strand breaks are repaired in an error-free manner by reference to the opposite double strand existing in the G2 phase of the cell cycle. *BRCA1/2* mutation carriers have one functional and one nonfunctional allele and can therefore carry out HR. However, the tumors they develop have lost the function of the second allele and are therefore HR deficient. PARP inhibitors prevent the repair of sporadically occurring single strand breaks and lead to an accumulation of single-strand breaks. When DNA replication takes place, these single-strand breaks are converted to double-strand breaks. In normal tissues, these are repaired by HR so PARP inhibitors are not particularly toxic. However, in the tumor arising in a *BRCA1/2* carrier HR is deficient, so the double strand breaks persist, leading to cell death. For a more detailed explanation, see reference 668.

Clinical Summary

PARP inhibitors have generally shown little or mild toxicity when given as single agents. The phase I study of rucaparib

showed no evidence of toxicity from the PARP inhibitor at doses that were capable of inducing significant inhibition of PARP in peripheral blood mononuclear cells and tumor biopsies (680). In a phase I trial of olaparib, doses were escalated to toxicity (681). Dose limiting toxicities occurred in 3 patients and were mood alteration, somnolence, and myelosuppression.

When PARP inhibitors have been used in combination with cytotoxic chemotherapy, there has been a marked potentiation of the myelosuppression induced by the chemotherapy; this is consistent in all the reported studies and exemplified by (682). Owing to this, at the time of writing, the clinical value of such combinations has not been established.

The most remarkable clinical results obtained to date results are those in patients with *BRCA1/2*-related cancers treated with olaparib. Phase II studies of olaparib have shown response rates of 41% in breast cancer (683) and 33% in ovarian cancer (684), both groups of patients having advanced, pretreated disease. High response rates have also been observed in relapsed serous ovarian cancer patients and in patients who are not carriers of a germline *BRCA* mutation (685). This is thought to be because the tumor has an acquired HR deficit, making it respond in the same way as one with an HR deficit resulting from a *BRCA1/2* mutation. The activity of PARP inhibitors in high-grade serous ovarian cancer has been further demonstrated by a randomized phase II maintenance study conducted in patients who received 2 or more platinum-based regimens and had a partial or complete response to their most recent platinum-based regimen. There was a significant improvement in progression-free survival from 4.8 to 8.4 months (hazard ratio = 0.35, $p < 0.001$), and the improvement was observed both in patients with and without *BRCA* mutations (686).

PARP inhibitors have many potential roles in gynecological cancers, including as single agents (as described above), to potentiate other drugs (especially platinum), and as potentiators of radiotherapy. These applications are currently an area of active clinical exploration.

Eribulin

Chemistry

Eribulin is a synthetic derivative of the natural product Halichondrin B, a product originally isolated from a marine sponge. It acts as a microtubule dynamics inhibitor. The chemical name for eribulin mesylate (the injectable form) is 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9H,15H-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4H)-one, 2-[(2S)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2R,3R,3aS,7R,8aS,9S,10aR,11S,12R,13aR,13bS,15S,18S,21S,24S,26R,28R,29aS)-, methanesulfonate (salt). It has a molecular weight of 826.0 (729.9 for free base). The empirical formula is $C_{40}H_{59}NO_{11} \cdot CH_4O_3S$.

Mechanism of Action

Eribulin binds to tubulin and sequesters it into nonproductive aggregates, thereby inhibiting mitosis and causing a G2/M cell cycle block.

Drug Disposition

Eribulin is administered intravenously. The majority of the dose is excreted unchanged in the feces, with only approximately 9% in the urine. There is little metabolism, with approximately 90% of the drug being excreted unchanged. The volume of distribution is approximately 40 L and the half-life about 40 hours.

Dosage

The recommended dose of eribulin for patients with normal hepatic function is 1.4 mg/m² administered intravenously over 2 to 5 minutes on days 1 and 8 of a 21-day cycle. Dose reductions to 0.7 mg/m² are recommended for patients with mild hepatic impairment and to 1.1 mg/m² for patients with moderate renal impairment.

Further dose reductions are recommended according to the level of myelosuppression encountered during treatment.

Side Effects and Toxicities

The dose-limiting toxicity of eribulin is myelosuppression. Peripheral neuropathy also occurs. In one study, grade 3 was seen in 8% (40/503) of patients and grade IV in 0.4% (2/503). This side effect is probably less frequent than with the taxanes (paclitaxel and docetaxel). QT prolongation has also been reported. Other adverse events that have been reported in greater than 10% of patients include asthenia, constipation, diarrhea, nausea, and vomiting.

Drug Interactions

As noted above there is little CYP mediated metabolism of eribulin and no significant drug interactions are expected [H71].

Clinical Summary

Eribulin is licensed for the third-line treatment of metastatic breast cancer. A randomized trial of eribulin versus single-agent therapy (chosen before randomization) showed an overall benefit of 2.6 months (10.6 ± 1.4 vs. 13.2 ± 1.1).

There are few data concerning its use in gynecological tumors. A phase II study in ovarian cancer enrolled 37 platinum-sensitive and 37 platinum-resistant patients and showed response rates of 5.5% and 19%, respectively [H72].

Ixabepilone

Chemistry

Ixabepilone is a semi-synthetic epothilone microtubule inhibitor. Epothilone is a natural product isolated from a myxobacterium, *Sorangium cellulosum*. Ixabepilone is modified by replacing the naturally occurring lactone in the macrocycle by a lactam, indented to reduce the rate of metabolism of the ring. The chemical name for ixabepilone is (1S,3S,7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione, and it has a molecular weight of 506.7.

Mechanism of Action

Ixabepilone stabilizes $\alpha\beta$ -II and $\alpha\beta$ -III microtubules, leading to the death of proliferating cells via a block in the mitotic phase of the cell cycle. Ixabepilone has a low affinity for the efflux pump proteins MRP1 and P-glycoprotein, which are known causes of resistance to taxanes. It is also active in human tumor xenografts that over-express β III tubulin isoforms or have tubulin mutations conferring resistance to taxanes. Further, it is active in human tumor xenograft models that are resistant to other commonly used anticancer drugs such as anthracyclines and vinca alkaloids [H73].

Drug Disposition

Following IV injection of ixabepilone, the mean volume of distribution has been reported as in excess of 1,000 L, indicating a very high tissue distribution [H73]. The clearance has been

reported as 475 ± 247 mL/min/m², the half-life at 14 hours [H74]. Plasma protein binding was in the region of 67% to 77% [H73]. Ixabepilone is eliminated primarily as the metabolized drug in the feces. Approximately 86% of an administered dose was eliminated in 7 days, with 65% of the dose in the feces and 21% of the dose in the urine. Unchanged ixabepilone was 1.6% and 5.6% of the recovered dose, respectively. Ixabepilone is extensively metabolized in the liver, and studies with human liver microsomes suggest that CYP3A4 is the primary route [H73].

Dosage

The recommended dosage of ixabepilone is 40 mg/m² administered intravenously over 3 hours every 3 weeks. Dose adjustments are recommended for hematological and neurological toxicities. One of the license indications for ixabepilone is for use in combination with capecitabine (see below). Ixabepilone with capecitabine is contraindicated in patients with AST or ALT $>2.5 \times$ ULN or bilirubin $>1 \times$ ULN due to increased risk of toxicity and neutropenia-related death [H73].

In order to minimize the chance of hypersensitivity reactions, it is recommended that all patients receive premedication with a H1 and H2 inhibitor. Patients who experience a hypersensitivity reaction should receive treatment with corticosteroids.

Side Effects and Toxicities

Dose-dependent myelosuppression can occur, with grade 4 neutropenia reported in 36% of patients. Myelosuppression is more severe in patients with hepatic impairment. Peripheral neuropathy

is common and has been reported in approximately 65% of patients treated, with 14% to 21% being grade 3/4.

Drug Interactions

Drug interactions are to be expected with other drugs that are metabolized by (e.g., ketoconazole) or induce (e.g., rifampin) CYP3A4. These 2 drugs have been shown to increase and decrease the exposure to ixabepilone by +79% and -43%, respectively. It is recommended that strong inhibitors or inducers of CYP3A4 are avoided where possible, and dose modifications are considered when any strong or weak inducer of inhibitor is used [H73].

Clinical Summary

Ixabepilone is licensed for use as monotherapy for the treatment of metastatic or locally advanced breast cancer after the failure of an anthracycline, a taxane and capecitabine, or in combination with capecitabine after the failure of an anthracycline and a taxane.

In a study of 752 patients randomized to capecitabine or capecitabine + ixabepilone, the progression-free survival increased from 4.1 months (3.1 to 4.3) to 5.7 months (4.8 to 6.7), $p < 0.0001$ [H73].

A phase II study of 51 patients with taxane and platinum-resistant ovarian cancer had an overall response rate of 14.3%, with 3 complete and 4 partial responses [H75].

A phase II trial in 52 patients with pretreated endometrial cancer documented one partial response [H76].

REFERENCES

1. Tozer N. Pharmacokinetics concepts basic to cancer chemotherapy. In: Ames MM, Powis G, Covach JS, eds. *Pharmacokinetics of Anti-Cancer Agents in Humans*. New York, NY: Elsevier; 1983.
2. Collins JM, Dedrick RL. Pharmacokinetics of anticancer drugs. In: Chabner B ed. *Pharmacologic Principles of Cancer Treatment*. Philadelphia, PA: WB Saunders; 1982:73.
3. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *New Engl J Med*. 1996;335:1950–1955.
4. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354(1):34–43.
5. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol*. 2001;19(4):1001–1007.
6. Hess LM, Benham-Hutchins M, Herzog TJ, et al. A meta-analysis of the efficacy of intraperitoneal cisplatin for the front-line treatment of ovarian cancer. *Int J Gynecol Cancer*. 2007;17(3):561–570.
7. Armstrong DK, Bundy B, Baergen R, et al. Randomized phase III study of intravenous (IV) paclitaxel and cisplatin versus IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial (GOG 172). *Proc Am Soc Clin Oncol*. 2002;21:201a (abstr 803).
8. Wenzel LB, Huang HQ, Armstrong DK, et al. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007;25(4):437–443.
9. Omura G, Blessing JA, Ehrlich CE, et al. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group Study. *Cancer*. 1986;57(9):1725–1730.
10. Markman M. Intraperitoneal therapy of ovarian cancer. *Semin Oncol*. 1998;25(3):356–360.
11. Markman M, Hakes T, Reichman B, et al. Phase II trial of weekly or biweekly intraperitoneal mitoxantrone in epithelial ovarian cancer. *J Clin Oncol*. 1991;9(6):978–982.
12. Deppe G, Malviya VK, Boike G, et al. Intraperitoneal doxorubicin in combination with systemic cisplatin and cyclophosphamide in the treatment of stage III ovarian cancer. *Eur J Gynaecol Oncol*. 1991;12(2):93–97.
13. Frasci G, Tortorello A, Facchini G, et al. Intraperitoneal (ip) cisplatin-mitoxantrone-interferon-alpha 2b in ovarian cancer patients with minimal residual disease. *Gynecol Oncol*. 1993;50(1):60–67.
14. Muggia FM. New and emerging intraperitoneal (IP) drugs for ovarian cancer treatment. *Semin Oncol*. 2006;33(6 Suppl. 12):S18–S24.
15. Markman M, Rowinsky E, Hakes T, et al. Phase I trial of intraperitoneal taxol: a Gynecologic Oncology Group study. *J Clin Oncol*. 1992;10(9):1485–1491.
16. Los G, Mutsaers PH, van der Vijgh WJ, et al. Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res*. 1989;49(12):3380–3384.
17. Fujiwara K, Suzuki S, Ishikawa H, et al. Preliminary toxicity analysis of intraperitoneal carboplatin in combination with intravenous paclitaxel chemotherapy for patients with carcinoma of the ovary, peritoneum, or fallopian tube. *Int J Gynecol Cancer*. 2005;15(3):426–431.
18. Sugarbaker P. An overview of peritonectomy, visceral resection and perioperative chemotherapy for peritoneal surface malignancy. In: Sugarbaker P, ed. *Cytoreductive Surgery and Perioperative Chemotherapy for Peritoneal Surface Malignancy, Textbook and Video Atlas*. Woodbury, CT: Cine-Med; 2012:1–30.
19. Sugarbaker P, Van der Speeten K, Stuart O, et al. Patient- and treatment-related variables, adverse events and their statistical relationship for treatment of peritoneal metastases. In: Sugarbaker P, ed. *Cytoreductive Surgery and Perioperative Chemotherapy for Peritoneal Surface Malignancy, Textbook and Video Atlas*. Woodbury, CT: Cine-Med; 2012:183–206.
20. Esquivel J. Technology of hyperthermic intraperitoneal chemotherapy in the United States, Europe, China, Japan, and Korea. *Cancer J*. 2009;15(3):249–254.
21. Van der Speeten K, Stuart OA, Chang D, et al. Changes induced by surgical and clinical factors in the pharmacology of intraperitoneal mitomycin C in 145 patients with peritoneal carcinomatosis. *Cancer*. 2010;68(1):147–156. Epub 2010 Sep 21.
22. Sugarbaker PH, Graves T, DeBruijn EA, et al. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. *Cancer Res*. 1990;50(18):5790–5794.

23. Alexander HR, Hanna N, Pingpank JF. Clinical results of cytoreduction and HIPEC for malignant peritoneal mesothelioma. *Cancer Treat Res*. 2007; 134:343–355.
24. Richards WG, Zellos L, Bueno R, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. *J Clin Oncol*. 2006; 24(10):1561–1567.
25. Urano M, Kuroda M, Nishimura Y. For the clinical application of thermochemotherapy given at mild temperatures. *Int J Hyperthermia*. 1999; 15(2):71–77.
26. Los G, Mutsaers PH, van der Vijgh WJ, et al. Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res*. 1989;49(12):3383–3384.
27. Howell SB, Pfeifle CE, Olshen RA. Intraperitoneal chemotherapy with melphalan. *Ann Intern Med*. 1984;101(1):14–18.
28. Sugarbaker PH, Stuart OA. Pharmacokinetic and phase II study of heated intraoperative intraperitoneal melphalan. *Cancer Chemother Pharmacol*. 2007;59(2):155. Epub 2006 Nov 8.
29. Sugarbaker PH, Stuart OA, Bijelic L. Intraperitoneal gemcitabine chemotherapy treatment for patients with resected pancreatic cancer, rationale and report of early data. *Int J Surg Oncol*. 2011; Article ID 161862: 7 pages. doi:10.1155/2011/161862.
30. Elias DM, Sideris L. Pharmacokinetics of heated intraoperative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis. *Surg Oncol Clin N Am*. 2003;12(3):755–769, xiv.
31. Zylberberg B, Dormont D, Madelenat P, et al. First-line intraperitoneal cisplatin-paclitaxel and intravenous ifosfamide in Stage IIIC ovarian epithelial cancer. *Eur J Gynaecol Oncol*. 2004;25(3):327–332.
32. Van der Speeten K, Stuart OA, Mahteme H, et al. Heat targeting of perioperative intravenous ifosfamide. *Int J Surg Oncol*. 2011; Article ID 185092: 9 pages. doi:10.1155/2011/185092.
33. Van der Speeten K, Stuart OA, Mahteme H, et al. Pharmacology of perioperative 5-fluorouracil. *J Surg Oncol*. 2010;102(7):730–735.
34. Mohamed F, Sugarbaker PH. Interperitoneal taxanes. *Surgical Oncol Clin N Am*. 2003;12(3):825–833.
35. Kuh HJ, Jang SH, Wientjes MG, et al. Determinants of paclitaxel penetration and accumulation in human solid tumor. *J Pharmacol Exp Ther*. 1999;290(2):871–880.
36. Mohamed F, Sugarbaker PH. Carrier solutions for intraperitoneal chemotherapy. *Surg Oncol Clin N Am*. 2003;12(3):813–824.
37. Sugarbaker PH, Gianola FJ, Speyer JL, et al. Prospective randomized trial of intravenous v intraperitoneal 5-FU in patients with advanced primary colon or rectal cancer. *Semin Oncol*. 1985; 12(3 Suppl 4):101–111.
38. Kelsen DP, Saltz L, Cohen AM, et al. A phase I trial of immediate postoperative intraperitoneal floxuridine and leucovorin plus systemic 5-fluorouracil and levamisole after resection of high risk colon cancer. *Cancer*. 1994;74(8):2224–2233.
39. Bijelic L. Adjuvant bidirectional chemotherapy with intraperitoneal pemetrexed combined with intravenous cisplatin for diffuse malignant peritoneal mesothelioma. *Gastroenterol Res Pract* 2012 (in press).
40. Pestieau SR, Stuart OA, Sugarbaker PH. Multi-targeted antifolate (MTA): pharmacokinetics of intraperitoneal administration in a rat model. *Eur J Surg Oncol*. 2000;26(7):696–700.
41. Gradishar WJ, Tjuland N, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23(31):7794–7803.
42. Rutty CJ, Connors TA. *In vitro* studies with hexamethylmelamine. *Biochem Pharmacol*. 1977; 26(24):2385–2391.
43. Rutty CJ, Connors TA, Nguyen Hoang N, et al. *In vivo* studies with hexamethylmelamine. *Eur J Cancer*. 1978;14(6):713–720.
44. Ames MM, Powis G, Kovach JS, et al. Disposition and metabolism of pentamethylmelamine and hexamethylmelamine in rabbits and humans. *Cancer Res*. 1979;39(12):5016–5021.
45. D'Incalci M, Bolis G, Mangioni C, et al. Variable oral absorption of hexamethylmelamine in man. *Cancer Treat Rep*. 1978;62(12):2117–2119.
46. Markman M, Blessing JA, Moore D, et al. Altretamine (hexamethylmelamine) in platinum-resistant and platinum-refractory ovarian cancer: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol*. 1998;69(3):226–229.
47. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999;340(15): 1137–1143.
48. Frasci G, Comella G, Comella P, et al. Carboplatin (CBDCA)-hexamethylmelamine (HMM)-oral etoposide (VP-16) first-line treatment of ovarian cancer patients with bulky disease: a phase II study. *Gynecol Oncol*. 1995;58(1):68–73.
49. Kristensen GB, Baekelandt M, Vergote IB, et al. A phase II study of carboplatin and hexamethylmelamine as induction chemotherapy in advanced epithelial ovarian carcinoma. *Eur J Cancer*. 1995;31A(11):1778–1780.
50. Division of Cancer Treatment N. *Annual Report to the Food and Drug Administration. Hexamethylmelamine (NSC 13875;IND #954)*. Washington, DC: U.S. Government Printing Office; 1988.
51. van der Hoop RG, van der Burg ME, ten Bokkel Huinink WW, et al. Incidence of neuropathy in 395 patients with ovarian cancer treated with or without cisplatin. *Cancer*. 1990;66(8):1697–1702.
52. Keldsen N, Havsteen H, Vergote I, et al. Altretamine (hexamethylmelamine) in the treatment of platinum-resistant ovarian cancer: a phase II study. *Gynecol Oncol*. 2003;88(2):118–122.
53. Rothenberg ML, Liu PY, Wilczynski S, et al. Phase II trial of oral altretamine for consolidation of clinical complete remission in women with stage III epithelial ovarian cancer: a Southwest Oncology Group trial (SWOG-9326). *Gynecol Oncol*. 2001;82(2):317–322.
54. Bruckner HW, Cohen CJ, Feuer E, et al. Modulation and intensification of a cyclophosphamide, hexamethylmelamine, doxorubicin, and cisplatin ovarian cancer regimen. *Obstet Gynecol*. 1989; 73(3 Pt 1):349–356.
55. Edmonson JH, Wieand HS, McCormack GW. Role of hexamethylmelamine in the treatment of ovarian cancer: where is the needle in the haystack? *J Natl Cancer Inst*. 1988;80(14): 1172–1173.
56. Hainsworth JD, Jones HW 3rd, Burnett LS, et al. The role of hexamethylmelamine in the combination chemotherapy of advanced ovarian cancer: a comparison of hexamethylmelamine, cyclophosphamide, doxorubicin, and cisplatin (H-CAP) versus cyclophosphamide, doxorubicin, and cisplatin (CAP). *Am J Clin Oncol*. 1990;13(5):410–415.
57. Baker LH, Opipari MI, Wilson H, et al. Mitomycin C, vincristine, and bleomycin therapy for advanced cervical cancer. *Obstet Gynecol*. 1978; 52(2):146–150.
58. Miralbelli CK, Huang CH, Crooke ST. Role of deoxyribonucleic acid topology in altering the site/sequence specificity of cleavage of deoxyribonucleic acid by bleomycin and talisomycin. *Biochemistry*. 1983;22(2):300–306.
59. Dorr RT. Bleomycin pharmacology: mechanism of action and resistance, and clinical pharmacokinetics. *Semin Oncol*. 1992;19(2 Suppl. 5):3–8.
60. Sebt SM, Jani JP, Mistry JS, et al. Metabolic inactivation: a mechanism of human tumor resistance to bleomycin. *Cancer Res*. 1991;51(1):227–232.
61. Alberts DS, Chen HS, Liu R, et al. Bleomycin pharmacokinetics in man. I. Intravenous administration. *Cancer Chemother Pharmacol*. 1978;1(3):177–181.
62. Ostrowski MJ. Intracavitary therapy with bleomycin for the treatment of malignant pleural effusions. *J Surg Oncol Suppl*. 1989;1:7–13.
63. Ruckdeschel JC, Moores D, Lee JY, et al. Intrapleural therapy for malignant pleural effusions. A randomized comparison of bleomycin and tetracycline. *Chest*. 1991;100(6):1528–1535.
64. Crooke ST, Comis RL, Einhorn LH, et al. Effects of variations in renal function on the clinical pharmacology of bleomycin administered as an iv bolus. *Cancer Treat Rep*. 1977;61(9):1631–1636.
65. Crooke ST, Luft F, Broughton A, et al. Bleomycin serum pharmacokinetics as determined by a radioimmunoassay and a microbiologic assay in a patient with compromised renal function. *Cancer*. 1977;39(4):1430–1434.
66. Oken MM, Crooke ST, Elson MK, et al. Pharmacokinetics of bleomycin after im administration in man. *Cancer Treat Rep*. 1981;65(5–6):485–489.
67. Samuels ML, Johnson DE, Holoye PY, et al. Large-dose bleomycin therapy and pulmonary toxicity. A possible role of prior radiotherapy. *JAMA*. 1976;235(11):1117–1120.
68. Ingrassia TS 3rd, Ryu JH, Trastek VF, et al. Oxygen-exacerbated bleomycin pulmonary toxicity. *Mayo Clin Proc*. 1991;66(2):173–178.
69. Katz EJ, Andrews PA, Howell SB. The effect of DNA polymerase inhibitors on the cytotoxicity of cisplatin in human ovarian carcinoma cells. *Cancer Commun*. 1990;2(4):159–164.
70. Maher J, Daly PA. Severe bleomycin lung toxicity: reversal with high dose corticosteroids. *Thorax*. 1993;48(1):92–94.
71. Nici L, Calabresi P. Amifostine modulation of bleomycin-induced lung injury in rodents. *Semin Oncol*. 1999;26(2 Suppl. 7):28–33.
72. Nici L, Santos-Moore A, Kuhn C, et al. Modulation of bleomycin-induced pulmonary toxicity in the hamster by the antioxidant amifostine. *Cancer*. 1998;83(9):2008–2014.
73. Kerr LD, Spiera H. Scleroderma in association with the use of bleomycin: a report of 3 cases. *J Rheumatol*. 1992;19(2):294–296.
74. Haerslev T, Avnstorp C, Joergensen M. Sudden onset of adverse effects due to low-dosage bleomycin indicates an idiosyncratic reaction. *Cutis*. 1993;52(1):45–46.
75. Yee GC, Crom WR, Champion JE, et al. Cisplatin-induced changes in bleomycin elimination. *Cancer Treat Rep*. 1983;67(6):587–589.
76. Bennett WM, Pastore L, Houghton DC. Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. *Cancer Treat Rep*. 1980; 64(8–9):921–924.
77. Crooke ST, Bradner WT. Bleomycin, a review. *J Med*. 1976;7(5):333–428.
78. Gerbrecht BM. Current Canadian experience with capecitabine: partnering with patients to optimize therapy. *Cancer Nursing*. 2003;26(2):161–167.
79. Chu E, DeVita VT. *Physicians' Cancer Chemotherapy Drug Manual* 2003. Sudbury, MA: Jones and Bartlett Publishers; 2003.
80. Largillier R, Etienne-Grimaldi M-C, Formento J-L, et al. Pharmacogenetics of capecitabine in advanced breast cancer patients. *Clin Cancer Res*. 2006; 12:5496–5502.

81. Knox R, Friedlos F, Lydall D, et al. Mechanism of cytotoxicity of anticancer platinum drugs: evidence that cis-diamminedichloroplatinum(II) and cis-diammine-(1,1-cyclobutanedicarboxylato) platinum(II) differ only in the kinetics of their interaction with DNA. *Cancer Res.* 1986;46 (4 Pt 2): 1972–1979.
82. Horacek P, Drobnik J. Interaction of cis-dichlorodiammineplatinum (II) with DNA. *Biochim Biophys Acta.* 1971;254(2):341–347.
83. DeNeve W, Valeriote F, Tapazoglou E, et al. Discrepancy between cytotoxicity and DNA interstrand crosslinking of carboplatin and cisplatin in vivo. *Invest New Drugs.* 1990;8(1):17–24.
84. Micetich KC, Barnes D, Erickson LC. A comparative study of the cytotoxicity and DNA-damaging effects of cis-(diammine) (1,1-cyclobutanedicarboxylato)-platinum(II) and cis-diamminedichloroplatinum(II) on L1210 cells. *Cancer Res.* 1985;45(9):4043–4047.
85. Fichtingerschepman A, Vandijkknijnenburg H, Vanderveldevisser S, et al. Cisplatin-DNA-adducts and carboplatin-DNA-adducts—is Pt-AG the cytotoxic lesion? *Carcinogenesis.* 1995;16(10): 2447–2453.
86. Burger H, Zoumaro-Djayoon A, Boersma A, et al. Differential transport of platinum compounds by the human organic cation transporter hOCT2 (hSLC22A2). *Br J Pharmacol.* 2010; 159(4):898–908.
87. Leblanc GL, Sundseth SS, Weber GF, et al. Platinum anticancer drugs modulate P-450 messenger RNA levels and differentially alter hepatic drugs and steroid-hormone metabolism in male and female rats. *Cancer Res.* 1992;52(3):540–547.
88. Waxma D, Sundseth S, Srivastava P, et al. Gene specific oligonucleotide probes for alpha, Mu, Pi and microsomal rat glutathione s-transferases-analysis of liver transferase expression and its modulation by hepatic enzyme inducers and platinum anticancer drugs. *Cancer Res.* 1992;52(20):5797–5802.
89. Natarajan G, Malathi R, Holler E. Increased DNA binding activity of cis-1,1-cyclobutanedicarboxylatodiammineplatinum(II) (Carboplatin) in the presence of nucleophiles and human breast cancer MCF-7 cell cytoplasmic extracts: activation theory revisited. *Biochem Pharmacol.* 1999; 58(20):5797–5802.
90. Aabo K, Adams M, Adnitt P, et al. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. Advanced Ovarian Cancer Trialists' Group. *Br J Cancer.* 1998;78(11):1479–1487.
91. du Bois A, Luck HJ, Meier W, et al. Carboplatin/paclitaxel versus cisplatin/paclitaxel as first-line chemotherapy in advanced ovarian cancer: an interim analysis of a randomized phase III trial of the Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group. *Semin Oncol.* 1997;24(5 Suppl. 15):S15–S21.
92. Harrap KR. Preclinical studies identifying carboplatin as a viable cisplatin alternative. *Cancer Treat Rev.* 1985;12 Suppl. A:21–33.
93. Wilkinson R, Cox PJ, Jones M, et al. Selection of potential second generation platinum compounds. *Biochem J.* 1978;60:851.
94. Zwelling LA, Kohn KW. Mechanism of action of cis-dichlorodiammineplatinum(II). *Cancer Treat Rep.* 1979;63(9–10):1439–1444.
95. Gaver RC, George AM, Deeb G. *In vitro* stability, plasma protein binding and blood cell partitioning of 14C-carboplatin. *Cancer Chemother Pharmacol.* 1987;20(4):271–276.
96. Shea TC, Flaherty M, Elias A, et al. A phase I clinical and pharmacokinetic study of carboplatin and autologous bone marrow support. *J Clin Oncol.* 1989;7(5):651–661.
97. Van Echo DA, Egorin MJ, Whitacre MY, et al. Phase I clinical and pharmacologic trial of carboplatin daily for 5 days. *Cancer Treat Rep.* 1984;68(9):1103–1114.
98. Horwich A, Dearnaley DP, Duchesne GM, et al. Simple nontoxic treatment of advanced metastatic seminoma with carboplatin. *J Clin Oncol.* 1989;7(8):1150–1156.
99. Misset B, Escudier B, Leclercq B, et al. Acute myocardiotoxicity during 5-fluorouracil therapy. *Intensive Care Med.* 1990;16(3):210–211.
100. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol.* 1989;7(11):1748–1756.
101. Martino G, Frusciantie V, Varraso A, et al. Efficacy of 51Cr-EDTA clearance to tailor a carboplatin therapeutic regimen in ovarian cancer patients. *Anticancer Res.* 1999;19(6C): 5587–5591.
102. Cockcroft DW, Gault MH. Prediction of creatinine clearance for serum creatinine. *Nephron.* 1976;16:31.
103. Belani CP, Kearns CM, Zuhowski EG, et al. Phase I trial, including pharmacokinetic and pharmacodynamic correlations, of combination paclitaxel and carboplatin in patients with metastatic non-small-cell lung cancer. *J Clin Oncol.* 1999;17(2):676–684.
104. Calvert AH, Boddy A, Bailey NP, et al. Carboplatin in combination with paclitaxel in advanced ovarian cancer: dose determination and pharmacokinetic and pharmacodynamic interactions. *Semin Oncol.* 1995;22(5 Suppl. 12):91–98; discussion 9–100.
105. Okamoto H, Nagatomo A, Kunitoh H, et al. Prediction of carboplatin clearance calculated by patient characteristics or 24-hour creatinine clearance: a comparison of the performance of three formulae. *Cancer Chemother Pharmacol.* 1998;42(4):307–312.
106. Wright J, Boddy A, Highley M, et al. Estimation of glomerular filtration rate in cancer patients. *Br J Cancer.* 2001;84(4):452–459.
107. Goldberg P, ed. *New Creatinine Test Raises Questions about Accuracy of Carboplatin Dosing*; 2010.
108. Sorensen BT, Stromgren A, Jakobsen P, et al. Dose-toxicity relationship of carboplatin in combination with cyclophosphamide in ovarian cancer patients. *Cancer Chemother Pharmacol.* 1991;28(5):397–401.
109. Neijt JP, du Bois A. Paclitaxel/carboplatin for the initial treatment of advanced ovarian cancer. *Semin Oncol.* 1999;26(1 Suppl. 2):78–83.
110. The International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet.* 2002; 360(9332):505–515.
111. Calvert AH, Harland SJ, Newell DR, et al. Early clinical studies with cis-diammine-1,1-cyclobutanedicarboxylate platinum II. *Cancer Chemother Pharmacol.* 1982;9(3):140–147.
112. Plezia PM, Alberts DS, Kessler J, et al. Immediate termination of intractable vomiting induced by cisplatin combination chemotherapy using an intensive five-drug antiemetic regimen. *Cancer Treat Rep.* 1984;68(12):1493–1495.
113. Canetta R, Rozencweig M, Carter SK. Carboplatin: the clinical spectrum to date. *Cancer Treat Rev.* 1985;12(suppl. A):125–136.
114. Markman M, Kennedy A, Webster K, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol.* 1999;17(4):1141.
115. Shukunami K, Kurokawa T, Kawakami Y, et al. Hypersensitivity reactions to intraperitoneal administration of carboplatin in ovarian cancer: the first report of a case. *Gynecol Oncol.* 1999; 72(3):431–432.
116. Travis LB, Holowaty EJ, Bergfeldt K, et al. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med.* 1999; 340(5):351–357.
117. Stiff PJ, McKenzie RS, Alberts DS, et al. Phase I clinical and pharmacokinetic study of high-dose mitoxantrone combined with carboplatin, cyclophosphamide, and autologous bone marrow rescue: high response rate for refractory ovarian carcinoma. *J Clin Oncol.* 1994;12(1):176–183.
118. Calvert AH. A review of the pharmacokinetics and pharmacodynamics of combination carboplatin/paclitaxel. *Semin Oncol.* 1997;24(1 Suppl. 2):S2–S5–S2–90.
119. Budd GT, Ganapathi R, Adelstein DJ, et al. Randomized trial of carboplatin plus amifostine versus carboplatin alone in patients with advanced solid tumors. *Cancer.* 1997;80(6):1134–1140.
120. Korst AE, van der Sterre ML, Eeltink CM, et al. Pharmacokinetics of carboplatin with and without amifostine in patients with solid tumors. *Clin Cancer Res.* 1997;3(5):697–703.
121. Markman M, Reichman B, Hakes T, et al. Evidence supporting the superiority of intraperitoneal cisplatin compared to intraperitoneal carboplatin for salvage therapy of small-volume residual ovarian cancer. *Gynecol Oncol.* 1993; 50(1):100–104.
122. Miyagi Y, Fujiwara K, Kigawa J, et al. Intraperitoneal carboplatin infusion may be a pharmacologically more reasonable route than intravenous administration as a systemic chemotherapy. A comparative pharmacokinetic analysis of platinum using a new mathematical model after intraperitoneal vs. intravenous infusion of carboplatin—a Sankai Gynecology Study Group (SGSG) study. *Gynecol Oncol.* 2005;99(3):591–596.
123. Los G, Verdegaa EM, Mutsaers PH, et al. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. *Cancer Chemother Pharmacol.* 1991;28(3):159–165.
124. Muggia FM, Groshen S, Russell C, et al. Intraperitoneal carboplatin and etoposide for persistent epithelial ovarian cancer: analysis of results by prior sensitivity to platinum-based regimens. *Gynecol Oncol.* 1993;50(2):232–238.
125. Reed E, Ozols RF, Tarone R, et al. Platinum-DNA adducts in leukocyte DNA correlate with disease response in ovarian cancer patients receiving platinum-based chemotherapy. *Proc Natl Acad Sci USA.* 1987;84(14):5024–5028.
126. Rice JA, Crothers DM, Pinto AL, et al. The major adduct of the antitumor drug cis-diamminedichloroplatinum(II) with DNA bends the duplex by approximately equal to 40 degrees toward the major groove. *Proc Natl Acad Sci USA.* 1988;85(12):4158–4161.
127. Perez RP. Cellular and molecular determinants of cisplatin resistance. *Eur J Cancer.* 1998;34(10): 1535–1542.
128. Reed E. Platinum-DNA adduct, nucleotide excision repair and platinum based anti-cancer chemotherapy. *Cancer Treat Rev.* 1998;24(5): 331–344.
129. Steffensen KD, Waldstrom M, Jakobsen A. The relationship of platinum resistance and ERCC1 protein expression in epithelial ovarian cancer. *Int J Gynecol Cancer.* 2009;19(5):820–825.
130. Rose PG, Mossbruger K, Fusco N, et al. Gemcitabine reverses cisplatin resistance: demonstration of activity in platinum- and

- multidrug-resistant ovarian and peritoneal carcinoma. *Gynecol Oncol.* 2003;88(1):17–21.
131. Cannistra SA. Cancer of the ovary. *N Engl J Med.* 2004;351(24):2519–2529.
 132. Cass I, Baldwin RL, Varkey T, et al. Improved survival in women with BRCA-associated ovarian carcinoma. *Cancer.* 2003;97(9):2187–2195.
 133. Tan DS, Rothermundt C, Thomas K, et al. “BRCAness” syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. *J Clin Oncol.* 2008;26(34):5530–5536. Epub 2008 Oct 27.
 134. Hennessy BT, Timms KM, Carey MS, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol.* 2010;28(22):3570–3576. Epub 2010 Jul 6.
 135. Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. *J Clin Oncol.* 2010;28(22):3555–3561. Epub 2010 Jun 14.
 136. Swisher EM, Sakai W, Karlan BY, et al. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. *Cancer Res.* 2008;68(8):2581–2586.
 137. Edwards SL, Brough R, Lord CJ, et al. Resistance to therapy caused by intragenic deletion in BRCA2. *Nature.* 2008;451(7182):1111–1115. Epub 2008 Feb 10.
 138. Sakai W, Swisher EM, Karlan BY, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature.* 2008;451(7182):1116–1120. Epub 2008 Feb 10.
 139. Safaei R. Role of copper transporters in the uptake and efflux of platinum containing drugs. *Cancer Lett.* 2006;234:34–39.
 140. Lee YY, Choi CH, Do IG, et al. Prognostic value of the copper transporters, CTR1 and CTR2, in patients with ovarian carcinoma receiving platinum-based chemotherapy. *Gynecol Oncol.* 2011;122(2):361–365. Epub 2011 May 13.
 141. Gifford G, Paul J, Vasey PA, et al. The Acquisition of hMLH1 Methylation in plasma DNA after chemotherapy predicts poor survival for ovarian cancer patients. *Clin Cancer Res.* 2004;10:4420–4426.
 142. Glasspool RM, Gore M, Rustin G, et al. Randomized phase II study of decitabine in combination with carboplatin compared with carboplatin alone in patients with recurrent advanced ovarian cancer. *J Clin Oncol.* 2009;27:15s.
 143. Roodhart JM, Daenen LG, Stigter EC, et al. Mesenchymal stem cells induce resistance to chemotherapy through the release of platinum-induced fatty acids. *Cancer Cell.* 2016;20(3):370–383.
 144. DeConti RC, Toftness BR, Lange RC, et al. Clinical and pharmacological studies with cis-diamminedichloroplatinum (II). *Cancer Res.* 1973;33(6):1310–1315.
 145. Gensia Sior Pharmaceuticals. Cisplatin Package Insert. 2000.
 146. Ehninger G, Haag C, Wilms K. Die Pharmakokinetik von cis-Diamminodichloroplatin. *Tumor Diagn Ther.* 1984;5:147.
 147. Schierl R, Rohrer B, Hohnloser J. Long-term platinum excretion in patients treated with cisplatin. *Cancer Chemother Pharmacol.* 1995;36:75–78.
 148. Earhart RH. Instability of cis-dichlorodiamminoplatin in dextrose solution. *Cancer Treat Rev.* 1979;6(62):1105.
 149. Eshaque M, McKay MJ, Theophande T, et al. p-Mannitol platinum complexes. *Wadley Med Bull.* 1976;7:338.
 150. Prestayko AW, Cadiz M, Crooke ST. Incompatibility of aluminum-containing iv administration equipment with cis-dichlorodiammineplatinum(II) administration. *Cancer Treat Rep.* 1979;63(11–12):2118–2119.
 151. Hayes DM, Cvitkovic E, Golbey RB, et al. High dose cis-platinum diammine dichloride: amelioration of renal toxicity by mannitol diuresis. *Cancer.* 1977;39(4):1372–1381.
 152. Rainey JM, Alberts DS. Safe, rapid administration schedule for cis-platinum-mannitol. *Med Pediatr Oncol.* 1978;4(4):371–375.
 153. Brock J, Alberts DS. Safe, rapid administration of cisplatin in the outpatient clinic. *Cancer Treat Rep.* 1986;70(12):1409–1414.
 154. Alberts DS, Delforge A. Maximizing the delivery of intraperitoneal therapy while minimizing drug toxicity and maintaining quality of life. *Semin Oncol.* 2006;33(6 Suppl. 12):S8–S17.
 155. Alberts DS, Markman M, Muggia F, et al. Proceedings of a GOG workshop on intraperitoneal therapy for ovarian cancer. *Gynecol Oncol.* 2006;103(3):783–792.
 156. Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 2006;100(1):27–32.
 157. NCCN. NCCN Antiemesis Guidelines version 2.2006. 2006 [updated. 2006; cited 3/11/2006]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.
 158. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. *J Clin Oncol.* 1987;5(5):756–767.
 159. Bonomi P, Blessing JA, Stehman FB, et al. Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 1985;3(8):1079–1085.
 160. Gandara DR, Wold H, Perez EA, et al. Cisplatin dose intensity in non-small cell lung cancer: phase II results of a day 1 and day 8 high-dose regimen. *J Natl Cancer Inst.* 1989;81(10):790–794.
 161. Holleran WM, DeGregorio MW. Evolution of high-dose cisplatin. *Invest New Drugs.* 1988;6(2):135–142.
 162. Gonzalez-Vitale JC, Hayes DM, Cvitkovic E, et al. Acute renal failure after cis-dichlorodiammineplatinum(II) and gentamicin-cephalothin therapies. *Cancer Treat Rep.* 1978;62(5):693–698.
 163. Madias NE, Harrington JT. Platinum nephrotoxicity. *Am J Med.* 1978;65(2):307–314.
 164. Fleming S, Peppard S, Ratanatharathorn V, et al. Ototoxicity from cis-platinum in patients with stages III and IV previously untreated squamous cell cancer of the head and neck. *Am J Clin Oncol.* 1985;8(4):302–306.
 165. Alberts DS, Noel JK. Cisplatin-associated neurotoxicity: can it be prevented? *Anticancer Drugs.* 1995;6(3):369–383.
 166. Cersosimo RJ. Cisplatin neurotoxicity. *Cancer Treat Rev.* 1989;16(4):195–211.
 167. Stengs CH, Klis SF, Huizing EH, et al. Protective effects of a neurotrophic ACTH(4-9) analog on cisplatin ototoxicity in relation to the cisplatin dose: an electrocochleographic study in albino guinea pigs. *Hear Res.* 1998;124(1–2):108–117.
 168. Rose PG. Amifostine cytoprotection with chemotherapy for advanced ovarian carcinoma. *Semin Oncol.* 1996;23(4 Suppl. 8):83–89.
 169. Willox JC, McAllister EJ, Sangster G, et al. Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. *Br J Cancer.* 1986;54(1):19–23.
 170. Morrow GR, Hickok JT, Rosenthal SN. Progress in reducing nausea and emesis. Comparisons of ondansetron (Zofran), granisetron (Kyrtil), and tropisetron (Navoban). *Cancer.* 1995;76(3):343–357.
 171. Latreille J, Pater J, Johnston D, et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 1998;16(3):1174–1178.
 172. Kris MG, Gralla RJ, Tyson LB, et al. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol.* 1989;7(1):108–114.
 173. Khan A, Hill JM, Grater W, et al. Atopic hypersensitivity to cis-dichlorodiammineplatinum(II) and other platinum complexes. *Cancer Res.* 1975;35(10):2766–2770.
 174. Von Hoff DD, Slavik M, Muggia FM. Letter: Allergic reactions to cis platinum. *Lancet.* 1976;1(7950):90.
 175. Wiesenfeld M, Reinders E, Corder M, et al. Successful re-treatment with cis-dichlorodiammineplatinum(II) after apparent allergic reactions. *Cancer Treat Rep.* 1979;63(2):219–221.
 176. Abels RI. Use of recombinant human erythropoietin in the treatment of anemia in patients who have cancer. *Semin Oncol.* 1992;19(3 Suppl. 8):29–35.
 177. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med.* 1995;332(15):1004–1014.
 178. de Jonge MJ, Loos WJ, Gelderblom H, et al. Phase I pharmacologic study of oral topotecan and intravenous cisplatin: sequence-dependent hematologic side effects. *J Clin Oncol.* 2000;18(10):2104–2115.
 179. Kemp G, Rose P, Lurain J, et al. Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. *J Clin Oncol.* 1996;14(7):2101–2112.
 180. Schuchter LM, Hensley ML, Meropol NJ, et al. American Society of Clinical Oncology C, Radiotherapy Expert P. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol.* 2002;20(12):2895–2903.
 181. NCI. NCI Clinical Announcement on Intraperitoneal Chemotherapy in Ovarian Cancer. 2006 [updated 2006; cited 5/1/07]; Available from: <http://ctep.cancer.gov/highlights/ovarian.html>.
 182. Hess LM, Alberts DS. What is the role of intraperitoneal therapy in advanced ovarian cancer? *Oncology.* 2007;21(2):227–232.
 183. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999;340(15):1154–1161.
 184. Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol.* 2000;18(8):1606–1613.
 185. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med.* 1999;340(15):1144–1153.
 186. Bagley CM Jr, Bostick FW, DeVita VT Jr. Clinical pharmacology of cyclophosphamide. *Cancer Res.* 1973;33(2):226–233.

187. Struck RF, Alberts DS, Horne K, et al. Plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous versus oral administration in a randomized, crossover trial. *Cancer Res.* 1987;47(10):2723–2726.
188. Cohen JL, Jao JY, Jusko WJ. Pharmacokinetics of cyclophosphamide in man. *Br J Pharmacol.* 1971;43(3):677–680.
189. Dorr RT, von Hoff DD. *Cancer Chemotherapy Handbook*. 2nd ed. Norwalk, CT: Appleton & Lange; 1994.
190. Kerbel RS, Vitoria-Petit A, Klement G, et al. 'Accidental' anti-angiogenic drugs. Anti-oncogene directed signal transduction inhibitors and conventional chemotherapeutic agents as examples. *Eur J Cancer.* 2000;36(10):1248–1257.
191. Colleoni M, Rocca A, Sandri MT, et al. Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. *Ann Oncol.* 2002;13(1):73–80.
192. Miscoria M, Tonetto F, Deroma L, et al. Exploratory predictive and prognostic factors in advanced breast cancer treated with metronomic chemotherapy. *Anticancer Drugs.* 2012; 23:326–334.
193. Gunther M, Wagner E, Ogris M. Acrolein: unwanted side product or contribution to anti-angiogenic properties of metronomic cyclophosphamide therapy? *J Cell Mol Med.* 2008; 12(6B):2704–2716. Epub 008 Feb 4.
194. Ghiringhelli F, Menard C, Puig PE, et al. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. *Cancer Immunol Immunother.* 2007;56(5):641–648. Epub 2006 Sep 8.
195. Ge Y, Domschke C, Stoiber N, et al. Metronomic cyclophosphamide treatment in metastasized breast cancer patients: immunological effects and clinical outcome. *Cancer.* 2012;61(3):353–362. Epub 2011 Sep 14.
196. Penel N, Adenis A, Bocci G. Cyclophosphamide-based metronomic chemotherapy: after 10 years of experience, where do we stand and where are we going? *Crit Rev Oncol Hematol.* 2012;82(1): 40–50.
197. De Fronzo RA, Braine H, Colvin M, et al. Water intoxication in man after cyclophosphamide therapy. Time course and relation to drug activation. *Ann Intern Med.* 1973;78(6):861–869.
198. Topilow AA, Rothenberg SP, Cottrell TS. Interstitial pneumonia after prolonged treatment with cyclophosphamide. *Am Rev Respir Dis.* 1973; 108(1):114–117.
199. Braverman AC, Antin JH, Plappert MT, et al. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. *J Clin Oncol.* 1991; 9(7):1215–1223.
200. Connors TA, Cox PJ, Farmer PB, et al. Some studies of the active intermediates formed in the microsomal metabolism of cyclophosphamide and isophosphamide. *Biochem Pharmacol.* 1974;23(1):115–129.
201. Wiemann MC, Cummings FJ, Kaplan HG, et al. Clinical and pharmacological studies of methotrexate-minimal leucovorin rescue plus fluorouracil. *Cancer Res.* 1982;42(9):3896–3900.
202. Dorr RT, Soble MJ, Alberts DS. Interaction of cimetidine but not ranitidine with cyclophosphamide in mice. *Cancer Res.* 1986;46(4 Pt 1): 1795–1799.
203. Struck RF, Alberts DS, Plezia PM, et al. Effect of the antiulcer drug ranitidine on the pharmacokinetics and hematologic toxicity of cyclophosphamide and its cytotoxic metabolites in patients. *Proc AACR.* 1988;29:187.
204. Harris NL, Brenner DE, Anthony LB, et al. The influence of ranitidine on the pharmacokinetics and toxicity of doxorubicin in rabbits. *Cancer Chemother Pharmacol.* 1988;21(4): 323–328.
205. Homesley HD. Single-agent therapy for nonmetastatic and low-risk gestational trophoblastic disease. *J Reprod Med.* 1998;43(1):69–74.
206. Williams SD. Ovarian germ cell tumors: an update. *Semin Oncol.* 1998;25(3):407–413.
207. Schwartz HS. Some determinants of the therapeutic efficacy of actinomycin D (NSC-3053), adriamycin (NSC-123127), and daunorubicin (NSC-83142). *Cancer Chemother Rep.* 1974; 58(1):55–62.
208. Knutsen T, Mickley LA, Ried T, et al. Cytogenetic and molecular characterization of random chromosomal rearrangements activating the drug resistance gene, MDR1/P-glycoprotein, in drug-selected cell lines and patients with drug refractory ALL. *Genes Chromosomes Cancer.* 1998;23(1):44–54.
209. Tattersall MH, Sodergren JE, Dengupta SK, et al. Pharmacokinetics of actinomycin D in patients with malignant melanoma. *Clin Pharmacol Ther.* 1975;17(6):701–708.
210. Brothman AR, Davis TP, Duffy JJ, et al. Development of an antibody to actinomycin D and its application for the detection of serum levels by radioimmunoassay. *Cancer Res.* 1982;42(3): 1184–1187.
211. Blatt J, Trigg ME, Pizzo PA, et al. Tolerance to single-dose dactinomycin in combination chemotherapy for solid tumors. *Cancer Treat Rep.* 1981;65(1–2):145–147.
212. Petrilli ES, Twigg LB, Blessing JA, et al. Single-dose actinomycin-D treatment for nonmetastatic gestational trophoblastic disease. A prospective phase II trial of the Gynecologic Oncology Group. *Cancer.* 1987;60(9):2173–2176.
213. Philips RS, Schwartz HS, Sternberg SS, et al. The toxicity of actinomycin D. *Ann N Y Acad Sci.* 1970;89:348.
214. Frei E 3rd. The clinical use of actinomycin. *Cancer Chemother Rep.* 1974;58(1):49–54.
215. Cohen IJ, Loven D, Schoenfeld T, et al. Dactinomycin potentiation of radiation pneumonitis: a forgotten interaction. *Pediatr Hematol Oncol.* 1991;8(2):187–192.
216. Francis P, Schneider J, Hann L, et al. Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer. *J Clin Oncol.* 1994;12(11):2301–2308.
217. Gelmon K. The taxoids: paclitaxel and docetaxel. *Lancet.* 1994;344(8932):1267–1272.
218. Bruno R, Sanderink GJ. Pharmacokinetics and metabolism of Taxotere (docetaxel). *Cancer Surv.* 1993;17:305–313.
219. Aapro MS. Phase I and pharmacokinetic study of RP 56976 in a new ethanol-free formulation of Taxotere. *Ann Oncol.* 1992;3:208–211.
220. Von Hoff DD. The taxoids: same roots, different drugs. *Semin Oncol.* 1997;24(4 Suppl. 13): S13–S–0.
221. Maisano R, Mare M, Zavattieri M, et al. Is weekly docetaxel an active and gentle chemotherapy in the treatment of metastatic breast cancer? *Anticancer Res.* 2003;23(2C):1923–1926.
222. Stemmler HJ, Gutschow K, Sommer H, et al. Weekly docetaxel (taxotere) in patients with metastatic breast cancer. *Ann Oncol.* 2001; 12(10):1393–1398.
223. Pronk LC, Schellens JH, Planting AS, et al. Phase I and pharmacologic study of docetaxel and cisplatin in patients with advanced solid tumors. *J Clin Oncol.* 1997;15(3):1071–1079.
224. Aihara T, Kim Y, Takatsuka Y. Phase II study of weekly docetaxel in patients with metastatic breast cancer. *Ann Oncol.* 2002;13(2):286–292.
225. Beer TM, Pierce WC, Lowe BA, et al. Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. *Ann Oncol.* 2001;12(9):1273–1279.
226. Berry W, Dakhil S, Gregurich MA, et al. Phase II trial of single-agent weekly docetaxel in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. *Semin Oncol.* 2001;28(4 Suppl. 15): 8–15.
227. Burstein HJ, Manola J, Younger J, et al. Docetaxel administered on a weekly basis for metastatic breast cancer. *J Clin Oncol.* 2000; 18(6):1212–1219.
228. Graziano F, Catalano V, Baldelli AM, et al. A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. *Ann Oncol.* 2000;11(10):1263–1266.
229. Hainsworth JD, Burris HA 3rd, Billings FT 3rd, et al. Weekly docetaxel with either gemcitabine or vinorelbine as second-line treatment in patients with advanced nonsmall cell lung carcinoma: phase II trials of the Minnie Pearl Cancer Research Network. *Cancer.* 2001;92(9):2391–2398.
230. Hainsworth JD, Burris HA 3rd, Litchy S, et al. Weekly docetaxel in the treatment of elderly patients with advanced nonsmall cell lung carcinoma. A Minnie Pearl Cancer Research Network Phase II Trial. *Cancer.* 2000;89(2):328–333.
231. Lilenbaum RC, Schwartz MA, Seigel L, et al. Phase II trial of weekly docetaxel in second-line therapy for nonsmall cell lung carcinoma. *Cancer.* 2001;92(8):2158–2163.
232. Mey U, Gorschluter M, Ziske C, et al. Weekly docetaxel in patients with pretreated metastatic breast cancer: a phase II trial. *Anticancer Drugs.* 2003;14(3):233–238.
233. Stemmler HJ, Gutschow K, Sommer H, et al. Weekly docetaxel (Taxotere) in patients with metastatic breast cancer. *Ann Oncol.* 2001; 12(10):1393–1398.
234. Valerio MR, Russo A, Latteri MA, et al. Weekly docetaxel as II line therapy in non-small cell lung cancer: an interim analysis of a phase II study. *Lung Cancer.* 2001;34(suppl. 4):S31–S35.
235. Kaye SB, Piccart M, Aapro M, et al. Phase II trials of docetaxel (Taxotere) in advanced ovarian cancer—an updated overview. *Eur J Cancer.* 1997;33(13):2167–2170.
236. Wanders J, Schrijvers D, Brunsch U, et al. The EORTC-ECTG experience with acute hypersensitivity reactions (HSR) in Taxotere studies. [Abstract]. *Proc ASCO.* 1993;12:73.
237. Galindo E, Kavanagh J, Fossella F, et al. Docetaxel (Taxotere) toxicities: analysis of a single institution experience with 168 patients (623 courses). *Proc Am Soc Clin Oncol.* 1994;13:164.
238. Zimmerman GC, Keeling JH, Lowry M, et al. Prevention of docetaxel-induced erythrocytopenia with local hypothermia. *J Natl Cancer Inst.* 1994;86(7):557–558.
239. Eisenhauer EA, Vermorken JB. The taxoids. Comparative clinical pharmacology and therapeutic potential. *Drugs.* 1998;55(1):5–30.
240. Verschraegen CF, Kudelka AP, Steger M, et al. Randomized phase II study of two dose levels of docetaxel in patients with advanced epithelial ovarian cancer who have failed paclitaxel chemotherapy. *Proc ASCO.* 1997;16:381a.
241. Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic

- Oncology Group study. *Gynecol Oncol.* 2003; 88(2):130–135.
242. Henry DW. Structure-activity relationships among daunorubicin and adriamycin analogs. *Cancer Treat Rep.* 1979;63(5):845–854.
243. Hasinoff BB, Davey JP. Adriamycin and its iron(III) and copper(II) complexes. Glutathione-induced dissociation; cytochrome c oxidase inactivation and protection; binding to cardiolipin. *Biochem Pharmacol.* 1988;37(19):3663–3669.
244. Myers CE, Gianni L, Simone CB, et al. Oxidative destruction of erythrocyte ghost membranes catalyzed by the doxorubicin-iron complex. *Biochemistry.* 1982;21(8):1707–1712.
245. Di Marco A, Zunino F, Silverstrini R, et al. Interaction of some daunomycin derivatives with deoxyribonucleic acid and their biological activity. *Biochem Pharmacol.* 1971;20(6):1323–1328.
246. Painter RB. Inhibition of DNA replicon initiation by 4-nitroquinoline 1-oxide, adriamycin, and ethyleneimine. *Cancer Res.* 1978;38(12):4445–4449.
247. Driscoll JS, Hazard GF Jr, Wood HB Jr, et al. Structure-antitumor activity relationships among quinone derivatives. *Cancer Chemother Rep.* 1974;4(2):1–362.
248. Goodman J, Hochstein P. Generation of free radicals and lipid peroxidation by redox cycling of adriamycin and daunomycin. *Biochem Biophys Res Commun.* 1977;77(2):797–803.
249. Kim SH, Kim JH. Lethal effect of adriamycin on the division cycle of HeLa cells. *Cancer Res.* 1972;32(2):323–325.
250. Ritch PS, Occhipinti SJ, Cunningham RE, et al. Schedule-dependent synergism of combinations of hydroxyurea with adriamycin and 1-beta-D-arabinofuranosylcytosine with adriamycin. *Cancer Res.* 1981;41(10):3881–3884.
251. Glisson BS, Ross WE. DNA topoisomerase II: a primer on the enzyme and its unique role as a multidrug target in cancer chemotherapy. *Pharmacol Ther.* 1987;32(2):89–106.
252. Tewey KM, Chen GL, Nelson EM, et al. Intercalative antitumor drugs interfere with the breakage-reunion reaction of mammalian DNA topoisomerase II. *J Biol Chem.* 1984;259(14):9182–9187.
253. Eksborg S, Ehrsson H, Ekqvist B. Protein binding of anthraquinone glycosides, with special reference to adriamycin. *Cancer Chemother Pharmacol.* 1982;10(1):7–10.
254. Piazza E, Brogginì M, Trabattini A, et al. Adriamycin distribution in plasma and blood cells of cancer patients with altered hematocrit. *Eur J Cancer Clin Oncol.* 1981;17(10):1089–1096.
255. Benjamin RS, Riggs CE Jr, Bachur NR. Plasma pharmacokinetics of adriamycin and its metabolites in humans with normal hepatic and renal function. *Cancer Res.* 1977;37(5):1416–1420.
256. Lee YT, Chan KK, Harris PA, et al. Distribution of adriamycin in cancer patients: tissue uptakes, plasma concentration after IV and hepatic IA administration. *Cancer.* 1980;45(9):2231–2239.
257. Egan PC, Costanza ME, Dodion P, et al. Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep.* 1985;69(12):1387–1389.
258. D'Incalci M, Brogginì M, Buscaglia M, et al. Transplacental passage of doxorubicin. *Lancet.* 1983;1(8314–8315):75.
259. Karp GI, von Oeyen P, Valone F, et al. Doxorubicin in pregnancy: possible transplacental passage. *Cancer Treat Rep.* 1983;67(9):773–777.
260. Roboz J, Gleicher N, Wu K, et al. Does doxorubicin cross the placenta? *Lancet.* 1979; 2(8156–8157):1382–1383.
261. Bachur NR. Adriamycin (NSC-123127) pharmacology. *Cancer Chemother Rep.* 1975;6:153.
262. Riggs CE Jr, Benjamin RS, Serpick AA, et al. Biliary disposition of adriamycin. *Clin Pharmacol Ther.* 1977;22(2):234–241.
263. Benjamin RS. A practical approach to Adriamycin (NSC-123127). *Cancer Chemother Rep.* 1975;6:191.
264. Chan KK, Chlebowski RT, Tong M, et al. Clinical pharmacokinetics of adriamycin in hepatoma patients with cirrhosis. *Cancer Res.* 1980;40(4):1263–1268.
265. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. *J Clin Oncol.* 1988;6(8):1321–1327.
266. Gessner T, Robert J, Bolanowska W, et al. Effects of prior therapy on plasma levels of adriamycin during subsequent therapy. *J Med.* 1981;12(2–3):183–193.
267. Morris RG, Reece PA, Dale BM, et al. Alteration in doxorubicin and doxorubicinol plasma concentrations with repeated courses to patients. *Ther Drug Monit.* 1989;11(4):380–383.
268. Robert J, Hoerni B. Age dependence of the early-phase pharmacokinetics of doxorubicin. *Cancer Res.* 1983;43(9):4467–4469.
269. Garnick MB, Ensminger WD, Israel M. A clinical-pharmacological evaluation of hepatic arterial infusion of adriamycin. *Cancer Res.* 1979;39(10):4105–4110.
270. Bern MM, McDermott W Jr, Cady B, et al. Intraarterial hepatic infusion and intravenous adriamycin for treatment of hepatocellular carcinoma: a clinical and pharmacology report. *Cancer.* 1978;42(2):399–405.
271. Chen HS, Gross JF. Intra-arterial infusion of anticancer drugs: theoretic aspects of drug delivery and review of responses. *Cancer Treat Rep.* 1980;64(1):31–40.
272. Creasey WA, McIntosh LS, Brescia T, et al. Clinical effects and pharmacokinetics of different dosage schedules of adriamycin. *Cancer Res.* 1976;36(1):216–221.
273. Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. *J Clin Oncol.* 1986;4(8):1162–1170.
274. Carmo-Pereira J, Costa FO, Henriques E, et al. A comparison of two doses of adriamycin in the primary chemotherapy of disseminated breast carcinoma. *Br J Cancer.* 1987;56(4):471–473.
275. Reilly JJ, Neifeld JP, Rosenberg SA. Clinical course and management of accidental adriamycin extravasation. *Cancer.* 1977;40(5):2053–2056.
276. Rudolph R, Stein RS, Pattillo RA. Skin ulcers due to adriamycin. *Cancer.* 1976;38(3):1087–1094.
277. Dorr RT, Dordal MS, Koenig LM, et al. High levels of doxorubicin in the tissues of a patient experiencing extravasation during a 4-day infusion. *Cancer.* 1989;64(12):2462–2464.
278. Dorr RT. Antidotes to vesicant chemotherapy extravasations. *Blood Rev.* 1990;4(1):41–60.
279. Lefrak EA, Pitha J, Rosenheim S, et al. Adriamycin (NSC-123127) cardiomyopathy. *Cancer Chemother Rep.* 1975;6:203.
280. Lenaz L, Page JA. Cardiotoxicity of adriamycin and related anthracyclines. *Cancer Treat Rev.* 1976;3(3):111–120.
281. Rinehart JJ, Lewis RP, Balcerzak SP. Adriamycin cardiotoxicity in man. *Ann Intern Med.* 1974;81(4):475–478.
282. Minow RA, Benjamin RS, Gottlieb JA. Adriamycin (NSC-123127) cardiomyopathy—an overview with determinants of risk factors. *Cancer Chemother Rep.* 1975;6:195.
283. Steinherz LJ, Steinherz PG, Tan CT, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA.* 1991;266(12):1672–1677.
284. Speyer J, Wasserheit C. Strategies for reduction of anthracycline cardiac toxicity. *Semin Oncol.* 1998;25(5):525–537.
285. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* 1979;91(5):710–717.
286. Bielack SS, Erttmann R, Winkler K, et al. Doxorubicin: effect of different schedules on toxicity and anti-tumor efficacy. *Eur J Cancer Clin Oncol.* 1989;25(5):873–882.
287. Donaldson SS, Glick JM, Wilbur JR. Letter: Adriamycin activating a recall phenomenon after radiation therapy. *Ann Intern Med.* 1974; 81(3):407–408.
288. Greco FA, Brereton HD, Kent H, et al. Adriamycin and enhanced radiation reaction in normal esophagus and skin. *Ann Intern Med.* 1976; 85(3):294–298.
289. Newburger PE, Cassady JR, Jaffe N. Esophagitis due to adriamycin and radiation therapy for childhood malignancy. *Cancer.* 1978;42(2): 417–423.
290. Sarosy GA, Brown TD, Von Hoff DD, et al. Phase I study of alpha 2-interferon plus doxorubicin in patients with solid tumors. *Cancer Res.* 1986;46(10):5368–5371.
291. Kefford RF, Woods RL, Fox RM, et al. Intracavitary adriamycin nitrogen mustard and tetracycline in the control of malignant effusions: a randomized study. *Med J Aust.* 1980;2(8):447–448.
292. Markman M, Howell SB, Green MR. Combination intracavitary chemotherapy for malignant pleural disease. *Cancer Drug Deliv.* 1984;1(4): 333–336.
293. Rose PG, Blessing JA, Buller RE, et al. Prolonged oral etoposide in recurrent or advanced non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2003;89(2):267–270.
294. Keller-Juslen C, Kuhn M, Stahelin H, et al. Synthesis and antimitotic activity of glycosidic lignan derivatives related to podophyllotoxin. *J Med Chem.* 1971;14(10):936–940.
295. Misra NC, Roberts DW. Inhibition by 4'-demethyl-epipodophyllotoxin 9-(4,6-O-2-thienylidene-beta-D-glucopyranoside) of human lymphoblast cultures in G2 phase of the cell cycle. *Cancer Res.* 1975;35(1):99–105.
296. Krishan A, Paika K, Frei E III. Cytofluorometric studies on the action of podophyllotoxin and epipodophyllotoxins (VM-26, VP-16-213) on the cell cycle traverse of human lymphoblasts. *J Cell Biol.* 1975;66(3):521–530.
297. Ross W, Rowe T, Glisson B, et al. Role of topoisomerase II in mediating epipodophyllotoxin-induced DNA cleavage. *Cancer Res.* 1984;44 (12 Pt 1):5857–5860.
298. Chen AY, Liu LF. DNA topoisomerases: essential enzymes and lethal targets. *Annu Rev Pharmacol Toxicol.* 1994;34:191–218.
299. Wozniak AJ, Ross WE. DNA damage as a basis for 4'-demethylepipodophyllotoxin-9-(4,6-O-ethylidene-beta-D-glucopyranoside) (etoposide) cytotoxicity. *Cancer Res.* 1983;43(1):120–124.
300. Smith PJ, Anderson CO, Watson JV. Predominant role for DNA damage in etoposide-induced cytotoxicity and cell cycle perturbation in human SV40-transformed fibroblasts. *Cancer Res.* 1986; 46(11):5641–5645.
301. Chatterjee S, Trivedi D, Petzold SJ, et al. Mechanism of epipodophyllotoxin-induced cell death in poly(adenosine diphosphate-ribose) synthesis-deficient V79 Chinese hamster cell lines. *Cancer Res.* 1990;50(9):2713–2718.
302. Wozniak AJ, Glisson BS, Hande KR, et al. Inhibition of etoposide-induced DNA damage and

- cytotoxicity in L1210 cells by dehydrogenase inhibitors and other agents. *Cancer Res.* 1984; 44(2):626–632.
303. Allen LM, Creaven PJ. Comparison of the human pharmacokinetics of VM-26 and VP-16, two antineoplastic epipodophyllotoxin glucopyranoside derivatives. *Eur J Cancer.* 1975;11(10): 697–707.
 304. D'Incalci M, Farina P, Sessa C, et al. Pharmacokinetics of VP16-213 given by different administration methods. *Cancer Chemother Pharmacol.* 1982;7(2-3):141–145.
 305. Hande KR, Wedlund PJ, Noone RM, et al. Pharmacokinetics of high-dose etoposide (VP-16-213) administered to cancer patients. *Cancer Res.* 1984;44(1):379–382.
 306. Stewart DJ, Richard MT, Hugenholtz H, et al. Penetration of VP-16 (etoposide) into human intracerebral and extracerebral tumors. *J Neuro Oncol.* 1984;2(2):133–139.
 307. D'Incalci M, Sessa C, Rossi C, et al. Pharmacokinetics of etoposide in gestochoriocarcinoma. *Cancer Treat Rep.* 1985;69(1):69–72.
 308. Creaven PJ, Newman SJ, Selawry OS, et al. Phase I clinical trial of weekly administration of 4'-demethylepipodophyllotoxin 9-(4,6-O-ethylidene-beta-D-glucopyranoside) (NSC-141540; VP-16-213). *Cancer Chemother Rep.* 1974;58(6): 901–907.
 309. Stewart CF, Arbuck SG, Fleming RA, et al. Changes in the clearance of total and unbound etoposide in patients with liver dysfunction. *J Clin Oncol.* 1990;8(11):1874–1879.
 310. Pfluger KH, Schmidt L, Merkel M, et al. Drug monitoring of etoposide (VP16-213). Correlation of pharmacokinetic parameters to clinical and biochemical data from patients receiving etoposide. *Cancer Chemother Pharmacol.* 1987;20(1): 59–66.
 311. Smyth RD, Pfeffer M, Scalzo A, et al. Bioavailability and pharmacokinetics of etoposide (VP-16). *Semin Oncol.* 1985;12(1 Suppl. 2):48–51.
 312. Harvey VJ, Slevin ML, Joel SP, et al. The effect of food and concurrent chemotherapy on the bioavailability of oral etoposide. *Br J Cancer.* 1985;52(3):363–367.
 313. Dorr RT, Alberts DS. Skin ulceration potential without therapeutic anticancer activity for epipodophyllotoxin commercial diluents. *Invest New Drugs.* 1983;1(2):151–159.
 314. Ozols RF. Oral etoposide for the treatment of recurrent ovarian cancer. *Drugs.* 1999;58(suppl. 3):43–49.
 315. Steward WP, Thatcher N, Edmundson JM, et al. Etoposide infusions for treatment of metastatic lung cancer. *Cancer Treat Rep.* 1984;68(6): 897–899.
 316. Rose PG, Blessing JA, Mayer AR, et al. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 1998;16(2):405–410.
 317. Morris M, Brader KR, Burke TW, et al. A phase II study of prolonged oral etoposide in advanced or recurrent carcinoma of the cervix. *Gynecol Oncol.* 1998;70(2):215–218.
 318. Rose PG, Blessing JA, Lewandowski GS, et al. A phase II trial of prolonged oral etoposide (VP-16) as second-line therapy for advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1996;63(1):101–104.
 319. Rose PG, Blessing JA, Van Le L, et al. Prolonged oral etoposide in recurrent or advanced squamous cell carcinoma of the cervix: a gynecologic oncology group study. *Gynecol Oncol.* 1998; 70(2):263–266.
 320. Hande KR, Wolff SN, Greco FA, et al. Etoposide kinetics in patients with obstructive jaundice. *J Clin Oncol.* 1990;8(6):1101–1107.
 321. Rozenzweig M, Von Hoff DD, Henney JE, et al. VM 26 and VP 16-213: a comparative analysis. *Cancer.* 1977;40(1):334–342.
 322. Anonymous. Epipodophyllotoxin VP 16213 in treatment of acute leukaemias, haematosarcomas, and solid tumours. *Br Med J.* 1973;3(5873): 199–202.
 323. Dombrowsky P, Nissen NI, Larsen V. Clinical investigation of a new podophyllum derivative, epipodophyllotoxin, 4'-demethyl-9-(4,6-O-2-thenylidene-D-glucopyranoside) (NSC-122819), in patients with malignant lymphomas and solid tumors. *Cancer Chemother Rep.* 1972;56(1):71–82.
 324. Aisner J, Whitacre M, VanEcho DA, et al. Doxorubicin, Cyclophosphamide and VP16-213 (ACE) in the treatment of small cell lung cancer. *Cancer Chemother Pharmacol.* 1982; 7(2-3):187–193.
 325. Dorr RT. Chemoprotectants for cancer chemotherapy. *Semin Oncol.* 1991;18(1 Suppl. 2): 48–58.
 326. Thant M, Hawley RJ, Smith MT, et al. Possible enhancement of vincristine neuropathy by VP-16. *Cancer.* 1982;49(5):859–864.
 327. Barakat RR, Almadrone L, Venkatraman ES, et al. A phase II trial of intraperitoneal cisplatin and etoposide as consolidation therapy in patients with stage II–IV epithelial ovarian cancer following negative surgical assessment. *Gynecol Oncol.* 1998;69(1):17–22.
 328. van Rijswijk RE, Hoekman K, Burger CW, et al. Experience with intraperitoneal cisplatin and etoposide and i.v. sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. *Ann Oncol.* 1997;8(12):1235–1241.
 329. Fields KK, Elfenbein GJ, Lazarus HM, et al. Maximum-tolerated doses of ifosfamide, carboplatin, and etoposide given over 6 days followed by autologous stem-cell rescue: toxicity profile. *J Clin Oncol.* 1995;13(2):323–332.
 330. Lotz JP, Andre T, Donsimoni R, et al. High dose chemotherapy with ifosfamide, carboplatin, and etoposide combined with autologous bone marrow transplantation for the treatment of poor-prognosis germ cell tumors and metastatic trophoblastic disease in adults. *Cancer.* 1995; 75(3):874–885.
 331. Rustum YM. Biochemical rationale for the 5-fluorouracil leucovorin combination and update of clinical experience. *J Chemother* 1990; 2(suppl. 1):5–11.
 332. Collins JM, Dedrick RL, King FG, et al. Nonlinear pharmacokinetic models for 5-fluorouracil in man: intravenous and intraperitoneal routes. *Clin Pharmacol Ther.* 1980;28(2):235–246.
 333. McDermott BJ, van den Berg HW, Murphy RF. Nonlinear pharmacokinetics for the elimination of 5-fluorouracil after intravenous administration in cancer patients. *Cancer Chemother Pharmacol.* 1982;9(3):173–178.
 334. Fraile RJ, Baker LH, Buroker TR, et al. Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and by slow infusion. *Cancer Res.* 1980;40(7):2223–2228.
 335. Schaaf LJ, Dobbs BR, Edwards IR, et al. Nonlinear pharmacokinetic characteristics of 5-fluorouracil (5-FU) in colorectal cancer patients. *Eur J Clin Pharmacol.* 1987;32(4): 411–418.
 336. Yoshida T, Araki E, Iigo M, et al. Clinical significance of monitoring serum levels of 5-fluorouracil by continuous infusion in patients with advanced colonic cancer. *Cancer Chemother Pharmacol.* 1990;26(5):352–354.
 337. Floyd RA, Hornbeck CL, Byfield JE, et al. Clearance of continuously infused 5-fluorouracil in adults having lung or gastrointestinal carcinoma with or without hepatic metastases. *Drug Intell Clin Pharm.* 1982;16(9):665–667.
 338. Santini J, Milano G, Thyss A, et al. 5-FU therapeutic monitoring with dose adjustment leads to an improved therapeutic index in head and neck cancer. *Br J Cancer.* 1989;59(2):287–290.
 339. Lokich JJ, Ahlgren JD, Gullo JJ, et al. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. *J Clin Oncol.* 1989;7(4):425–432.
 340. Moertel CG. Chemotherapy of gastrointestinal cancer. *N Engl J Med.* 1978;299(19):1049–1052.
 341. Moertel CG, Schutt AJ, Reitemeier RJ, et al. A comparison of 5-fluorouracil administered by slow infusion and rapid injection. *Cancer Res.* 1972;32(12):2717–2719.
 342. Nadler SH. Oral administration of fluorouracil. A preliminary trial. *Arch Surg.* 1968; 97(4):654–656.
 343. Horton J, Olson KB, Sullivan J, et al. 5-FU in cancer: an improved regimen. *Ann Intern Med.* 1970;73:897.
 344. Jacobs EM, Reeves WJ Jr, Wood DA, et al. Treatment of cancer with weekly intravenous 5-fluorouracil. Study by the Western Cooperative Cancer Chemotherapy Group (WCCCG). *Cancer.* 1971;27(6):1302–1305.
 345. Bruckner HW, Glass LL, Chesser MR. Dose-dependent leucovorin efficacy with an intermittent high-dose 5-fluorouracil schedule. *Cancer Invest.* 1990;8(3-4):321–326.
 346. Doroshow JH, Multhaup P, Leong L, et al. Prospective randomized comparison of fluorouracil versus fluorouracil and high-dose continuous infusion leucovorin calcium for the treatment of advanced measurable colorectal cancer in patients previously unexposed to chemotherapy. *J Clin Oncol.* 1990;8(3):491–501.
 347. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol.* 1999;17(5):1339–1348.
 348. Curran CF, Luce JK. Fluorouracil and palmar-plantar erythrodysesthesia. *Ann Intern Med.* 1989;111(10):858.
 349. Lopez AM, Wallace L, Dorr RT, et al. Topical DMSO treatment for pegylated liposomal doxorubicin-induced palmar-plantar erythrodysesthesia. *Cancer Chemother Pharmacol.* 1999;44(4):303–306.
 350. Malet-Martino M, Martino R. Clinical studies of three oral prodrugs of 5-fluorouracil (capecitabine, UFT, S-1): a review. *Oncologist.* 2002;7(4):288–323.
 351. Nagore E, Insa A, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome. Incidence, recognition and management. *Am J Clin Dermatol.* 2000;1(4):225–234.
 352. Hrushesky WJ. Serpentine supravenuous 5-fluorouracil (NSC-19893) hyperpigmentation. *Cancer Treat Rep.* 1976;60(5):639.
 353. Boileau G, Piro AJ, Lahiri SR, et al. Cerebellar ataxia during 5-fluorouracil (NSC-19893) therapy. *Cancer Chemother Rep.* 1971;55(5): 595–598.

354. Gottlieb JA, Luce JK. Cerebellar ataxia with weekly 5-fluorouracil administration. *Lancet*. 1971;1(7690):138–139.
355. Cianci G, Morelli MF, Cannita K, et al. Prophylactic options in patients with 5-fluorouracil-associated cardiotoxicity. *Br J Cancer*. 2003; 88(10):1507–1509.
356. Diasio RB, Beavers TL, Carpenter JT. Familial deficiency of dihydropyrimidine dehydrogenase. Biochemical basis for familial pyrimidinemia and severe 5-fluorouracil-induced toxicity. *J Clin Invest*. 1988;81(1):47–51.
357. Lu Z, Zhang R, Diasio RB. Population characteristics of hepatic dihydropyrimidine dehydrogenase activity, a key metabolic enzyme in 5-fluorouracil chemotherapy. *Clin Pharmacol Ther*. 1995;58(5):512–522.
358. Curran CF, Luce JK. Accidental acute exposure to fluorouracil. *Oncol Nurs Forum*. 1989; 16(4):468.
359. Muggia FM, Liu PY, Alberts DS, et al. Intraperitoneal mitoxantrone or floxuridine: effects on time-to-failure and survival in patients with minimal residual ovarian cancer after second-look laparotomy—a randomized phase II study by the Southwest Oncology Group. *Gynecol Oncol*. 1996;61(3):395–402.
360. Muggia FM, Jeffers S, Muderspach L, et al. Phase III study of intraperitoneal floxuridine and platinum (cisplatin and/or carboplatin). *Gynecol Oncol*. 1997;66(2):290–294.
361. Speyer JL, Sugarbaker PH, Collins JM, et al. Portal levels and hepatic clearance of 5-fluorouracil after intraperitoneal administration in humans. *Cancer Res*. 1981;41(5):1916–1922.
362. Suhrland LG, Weisberger AA. Intracavitary 5-fluorouracil in malignant effusions. *Arch Intern Med*. 1965;116:431.
363. Belpomme D, Krakowski I, Beauduin M, et al. Gemcitabine combined with cisplatin as first-line treatment in patients with epithelial ovarian cancer: a phase II study. *Gynecol Oncol*. 2003; 91(1):32–38.
364. Fowler WC Jr, Van Le L. Gemcitabine as a single-agent treatment for ovarian cancer. *Gynecol Oncol*. 2003;90(2 Pt 2):S21–S23.
365. Hansen SW, Tuxen MK, Sessa C. Gemcitabine in the treatment of ovarian cancer. *Ann Oncol*. 1999;10(suppl. 1):51–53.
366. Markman M, Webster K, Zanotti K, et al. Phase 2 trial of single-agent gemcitabine in platinum-paclitaxel refractory ovarian cancer. *Gynecol Oncol*. 2003;90(3):593–596.
367. Zarba JJ, Jaremtchuk AV, Gonzalez Jazey P, et al. A phase I-II study of weekly cisplatin and gemcitabine with concurrent radiotherapy in locally advanced cervical carcinoma. *Ann Oncol*. 2003;14(8):1285–1290.
368. Huang P, Chubb S, Hertel LW, et al. Action of 2',2'-difluorodeoxycytidine on DNA synthesis. *Cancer Res*. 1991;51(22):6110–6117.
369. Plunkett W, Huang P, Gandhi V. Preclinical characteristics of gemcitabine. *Anticancer Drugs*. 1995;6(suppl. 6):7–13.
370. Heinemann V, Xu YZ, Chubb S, et al. Inhibition of ribonucleotide reduction in CCRF-CEM cells by 2',2'-difluorodeoxycytidine. *Mol Pharmacol*. 1990;38(4):567–572.
371. Abbruzzese JL, Grunewald R, Weeks EA, et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol*. 1991;9(3):491–498.
372. Eli Lilly and Company. Gemzar (Gemcitabine HCl) for Injection. 2003 [updated 2003; cited 11/5/03]; Available from: <http://pi.lilly.com/us/gemzar.pdf>.
373. Allerheiligen S, Johnson R, Hatcher B, et al. Gemcitabine pharmacokinetics are influenced by gender, body surface area, and duration of infusion. *Proc ASCO*. 1994;13:136.
374. Storniolo AM, Allerheiligen SR, Pearce HL. Preclinical, pharmacologic, and phase I studies of gemcitabine. *Semin Oncol*. 1997;24(2 Suppl. 7): S7–S7-7.
375. van Moorsel CJ, Kroep JR, Pinedo HM, et al. Pharmacokinetic schedule finding study of the combination of gemcitabine and cisplatin in patients with solid tumors. *Ann Oncol*. 1999; 10(4):441–448.
376. O'Rourke TJ, Brown TD, Havlin K, et al. Phase I clinical trial of gemcitabine given as an intravenous bolus on 5 consecutive days. *Eur J Cancer*. 1994;30A(3):417–418.
377. Hui YF, Reitz J. Gemcitabine: a cytidine analogue active against solid tumors. *Am J Health Syst Pharm*. 1997;54(2):162–170; quiz 97-8.
378. D'Agostino G, Amant F, Berteloot P, et al. Phase II study of gemcitabine in recurrent platinum- and paclitaxel-resistant ovarian cancer. *Gynecol Oncol*. 2003;88(3):266–269.
379. Bergmann AM, Ruiz van Haperen VM, Veerman G, et al. Synergistic interaction between cisplatin and gemcitabine *in vitro*. *Clin Cancer Res*. 1996;2:521.
380. van Moorsel CJ, Pinedo HM, Veerman G, et al. Mechanisms of synergism between cisplatin and gemcitabine in ovarian and non-small cell lung cancer cell lines. *Br J Cancer*. 1999;80:981.
381. Ledermann JA, Gabra H, Jayson GC, et al. Inhibition of carboplatin-induced DNA inter-strand cross-link repair by gemcitabine in patients receiving these drugs for platinum-resistant ovarian cancer. *Clin Cancer Res*. 2010; 16(19):4899–4905. Epub 2010 Aug 18.
382. Bauknecht T, Hefti A, Morack G, et al. Gemcitabine combined with cisplatin as first-line treatment in patients 60 years or older with epithelial ovarian cancer: a phase II study. *Int J Gynecol Cancer*. 2003;13(2):130–137.
383. Nogue M, Cirera L, Arcusa A, et al. Phase II study of gemcitabine and cisplatin in chemonaïve patients with advanced epithelial ovarian cancer. *Anticancer Drugs*. 2002;13(8):839–845.
384. Nagourney RA, Brewer CA, Radecki S, et al. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol*. 2003;88(1):35–39.
385. Aapro MS, Martin C, Hatty S. Gemcitabine—a safety review. *Anticancer Drugs*. 1998;9(3): 191–201.
386. Serke S, Riess H, Oettle H, et al. Elevated reticulocyte count—a clue to the diagnosis of haemolytic-uraemic syndrome (HUS) associated with gemcitabine therapy for metastatic duodenal papillary carcinoma: a case report. *Br J Cancer*. 1999;79(9–10):1519–1521.
387. Pavlakis N, Bell DR, Millward MJ, et al. Fatal pulmonary toxicity resulting from treatment with gemcitabine. *Cancer*. 1997;80(2):286–291.
388. Sauer-Heilborn A, Kath R, Schneider CP, et al. Severe non-haematological toxicity after treatment with gemcitabine. *J Cancer Res Clin Oncol*. 1999;125(11):637–640.
389. Markman M, Kennedy A, Sutton G, et al. Phase 2 trial of single agent ifosfamide/mesna in patients with platinum/paclitaxel refractory ovarian cancer who have not previously been treated with an alkylating agent. *Gynecol Oncol*. 1998;70(2):272–274.
390. Sutton G. Ifosfamide and mesna in epithelial ovarian carcinoma. *Gynecol Oncol*. 1993; 51(1):104–108.
391. Sutton GP, Blessing JA, DeMars LR, et al. A phase II Gynecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. *Gynecol Oncol*. 1996;63(1):25–27.
392. Allen LM, Creaven PJ. Activation of the anti-neoplastic drug isophosphamide by rat liver microsomes. *J Pharm Pharmacol*. 1972;24(7): 585–586.
393. Allen LM, Creaven PJ. Interaction of mechlorethamine and isophosphamide with bovine serum albumin and rat liver microsomes. *J Pharm Sci*. 1973;62(5):854–856.
394. Boal JH, Williamson M, Boyd VL, et al. 31P NMR studies of the kinetics of bisalkylation by isophosphoramide mustard: comparisons with phosphoramide mustard. *J Med Chem*. 1989; 32(8):1768–1773.
395. Creaven PJ, Allen LM, Cohen MH, et al. Studies on the clinical pharmacology and toxicology of isophosphamide (NSC-109724). *Cancer Treat Rep*. 1976;60(4):445–449.
396. Allen LM, Creaven PJ, Nelson RL. Studies on the human pharmacokinetics of isophosphamide (NSC-109724). *Cancer Treat Rep*. 1976; 60(4):451–458.
397. Stuart-Harris RC, Harper PG, Parsons CA, et al. High-dose alkylation therapy using ifosfamide infusion with mesna in the treatment of adult advanced soft-tissue sarcoma. *Cancer Chemother Pharmacol*. 1983;11(2):69–72.
398. Nelson RL, Creaven PJ, Cohen MH, et al. Phase I clinical trial of a 3-day divided dose schedule of ifosfamide (NSC 109724). *Eur J Cancer*. 1976;12(3):195–198.
399. Mateu J, Alzamora M, Franco M, et al. Ifosfamide extravasation. *Ann Pharmacother*. 1994; 28(11):1243–1244.
400. Papadimitriou CA, Kouroussis C, Mouloupoulos LA, et al. Ifosfamide, paclitaxel and cisplatin first-line chemotherapy in advanced, suboptimally debulked epithelial ovarian cancer. *Cancer*. 2001;92(7):1856–1863.
401. Zanetta G, Fei F, Parma G, et al. Paclitaxel, ifosfamide and cisplatin (TIP) chemotherapy for recurrent or persistent squamous-cell cervical cancer. *Ann Oncol*. 1999;10(10):1171–1174.
402. Morgan LR, Harrison EF, Hawke JE, et al. Toxicity of single- vs. fractionated-dose ifosfamide in non-small cell lung cancer: a multi-center study. *Semin Oncol*. 1982;9(4 Suppl. 1):66–70.
403. Rodriguez V, McCreddie KB, Keating MJ, et al. Isophosphamide therapy for hematologic malignancies in patients refractory to prior treatment. *Cancer Treat Rep*. 1978;62(4):493–497.
404. Van Dyk JJ, Falkson HC, Van der Merwe AM, et al. Unexpected toxicity in patients treated with iphosphamide. *Cancer Res*. 1972;32(5):921–924.
405. DeFronzo RA, Abeloff M, Braine H, et al. Renal dysfunction after treatment with isophosphamide (NSC-109724). *Cancer Chemother Rep*. 1974; 58(3):375–382.
406. Goren MP, Wright RK, Pratt CB, et al. Potentiation of ifosfamide neurotoxicity, hematotoxicity, and tubular nephrotoxicity by prior cis-diamminedichloroplatinum(II) therapy. *Cancer Res*. 1987;47(5):1457–1460.
407. Hacke M, Schmoll HJ, Alt JM, et al. Nephrotoxicity of cis-diamminedichloroplatinum with or without ifosfamide in cancer treatment. *Clin Physiol Biochem*. 1983;1(1):17–26.
408. Bhardwaj A, Badesha PS. Ifosfamide-induced nonconvulsive status epilepticus. *Ann Pharmacother*. 1995;29(12):1237–1239.
409. Creemers GJ, Lund B, Verweij J. Topoisomerase I inhibitors: topotecan and irinotecan. *Cancer Treat Rev*. 1994;20(1):73–96.
410. Rothenberg ML, Kuhn JG, Burris HA 3rd, et al. Phase I and pharmacokinetic trial of

- weekly CPT-11. *J Clin Oncol*. 1993;11(11):2194-2204.
411. Abigerges D, Chabot GG, Armand JP, et al. Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients. *J Clin Oncol*. 1995;13(1):210-221.
 412. Irvin WP, Price FV, Bailey H, et al. A phase II study of irinotecan (CPT-11) in patients with advanced squamous cell carcinoma of the cervix. *Cancer*. 1998;82(2):328-333.
 413. Look KY, Blessing JA, Levenback C, et al. A phase II trial of CPT-11 in recurrent squamous carcinoma of the cervix: a gynecologic oncology group study. *Gynecol Oncol*. 1998;70(3):334-338.
 414. Verschraegen CF, Levy T, Kudelka AP, et al. Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. *J Clin Oncol*. 1997;15(2):625-631.
 415. Rowinsky EK, Grochow LB, Ettinger DS, et al. Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) administered as a ninety-minute infusion every 3 weeks. *Cancer Res*. 1994;54(2):427-436.
 416. Gupta E, Lestingi TM, Mick R, et al. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. *Cancer Res*. 1994;54(14):3723-3725.
 417. Iyer L, King CD, Whittington PF, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. *J Clin Invest*. 1998;101(4):847-854.
 418. Ando Y, Saka H, Asai G, et al. UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. *Ann Oncol*. 1998;9(8):845-847.
 419. Cottu PH, Extra JM, Lerebours F, et al. [Clinical activity spectrum of irinotecan]. *Bull Cancer*. 1998;Spec No: 21-5.
 420. Eisenhauer EA, Vermorken JB. New drugs in gynecologic oncology. *Curr Opin Oncol*. 1996;8(5):408-414.
 421. Verschraegen CF. Irinotecan for the treatment of cervical cancer. *Oncology (Huntingt)*. 2002;16(5 Suppl. 5):32-34.
 422. Chitapanarux I, Tonusin A, Sukthomya V, et al. Phase II clinical study of irinotecan and cisplatin as first-line chemotherapy in metastatic or recurrent cervical cancer. *Gynecol Oncol*. 2003;89(3):402-407.
 423. Alza Corporation. DOXIL (doxorubicin HCl liposome injection) package insert; 2001 Contract No.: Document Number.
 424. Gabizon A, Catane R, Uzieli B, et al. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. *Cancer Res*. 1994;54(4):987-992.
 425. Alberts DS, Garcia DJ. Safety aspects of pegylated liposomal doxorubicin in patients with cancer. *Drugs*. 1997;54(suppl. 4):30-35.
 426. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001;19(14):3312-3322.
 427. Chang SY, Evans TL, Alberts DS. The stability of melphalan in the presence of chloride ion. *J Pharm Pharmacol*. 1979;31(12):853-854.
 428. Goodman GE, Chang SE, Alberts DS. The antitumor activity of melphalan and its hydrolysis products. *Proc AACR*. 1980;21:1207.
 429. Goldenberg GJ, Lam HY, Begleiter A. Active carrier-mediated transport of melphalan by two separate amino acid transport systems in LPC-1 plasmacytoma cells *in vitro*. *J Biol Chem*. 1979;254(4):1057-1064.
 430. Alberts DS, Chang SY, Chen HS, et al. Oral melphalan kinetics. *Clin Pharmacol Ther*. 1979;26(6):737-745.
 431. Evans TL, Chang SY, Alberts DS, et al. *In vitro* degradation of L-phenylalanine mustard (L-PAM). *Cancer Chemother Pharmacol*. 1982;8(2):175-178.
 432. Alberts DS, Peng YM, Fisher B. Minimal melphalan (LPAM) systemic availability (SA): a potential cause for failure of adjuvant breast cancer trials. *Proc ASCO*. 1984;3:C149.
 433. Bosanquet AG, Gilby ED. Pharmacokinetics of oral and intravenous melphalan during routine treatment of multiple myeloma. *Eur J Cancer Clin Oncol*. 1982;18(4):355-362.
 434. Rutledge F. Chemotherapy of ovarian cancer with melphalan. *Clin Obstet Gynecol*. 1968;11(2):354-366.
 435. Taetle R, Dickman PS, Feldman PS. Pulmonary histopathologic changes associated with melphalan therapy. *Cancer*. 1978;42(3):1239-1245.
 436. Einhorn N. Acute leukemia after chemotherapy (melphalan). *Cancer*. 1978;41(2):444-447.
 437. Greene MH, Harris EL, Gershenson DM, et al. Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann Intern Med*. 1986;105(3):360-367.
 438. Lazarus HM, Gray R, Ciobanu N, et al. Phase I trial of high-dose melphalan, high-dose etoposide and autologous bone marrow re-infusion in solid tumors: an Eastern Cooperative Oncology Group (ECOG) study. *Bone Marrow Transplant*. 1994;14(3):443-448.
 439. Weaver CH, Bensinger WI, Appelbaum FR, et al. Phase I study of high-dose busulfan, melphalan and thiopeta with autologous stem cell support in patients with refractory malignancies. *Bone Marrow Transplant*. 1994;14(5):813-819.
 440. Alberts DS, Young L, Mason N, et al. *In vitro* evaluation of anticancer drugs against ovarian cancer at concentrations achievable by intraperitoneal administration. *Semin Oncol*. 1985;12(3 Suppl. 4):38-42.
 441. Howell SB, Pfeifle CE, Olshen RA. Intraperitoneal chemotherapy with melphalan. *Ann Intern Med*. 1984;101(1):14-18.
 442. Zaharko DS, Fung WP, Yang KH. Relative biochemical aspects of low and high doses of methotrexate in mice. *Cancer Res*. 1977;37(6):1602-1607.
 443. Jolivet J, Schilsky RL, Bailey BD, et al. Synthesis, retention, and biological activity of methotrexate polyglutamates in cultured human breast cancer cells. *J Clin Invest*. 1982;70(2):351-360.
 444. Alt FW, Kellems RE, Bertino JR, et al. Selective multiplication of dihydrofolate reductase genes in methotrexate-resistant variants of cultured murine cells. 1978. *Biotechnology*. 1992;24:397-410.
 445. Calvert AH, Jones TR, Jackman AL, et al. 2-Amino-4-hydroxyquinazolines with dual metabolic loci in methotrexate resistant cells. *Proc AACR*. 1979;20:24.
 446. Weinstein G, Newburger A, Troner M. Cell kinetic synchronization of human malignant melanoma (MM) with low-dose methotrexate (MTX) *in vivo*. *Proc AACR*. 1979;20:403.
 447. Chello PL, Sirotak FM, Dorick DM. Alterations in the kinetics of methotrexate transport during growth of L1210 murine leukemia cells in culture. *Mol Pharmacol*. 1980;18(2):274-280.
 448. Campbell MA, Perrier DG, Dorr RT, et al. Methotrexate: bioavailability and pharmacokinetics. *Cancer Treat Rep*. 1985;69(7-8):833-838.
 449. Ignoffo RJ, Oie S, Friedman MA. Pharmacokinetics of methotrexate administered via the hepatic artery. *Cancer Chemother Pharmacol*. 1981;5(4):217-220.
 450. Aherne GW, Piali E, Marks V, et al. Prolongation and enhancement of serum methotrexate concentrations by probenecid. *Br Med J*. 1978;1(6120):1097-1099.
 451. Huffman DH, Wan SH, Azarnoff DL, et al. Pharmacokinetics of methotrexate. *Clin Pharmacol Ther*. 1973;14(4):572-579.
 452. Stoller RG, Jacobs SA, Drake JC, et al. Pharmacokinetics of high-dose methotrexate (NSC-740). *Cancer Chemother Rep*. 1975;6:91.
 453. Wang YM, Sutow WW, Romsdahl MM, et al. Age-related pharmacokinetics of high-dose methotrexate in patients with osteosarcoma. *Cancer Treat Rep*. 1979;63(3):405-410.
 454. Evans WE, Pratt CB. Effect of pleural effusion on high-dose methotrexate kinetics. *Clin Pharmacol Ther*. 1978;23(1):68-72.
 455. Ben Venue Laboratories. Methotrexate Injection, USP. Package Insert; 2000 Contract No.: Document Number.
 456. Everts CS, Westcott JL, Bragg DG. Methotrexate therapy and pulmonary disease. *Radiology*. 1973;107(3):539-543.
 457. Creaven GB, Morgan RG. Alteration of methotrexate (MTX) pharmacokinetics by gut sterilization in man. *Proc AACR*. 1975;16:134.
 458. Cadman E, Heimer R, Davis L. Enhanced 5-fluorouracil nucleotide formation after methotrexate administration: explanation for drug synergism. *Science*. 1979;205(4411):1135-1137.
 459. Bowen D, White JC, Goldman ID. A basis for fluoropyrimidine-induced antagonism to methotrexate in Ehrlich ascites tumor cells *in vitro*. *Cancer Res*. 1978;38(1):219-222.
 460. Stoller RG, Hande KR, Jacobs SA, et al. Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. *N Engl J Med*. 1977;297(12):630-634.
 461. Stoller RG, Kaplan HG, Cummings FJ, et al. A clinical and pharmacological study of high-dose methotrexate with minimal leucovorin rescue. *Cancer Res*. 1979;39(3):908-912.
 462. Von Hoff DD, Penta JS, Helman LJ, et al. Incidence of drug-related deaths secondary to high-dose methotrexate and citrovorum factor administration. *Cancer Treat Rep*. 1977;61(4):745-748.
 463. Crooke ST, Bradner WT. Mitomycin C: a review. *Cancer Treat Rev*. 1976;3(3):121-139.
 464. Lown JW, Weir G. Studies related to antitumor antibiotics. Part XIV. Reactions of mitomycin B with DNA. *Can J Biochem*. 1978;56(5):269-304.
 465. Tomas M, Chowdary D, Lipman R, et al. Reaction of DNA with chemically or enzymatically activated mitomycin C: isolation and structure of the major covalent adduct. *Proc Natl Acad Sci USA*. 1986;83:6702.
 466. Dusre L, Covey JM, Collins C, et al. DNA damage, cytotoxicity and free radical formation by mitomycin C in human cells. *Chem Biol Interact*. 1989;71(1):63-78.
 467. Kennedy KA, Rockwell S, Sartorelli AC. Preferential activation of mitomycin C to cytotoxic metabolites by hypoxic tumor cells. *Cancer Res*. 1980;40(7):2356-2360.
 468. Matsumoto S, Shigeoka T, Takakura Y, et al. Cellular interaction and *in vitro* antitumor effect of various mitomycin C prodrugs in mitomycin C-resistant L1210 leukemia cell lines. *Chem Pharm Bull (Tokyo)*. 1987;35(9):3792-3799.

469. Taylor CW, Brattain MG, Yeoman LC. Occurrence of cytosolic protein and phosphoprotein changes in human colon tumor cells with the development of resistance to mitomycin C. *Cancer Res.* 1985;45(9):4422–4427.
470. Dorr RT, Liddil JD, Trent JM, et al. Mitomycin C resistant L1210 leukemia cells: association with pleiotropic drug resistance. *Biochem Pharmacol.* 1987;36(19):3115–3120.
471. van Hazel GA, Scott M, Rubin J, et al. Pharmacokinetics of mitomycin C in patients receiving the drug alone or in combination. *Cancer Treat Rep.* 1983;67(9):805–810.
472. Verweij J, den Hartigh J, Stuurman M, et al. Relationship between clinical parameters and pharmacokinetics of mitomycin C. *J Cancer Res Clin Oncol.* 1987;113(1):91–94.
473. Schilcher RB, Young JD, Ratanatharathorn V, et al. Clinical pharmacokinetics of high-dose mitomycin C. *Cancer Chemother Pharmacol.* 1984;13(3):186–190.
474. den Hartigh J, McVie JG, van Oort WJ, et al. Pharmacokinetics of mitomycin C in humans. *Cancer Res.* 1983;43(10):5017–5021.
475. Malviya VK, Young JD, Boike G, et al. Pharmacokinetics of mitomycin-C in plasma and tumor tissue of cervical cancer patients and in selected tissues of female rats. *Gynecol Oncol.* 1986;25(2):160–170.
476. Hu E, Howell SB. Pharmacokinetics of intra-arterial mitomycin C in humans. *Cancer Res.* 1983;43(9):4474–4477.
477. Argenta LC, Manders EK. Mitomycin C extravasation injuries. *Cancer.* 1983;51(6):1080–1082.
478. Lokich J, Perri J, Fine N, et al. Mitomycin C: phase I study of a constant infusion ambulatory treatment schedule. *Am J Clin Oncol.* 1982;5(4):443–447.
479. Tseng MH, Luch J, Mittelman A. Regional intra-arterial mitomycin C infusion in previously treated patients with metastatic colorectal cancer and concomitant measurement of serum drug level. *Cancer Treat Rep.* 1984;68(11):1319–1324.
480. Hanna WT, Krauss S, Regester RF, et al. Renal disease after mitomycin C therapy. *Cancer.* 1981;48(12):2583–2588.
481. Valavaara R, Nordman E. Renal complications of mitomycin C therapy with special reference to the total dose. *Cancer.* 1985;55(1):47–50.
482. Lazarus HM, Gottfried MR, Herzig RH, et al. Venocclusive disease of the liver after high-dose mitomycin C therapy and autologous bone marrow transplantation. *Cancer.* 1982;49(9):1789–1795.
483. Johnston-Early A, Cohen MH. Mitomycin C-induced skin ulceration remote from infusion site. *Cancer Treat Rep.* 1981;65(5–6):529.
484. Wood HA, Ellerhorst-Ryan JM. Delayed adverse skin reactions associated with mitomycin-C administration. *Oncol Nurs Forum.* 1984;11(4):14–18.
485. Olver IN, Aisner J, Hament A, et al. A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. *J Clin Oncol.* 1988;6(11):1732–1735.
486. Chang AY, Kuebler JP, Pandya KJ, et al. Pulmonary toxicity induced by mitomycin C is highly responsive to glucocorticoids. *Cancer.* 1986;57(12):2285–2290.
487. Koga S, Hamazoe R, Maeta M, et al. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer.* 1988;61(2):232–237.
488. Fujimoto S, Shrestha RD, Kokubun M, et al. [Pharmacokinetic analysis in intraperitoneal hyperthermic perfusion using mitomycin C in far-advanced gastric cancer]. *Gan To Kagaku Ryoho.* 1989;16(7):2411–2415.
489. Graham MA, Lockwood GF, Greenslade D, et al. Clinical pharmacokinetics of oxaliplatin: a critical review. *Clin Cancer Res.* 2000;6(4):1205–1218.
490. Sanofi-Synthelabo. Eloxatin (Oxaliplatin for injection) Package Insert. 2002.
491. Fracasso PM, Blessing JA, Morgan MA, et al. Phase II study of oxaliplatin in platinum-resistant and refractory ovarian cancer: a gynecologic group study. *J Clin Oncol.* 2003;21(15):2856–2859.
492. Fracasso PM, Blessing JA, Wolf J, et al. Phase II evaluation of oxaliplatin in previously treated squamous cell carcinoma of the cervix: a gynecologic oncology group study. *Gynecol Oncol.* 2003;90(1):177–180.
493. Gamelin E, Gamelin L, Bossi L, et al. Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. *Semin Oncol.* 2002;29(5 Suppl. 15):21–33.
494. Bounoux P, Dieras V, Petit T, et al. A multicenter phase II study of Oxaliplatin (OXA) as a single agent in platinum (PT) and/or Taxanes (TX) pretreated advanced ovarian cancer (AOC): final results. *Proc ASCO.* 1999;18:368a.
495. Dieras V, Bounoux P, Petit T, et al. Multicentre phase II study of oxaliplatin as a single-agent in cisplatin/carboplatin +/- taxane-pretreated ovarian cancer patients. *Ann Oncol.* 2002;13(2):258–266.
496. Chollet P, Bensmaine MA, Brienza S, et al. Single agent activity of oxaliplatin in heavily pretreated advanced epithelial ovarian cancer. *Ann Oncol.* 1996;7(10):1065–1070.
497. Dorr RT. Pharmacology of the taxanes. *Pharmacotherapy.* 1997;17(5 Pt 2):96S–104S.
498. Markman M, Kennedy A, Webster K, et al. Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol.* 2000;18(1):102–105.
499. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol.* 1994;12(12):2654–2666.
500. Tsavaris NB, Kosmas C. Risk of severe acute hypersensitivity reactions after rapid paclitaxel infusion of less than 1-h duration. *Cancer Chemother Pharmacol.* 1998;42(6):509–511.
501. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003;21(17):3194–3200.
502. Alberts DS, Markman M, Armstrong D, et al. Intraperitoneal therapy for stage III ovarian cancer: a therapy whose time has come! *J Clin Oncol.* 2002;20(19):3944–3946.
503. Boruta DM 2nd, Fowler WC Jr, Gehrig PA, et al. Weekly paclitaxel infusion as salvage therapy in ovarian cancer. *Cancer Invest.* 2003;21(5):675–681.
504. Sharma R, Graham J, Blagden S, et al. Sustained platelet-sparing effect of weekly low dose paclitaxel allows effective, tolerable delivery of extended dose dense weekly carboplatin in platinum resistant/refractory epithelial ovarian cancer. *BMC Cancer.* 2011;11:289.
505. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol.* 2008;26(10):1642–1649.
506. Rowinsky EK, Eisenhauer EA, Chaudhry V, et al. Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol.* 1993;20(4 Suppl. 3):1–15.
507. Peereboom DM, Donehower RC, Eisenhauer EA, et al. Successful re-treatment with taxol after major hypersensitivity reactions. *J Clin Oncol.* 1993;11(5):885–890.
508. Rowinsky EK, Kaufmann SH, Baker SD, et al. Sequences of topotecan and cisplatin: phase I, pharmacologic, and *in vitro* studies to examine sequence dependence. *J Clin Oncol.* 1996;14(12):3074–3084.
509. Chang SM, Kuhn JG, Rizzo J, et al. Phase I study of paclitaxel in patients with recurrent malignant glioma: a North American Brain Tumor Consortium report. *J Clin Oncol.* 1998;16(6):2188–2194.
510. Francis P, Rowinsky E, Schneider J, et al. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot study. *J Clin Oncol.* 1995;13(12):2961–2967.
511. Markman M, Brady MF, Spirtos NM, et al. Phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube, and peritoneum: a Gynecologic Oncology Group Study. *J Clin Oncol.* 1998;16(8):2620–2624.
512. Thigpen T, Vance RB, Khansur T. The platinum compounds and paclitaxel in the management of carcinomas of the endometrium and uterine cervix. *Semin Oncol.* 1995;22(5 Suppl. 12):67–75.
513. Woo HL, Swenerton KD, Hoskins PJ. Taxol is active in platinum-resistant endometrial adenocarcinoma. *Am J Clin Oncol.* 1996;19(3):290–291.
514. Ball HG, Blessing JA, Lentz SS, et al. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1996;62(2):278–281.
515. Lissoni A, Zanetta G, Losa G, et al. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. *Ann Oncol.* 1996;7(8):861–863.
516. Lincoln S, Blessing JA, Lee RB, et al. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2003;88(3):277–281.
517. Papadimitriou CA, Sarris K, Mouloupos LA, et al. Phase II trial of paclitaxel and cisplatin in metastatic and recurrent carcinoma of the uterine cervix. *J Clin Oncol.* 1999;17(3):761–766.
518. Piver MS, Ghamande SA, Eltabakh GH, et al. First-line chemotherapy with paclitaxel and platinum for advanced and recurrent cancer of the cervix—a phase II study. *Gynecol Oncol.* 1999;75(3):334–337.
519. Chattopadhyay S, Moran RG, Goldman ID. Pemetrexed: biochemical and cellular pharmacology, mechanisms, and clinical applications. *Mol Cancer Ther.* 2007;6(2):404–417.
520. Slichenmyer WJ, Rowinsky EK, Donehower RC, et al. The current status of camptothecin analogues as antitumor agents. *J Natl Cancer Inst.* 1993;85(4):271–291.
521. O'Dwyer PJ, LaCreta FP, Haas NB, et al. Clinical, pharmacokinetic and biological studies of topotecan. *Cancer Chemother Pharmacol.* 1994;34 Suppl:S46–S52.
522. Stewart CF, Baker SD, Heideman RL, et al. Clinical pharmacodynamics of continuous infusion topotecan in children: systemic exposure predicts hematologic toxicity. *J Clin Oncol.* 1994;12(9):1946–1954.

523. Minami H, Beijnen JH, Verweij J, et al. Limited sampling model for area under the concentration time curve of total topotecan. *Clin Cancer Res.* 1996;2(1):43–46.
524. van Warmerdam LJ, Verweij J, Rosing H, et al. Limited sampling models for topotecan pharmacokinetics. *Ann Oncol.* 1994;5(3):259–264.
525. McCabe FL, Johnson RK. Comparative activity of oral and parenteral topotecan in murine tumor models: efficacy of oral topotecan. *Cancer Invest.* 1994;12(3):308–313.
526. Clarke-Pearson DL, Van Le L, Iveson T, et al. Oral topotecan as single-agent second-line chemotherapy in patients with advanced ovarian cancer. *J Clin Oncol.* 2001;19(19):3967–3975.
527. Gore M, Oza A, Rustin G, et al. A randomised trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer. *Eur J Cancer.* 2002;38(1):57–63.
528. von Pawel J, Gatzemeier U, Pujol JL, et al. Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. *J Clin Oncol.* 2001;19(6):1743–1749.
529. Stevenson JP, Scher RM, Kosierowski R, et al. Phase II trial of topotecan as a 21-day continuous infusion in patients with advanced or metastatic adenocarcinoma of the pancreas. *Eur J Cancer.* 1998;34(9):1358–1362.
530. Von Hoff DD, Burris HA 3rd, Eckardt J, et al. Preclinical and phase I trials of topoisomerase I inhibitors. *Cancer Chemother Pharmacol.* 1994;34 Suppl:S41–S45.
531. Morris RT. Weekly topotecan in the management of ovarian cancer. *Gynecol Oncol.* 2003;90(3 Pt 2):S34–S38.
532. Rowinsky EK. Weekly topotecan: an alternative to topotecan's standard daily x 5 schedule? *Oncologist.* 2002;7(4):324–330.
533. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol.* 1997;15(6):2183–2193.
534. O'Reilly S, Rowinsky EK, Slichenmyer W, et al. Phase I and pharmacologic study of topotecan in patients with impaired renal function. *J Clin Oncol.* 1996;14(12):3062–3073.
535. O'Reilly S, Rowinsky E, Slichenmyer W, et al. Phase I and pharmacologic studies of topotecan in patients with impaired hepatic function. *J Natl Cancer Inst.* 1996;88(12):817–824.
536. O'Reilly S, Fleming GF, Barker SD, et al. Phase I trial and pharmacologic trial of sequences of paclitaxel and topotecan in previously treated ovarian epithelial malignancies: a Gynecologic Oncology Group study. *J Clin Oncol.* 1997;15(1):177–186.
537. Gordon AN, Hancock KC, Matthews CM, et al. Phase I study of alternating doublets of topotecan/carboplatin and paclitaxel/carboplatin in patients with newly diagnosed, advanced ovarian cancer. *Gynecol Oncol.* 2002;85(1):129–135.
538. Hammond LA, Eckardt JR, Ganapathi R, et al. A phase I and translational study of sequential administration of the topoisomerase I and II inhibitors topotecan and etoposide. *Clin Cancer Res.* 1998;4(6):1459–1467.
539. Mok TS, Wong H, Zee B, et al. A Phase I–II study of sequential administration of topotecan and oral etoposide (topoisomerase I and II inhibitors) in the treatment of patients with small cell lung carcinoma. *Cancer.* 2002;95(7):1511–1519.
540. Chen AY, Choy H, Rothenberg ML. DNA topoisomerase I-targeting drugs as radiation sensitizers. *Oncology (Huntingt).* 1999;13(10 Suppl. 5):39–46.
541. Rave-Frank M, Glomme S, Hertig J, et al. Combined effect of topotecan and irradiation on the survival and the induction of chromosome aberrations *in vitro*. *Strahlenther Onkol.* 2002;178(9):497–503.
542. Hofstra LS, Bos AM, de Vries EG, et al. A phase I and pharmacokinetic study of intraperitoneal topotecan. *Br J Cancer.* 2001;85(11):1627–1633.
543. Plaxe SC, Christen RD, O'Quigley J, et al. Phase I and pharmacokinetic study of intraperitoneal topotecan. *Invest New Drugs.* 1998;16(2):147–153.
544. Long HJ 3rd, Rayson S, Podratz KC, et al. Long-term survival of patients with advanced/recurrent carcinoma of cervix and vagina after neoadjuvant treatment with methotrexate, vinblastine, doxorubicin, and cisplatin with or without the addition of mogranostim, and review of the literature. *Am J Clin Oncol.* 2002;25(6):547–551.
545. Gebbia V, Testa A, Borsellino N, et al. Cisplatin and vinorelbine in advanced and/or metastatic adenocarcinoma of the endometrium: a new highly active chemotherapeutic regimen. *Ann Oncol.* 2001;12(6):767–772.
546. Aravantinos G, Bafaloukos D, Fountzilas G, et al. Phase II study of docetaxel-vinorelbine in platinum-resistant, paclitaxel-pretreated ovarian cancer. *Ann Oncol.* 2003;14(7):1094–1099.
547. Noble RR, Beer CT. Experimental observations concerning the mode of action of vinca alkaloids. In: Wih S, ed. *The Vinca Alkaloids in the Chemotherapy of Malignant Disease*. Alburham, England: John Sherrat & Sons; 1968:4.
548. Velban (vinblastine sulfate for injection, USP). *Physicians Desk Reference*. 55th ed. Montvale, NJ: Medical Economics Company; 2001.
549. Owellen RJ, Hartke CA. The pharmacokinetics of 4-acetyl tritium vinblastine in two patients. *Cancer Res.* 1975;35(4):975–980.
550. Lucas VS, Huang AT. Vinblastine-related pain in tumors. *Cancer Treat Rep.* 1977;61(9):1735–1736.
551. Teutsch C, Lipton A, Harvey HA. Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. *Cancer Treat Rep.* 1977;61(5):925–926.
552. Ginsberg SJ, Comis RL, Fitzpatrick AV. Vinblastine and inappropriate ADH secretion. *N Engl J Med.* 1977;296(16):941.
553. Cohlant SW, Kitay D. The teratogenic effect of vincalkeboline in the pregnant rat. *J Pediatr.* 1965;66(6):541.
554. Dorr RT, Alberts DS. Vinca alkaloid skin toxicity: antidote and drug disposition studies in the mouse. *J Natl Cancer Inst.* 1985;74(1):113–120.
555. Blajman C, Balbiani L, Block J, et al. A prospective, randomized Phase III trial comparing combination chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil with vinorelbine plus doxorubicin in the treatment of advanced breast carcinoma. *Cancer.* 1999;85(5):1091–1097.
556. Llobart-Cussac A, Pivrot X, Rhor-Alvarado A, et al. First-line vinorelbine-mitoxantrone combination in metastatic breast cancer patients relapsing after an adjuvant anthracycline regimen: results of a phase II study. *Oncology.* 1998;55(5):384–390.
557. Burger RA, DiSaia PJ, Roberts JA, et al. Phase II trial of vinorelbine in recurrent and progressive epithelial ovarian cancer. *Gynecol Oncol.* 1999;72(2):148–153.
558. Morris M, Brader KR, Levenback C, et al. Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. *J Clin Oncol.* 1998;16(3):1094–1098.
559. Peacock NW, Burris HA, Dieras V, et al. A phase I trial of vinorelbine in combination with mitoxantrone in patients with refractory solid tumors. *Invest New Drugs.* 1998;16(1):37–43.
560. Mangeney P, Andriamialisoa RZ, Lallemand JY, et al. 5'-Nor-anhydrovinblastine, prototype of a new class of vinblastine derivatives. *Tetrahedron.* 1979;35:2175.
561. Johnson SA, Harper P, Hortobagyi GN, et al. Vinorelbine: an overview. *Cancer Treat Rev.* 1996;22(2):127–142.
562. Marquet P, Lachatre G, Debord J, et al. Pharmacokinetics of vinorelbine in man. *Eur J Clin Pharmacol.* 1992;42(5):545–547.
563. Wargin WA, Lucas VS. The clinical pharmacokinetics of vinorelbine (Navelbine). *Semin Oncol.* 1994;21(5 Suppl. 10):21–27.
564. Leveque D, Jehl F. Clinical pharmacokinetics of vinorelbine. *Clin Pharmacokinet.* 1996;31(3):184–197.
565. Lozano M, Muro H, Triguboff E, et al. A randomized trial for effective prevention of Navelbine (NVB) related phlebitis. *Proc ASCO.* 1995;14:535.
566. Trissel LA, Martinez JF. Visual, turbidimetric, and particle-content assessment of compatibility of vinorelbine tartrate with selected drugs during simulated Y-site injection. *Am J Hosp Pharm.* 1994;51(4):495–499.
567. Gershenson DM, Burke TW, Morris M, et al. A phase I study of a daily x3 schedule of intravenous vinorelbine for refractory epithelial ovarian cancer. *Gynecol Oncol.* 1998;70(3):404–409.
568. Havlin KA, Ramirez MJ, Legler CM, et al. Inability to escalate vinorelbine dose intensity using a daily x3 schedule with and without filgrastim in patients with metastatic breast cancer. *Cancer Chemother Pharmacol.* 1999;43(1):68–72.
569. Weiss AJ, Sabol J, Lackman RD. Concurrent administration of vinorelbine with recombinant human granulocyte colony-stimulating factor: an effective method of increasing dose intensity. *Am J Clin Oncol.* 1999;22(1):38–41.
570. Hohnke JA. A summary of vinorelbine (Navelbine) safety data from North American clinical trials. *Semin Oncol.* 1994;21(5 Suppl. 10):42–46; discussion 6–7.
571. Gebbia V, Testa A, Valenza R, et al. Acute pain syndrome at tumour site in neoplastic patients treated with vinorelbine: report of unusual toxicity. *Eur J Cancer.* 1994;30A(6):889.
572. Kornek GV, Kornfehl H, Hejna M, et al. Acute tumor pain in patients with head and neck cancer treated with vinorelbine. *J Natl Cancer Inst.* 1996;88(21):1593.
573. Raderer M, Kornek G, Hejna M, et al. Acute pulmonary toxicity associated with high-dose vinorelbine and mitomycin C. *Ann Oncol.* 1996;7(9):973–975.
574. Garrett CA, Simpson TA Jr. Syndrome of inappropriate antidiuretic hormone associated with vinorelbine therapy. *Ann Pharmacother.* 1998;32(12):1306–1309.
575. Hoff PM, Valero V, Ibrahim N, et al. Hand-foot syndrome following prolonged infusion of high doses of vinorelbine. *Cancer.* 1998;82(5):965–969.
576. Liebmann J, Friedman K. Adynamic ileus in a patient with non-small-cell lung cancer after treatment with vinorelbine. *Am J Med.* 1996;101(6):658–659.
577. Raderer M, Kornek G, Scheithauer W. Re: vinorelbine-induced pancreatitis: a case report. *J Natl Cancer Inst.* 1998;90(4):329.
578. Budman DR. Vinorelbine (Navelbine): a third-generation vinca alkaloid. *Cancer Invest.* 1997;15(5):475–490.
579. Zhou-Pan XR, Serec E, Zhou XJ, et al. Involvement of human liver cytochrome P450 3A in vinblastine metabolism: drug interactions. *Cancer Res.* 1993;53(21):5121–5126.
580. Ozols RF, Hogan WM, Ostchega Y, et al. MVP (mitomycin, vinblastine, and progesterone):

- a second-line regimen in ovarian cancer with a high incidence of pulmonary toxicity. *Cancer Treat Rep.* 1983;67(7-8):721-722.
581. Parimoo D, Jeffers S, Muggia FM. Severe neurotoxicity from vinorelbine-paclitaxel combinations. *J Natl Cancer Inst.* 1996;88(15):1079-1080.
 582. Tibaldi C, Pazzagli I, Berrettini S, et al. A case of ototoxicity in a patient with metastatic carcinoma of the breast treated with paclitaxel and vinorelbine. *Eur J Cancer.* 1998;34(7):1133-1134.
 583. Bajetta E, Di Leo A, Biganzoli L, et al. Phase II study of vinorelbine in patients with pretreated advanced ovarian cancer: activity in platinum-resistant disease. *J Clin Oncol.* 1996;14(9):2546-2551.
 584. Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. *Cancer.* 1998;83(6):1142-1152.
 585. Plourde PV, Dyroff M, Dukes M. Arimidex: a potent and selective fourth-generation aromatase inhibitor. *Breast Cancer Res Treat.* 1994;30(1):103-111.
 586. NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms; 2012 Contract No.: Document Number.
 587. Koshiyama M, Yoshida M, Konishi M, et al. Expression of pS2 protein in endometrial carcinomas: correlation with clinicopathologic features and sex steroid receptor status. *Int J Cancer.* 1997;74(3):237-244.
 588. Watanabe K, Sasano H, Harada N, et al. Aromatase in human endometrial carcinoma and hyperplasia. Immunohistochemical, *in situ* hybridization, and biochemical studies. *Am J Pathol.* 1995;146(2):491-500.
 589. Rose PG, Brunetto VL, VanLe L, et al. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2000;78(2):212-216.
 590. Tredway DR, Buraglio M, Hemsey G, et al. A phase I study of the pharmacokinetics, pharmacodynamics, and safety of single- and multiple-dose anastrozole in healthy, premenopausal female volunteers. *Fertil Steril.* 2004;82(6):1587-1593.
 591. Agorastos T, Vaitis V, Pantazis K, et al. Aromatase inhibitor anastrozole for treating endometrial hyperplasia in obese postmenopausal women. *Eur J Obstet Gynecol Reprod Biol.* 2005;118(2):239-240.
 592. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer; 2012 Contract No.: Document Number.
 593. Rao GG, Miller DS. Clinical applications of hormonal therapy in ovarian cancer. *Curr Treat Options Oncol.* 2005;6(2):97-102.
 594. Freeman SA, Modesitt SC. Anastrozole therapy in recurrent ovarian adult granulosa cell tumors: a report of 2 cases. *Gynecol Oncol.* 2006;103(2):755-758. Epub 2006 Jul 25.
 595. Li YF, Fu S, Hu W, et al. Systemic anticancer therapy in gynecological cancer patients with renal dysfunction. *Int J Gynecol Cancer.* 2007;17(4):739-763.
 596. Smyth JF, Gourley C, Walker G, et al. Anti-estrogen therapy is active in selected ovarian cancer cases: the use of letrozole in estrogen receptor-positive patients. *Clin Cancer Res.* 2007;13(12):3617-3622.
 597. Rao GG, Miller DS. Hormonal therapy in epithelial ovarian cancer. *Expert Rev Anticancer Ther.* 2006;6(1):43-47.
 598. Bertelli G, Venturini M, Del Mastro L, et al. Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study. *Ann Oncol.* 2002;13(6):883-888.
 599. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.
 600. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003;289(20):2651-2662.
 601. Imai M, Jobo T, Sato R, et al. Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus-usefulness and limitations. *Eur J Gynaecol Oncol.* 2001;22(3):217-220.
 602. Kobiashvili H, Charkviani L, Charkviani T. Organ preserving method in the management of atypical endometrial hyperplasia. *Eur J Gynaecol Oncol.* 2001;22(4):297-299.
 603. Bafaloukos D, Aravantinos G, Samonis G, et al. Carboplatin, methotrexate and 5-fluorouracil in combination with medroxyprogesterone acetate (JMF-M) in the treatment of advanced or recurrent endometrial carcinoma: A Hellenic cooperative oncology group study. *Oncology.* 1999;56(3):198-201.
 604. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Oncol.* 1999;17(6):1736-1744.
 605. Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004;92(1):10-14.
 606. Wilailak S, Linasmita V, Srisupundit S. Phase II study of high-dose megestrol acetate in platinum-refractory epithelial ovarian cancer. *Anticancer Drugs.* 2001;12(9):719-724.
 607. Katzenellenbogen BS, Choi I, Delage-Mourroux R, et al. Molecular mechanisms of estrogen action: selective ligands and receptor pharmacology. *J Steroid Biochem Mol Biol.* 2000;74(5):279-285.
 608. PDR Electronic Library, Vol 6.0.0a. *Thomas Medical Economics*; 2003 [updated. 2003; cited]; Available from <http://www.pdr.net>.
 609. Varras M, Polyzos D, Akrivis C. Effects of tamoxifen on the human female genital tract: review of the literature. *Eur J Gynaecol Oncol.* 2003;24(3-4):258-268.
 610. Day R. Quality of life and tamoxifen in a breast cancer prevention trial: a summary of findings from the NSABP P-1 study. National Surgical Adjuvant Breast and Bowel Project. *Ann NY Acad Sci.* 2001;949:143-150.
 611. Hatch KD, Beecham JB, Blessing JA, et al. Responsiveness of patients with advanced ovarian carcinoma to tamoxifen. A Gynecologic Oncology Group study of second-line therapy in 105 patients. *Cancer.* 1991;68(2):269-271.
 612. Ahlgren JD, Ellison NM, Gottlieb RJ, et al. Hormonal palliation of chemoresistant ovarian cancer: three consecutive phase II trials of the Mid-Atlantic Oncology Program. *J Clin Oncol.* 1993;11(10):1957-1968.
 613. Gelmann EP. Tamoxifen for the treatment of malignancies other than breast and endometrial carcinoma. *Semin Oncol.* 1997;24(1 Suppl. 1):S1-65-S1-70.
 614. Markman M, Isevinger KA, Hatch KD, et al. Tamoxifen in platinum-refractory ovarian cancer: a Gynecologic Oncology Group Ancillary Report. *Gynecol Oncol.* 1996;62(1):4-6.
 615. Covens A, Thomas G, Shaw P, et al. A phase II study of leuprolide in advanced/recurrent endometrial cancer. *Gynecol Oncol.* 1997;64(1):126-129.
 616. Lhomme C, Vennin P, Callet N, et al. A multicenter phase II study with triptorelin (sustained-release LHRH agonist) in advanced or recurrent endometrial carcinoma: a French anticancer federation study. *Gynecol Oncol.* 1999;75(2):187-193.
 617. Marelli MM, Moretti RM, Januszkiewicz-Caulier J, et al. Gonadotropin-releasing hormone (GnRH) receptors in tumors: a new rationale for the therapeutical application of GnRH analogs in cancer patients? *Curr Cancer Drug Targets.* 2006;6(3):257-269.
 618. Grundker C, Emons G. Role of gonadotropin-releasing hormone (GnRH) in ovarian cancer. *Reprod Biol Endocrinol.* 2003;1:65.
 619. Strohmeier D. Pathophysiology of tumor angiogenesis and its relevance in renal cell cancer. *Anticancer Res.* 1999;19(2C):1557-1561.
 620. Maloney H, Langer I, Kiss R, et al. Mechanisms of tumor angiogenesis and therapeutic implications: angiogenesis inhibitors. *Clin Exp Metastasis.* 1999;17(1):1-14.
 621. Burger RA. Overview of anti-angiogenic agents in development for ovarian cancer. *Gynecol Oncol.* 2011;121(1):230-238. Epub 2011 Jan 8.
 622. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971;285(21):1182-1186.
 623. Folkman J, Watson K, Ingber D, et al. Induction of angiogenesis during the transition from hyperplasia to neoplasia. *Nature.* 1989;339(6219):58-61.
 624. Gimbrone MA Jr, Leapman SB, Cotran RS, et al. Tumor dormancy in vivo by prevention of neovascularization. *J Exp Med.* 1972;136(2):261-276.
 625. Srivastava A, Laidler P, Davies RP, et al. The prognostic significance of tumor vascularity in intermediate-thickness (0.76-4.0 mm thick) skin melanoma. A quantitative histologic study. *Am J Pathol.* 1988;133(2):419-423.
 626. Abulafia O, Triest WE, Sherer DM. Angiogenesis in primary and metastatic epithelial ovarian carcinoma. *Am J Obstet Gynecol.* 1997;177(3):541-547.
 627. Alvarez AA, Krigman HR, Whitaker RS, et al. The prognostic significance of angiogenesis in epithelial ovarian carcinoma. *Clin Cancer Res.* 1999;5(3):587-591.
 628. Cooper RA, Wilks DP, Logue JP, et al. High tumor angiogenesis is associated with poorer survival in carcinoma of the cervix treated with radiotherapy. *Clin Cancer Res.* 1998;4(11):2795-2800.
 629. Kaku T, Hirakawa T, Kamura T, et al. Angiogenesis in adenocarcinoma of the uterine cervix. *Cancer.* 1998;83(7):1384-1390.
 630. Kaku T, Kamura T, Kinukawa N, et al. Angiogenesis in endometrial carcinoma. *Cancer.* 1997;80(4):741-747.
 631. Sauer G, Deissler H. Angiogenesis: prognostic and therapeutic implications in gynecologic and breast malignancies. *Curr Opin Obstet Gynecol.* 2003;15(1):45-49.
 632. Paley PJ. Angiogenesis in ovarian cancer: molecular pathology and therapeutic strategies. *Curr Oncol Rep.* 2002;4(2):165-174.
 633. Sieczkiewicz GJ, Hussain M, Kohn EC. Angiogenesis and metastasis. *Cancer Treat Res.* 2002;107:353-381.
 634. Folkman J. Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med.* 1995;333(26):1757-1763.

635. Gerber HP, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in pre-clinical studies. *Cancer Res.* 2005;65(3):671–680.
636. Zand B, Coleman RL, Sood AK. Targeting angiogenesis in gynecologic cancers. *Hematol Oncol Clin North Am.* 2012;26(3):543–563, viii.
637. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473–2483.
638. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011;365(26):2484–2496.
639. Holland CM, Day K, Evans A, et al. Expression of the VEGF and angiopoietin genes in endometrial atypical hyperplasia and endometrial cancer. *Br J Cancer.* 2003;89(5):891–898.
640. Gadducci A, Viciava P, Cosio S, et al. Vascular endothelial growth factor (VEGF) expression in primary tumors and peritoneal metastases from patients with advanced ovarian carcinoma. *Anticancer Res.* 2003;23(3C):3001–3008.
641. Gaffney DK, Haslam D, Tsodikov A, et al. Epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) negatively affect overall survival in carcinoma of the cervix treated with radiotherapy. *Int J Radiat Oncol Biol Phys.* 2003;56(4):922–928.
642. Frumovitz M, Sood AK. Vascular endothelial growth factor (VEGF) pathway as a therapeutic target in gynecologic malignancies. *Gynecol Oncol.* 2007;104(3):768–778.
643. Wright JD, Viviano D, Powell MA, et al. Bevacizumab combination therapy in heavily pretreated, recurrent cervical cancer. *Gynecol Oncol.* 2006;103(2):489–493.
644. Cohn DE, Valmadre S, Resnick KE, et al. Bevacizumab and weekly taxane chemotherapy demonstrates activity in refractory ovarian cancer. *Gynecol Oncol.* 2006;102(2):134–139.
645. Monk BJ, Choi DC, Pugmire G, et al. Activity of bevacizumab (rhMAB VEGF) in advanced refractory epithelial ovarian cancer. *Gynecol Oncol.* 2005;96(3):902–905.
646. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without Bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30(17):2039–2045. Epub 12 Apr 23.
647. Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? *Gynecol Oncol.* 2007;105(1):3–6.
648. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. *Gynecol Oncol.* 2010;117(3):497–504. Epub 2010 Apr 2.
649. Numnum TM, Rocconi RP, Whitworth J, et al. The use of bevacizumab to palliate symptomatic ascites in patients with refractory ovarian carcinoma. *Gynecol Oncol.* 2006;102(3):425–428. Epub 2006 Jun 23.
650. Matulonis UA. Bevacizumab and its use in epithelial ovarian cancer. *Future Oncol.* 2011;7(3):365–379. Epub 2011 Feb 16.
651. Kesterson JP, Mhawech-Fauceglia P, Lele S. The use of bevacizumab in refractory ovarian granulosa-cell carcinoma with symptomatic relief of ascites: a case report. *Gynecol Oncol.* 2008;111(3):527–529. Epub 2008 Aug 16.
652. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol.* 2009;27(1):127–145. Epub 2008 Nov 17.
653. van Dalen EC, Caron HN, Dickinson HO, et al. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane.* (6):CD003917.
654. Bertino JR. “Rescue” techniques in cancer chemotherapy: use of leucovorin and other rescue agents after methotrexate treatment. *Semin Oncol.* 1977;4(2):203–216.
655. Kamen BA, Winick NJ. High dose methotrexate therapy: insecure rationale? *Biochem Pharmacol.* 1988;37(14):2713–2715.
656. Tew KD, Houghton PJ, Houghton JA. *Preclinical and Clinical Modulation of Anticancer Drugs.* Boca Raton, FL: CRC Press; 1993.
657. Erlichman C. Fluorouracil and leucovorin for metastatic colorectal cancer. *J Chemother.* 1990;2(suppl. 1):38–40.
658. Zaniboni A, Arcangeli G, Meriggi F, et al. Low-dose 6-S leucovorin and 5-fluorouracil as salvage treatment in metastatic breast cancer. [Abstract]. *Proc ASCO.* 1994;13:91.
659. Kobayashi K, Schilsky RL. Update on biochemical modulation of chemotherapeutic agents. *Oncology (Huntingt).* 1993;7(5):99–106, 9; discussion 10–4, 17.
660. Barnhart K, Coutifaris C, Esposito M. The pharmacology of methotrexate. *Expert Opin Pharmacother.* 2001;2(3):409–417.
661. Elit L, Covens A, Osborne R, et al. High-dose methotrexate for gestational trophoblastic disease. *Gynecol Oncol.* 1994;54(3):282–287.
662. Sekharan PK, Sreedevi NS, Radhadevi VP, et al. Management of postmolar gestational trophoblastic disease with methotrexate and folinic acid: 15 years of experience. *J Reprod Med.* 2006;51(10):835–840.
663. Brock N, Pohl J, Stekar J, et al. Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention—III. Profile of action of sodium 2-mercaptopethane sulfonate (mesna). *Eur J Cancer Clin Oncol.* 1982;18(12):1377–1387.
664. Burkert H. Clinical overview of mesna. *Cancer Treat Rev.* 1983;10 Suppl. A:175–181.
665. Goren MP, McKenna LM, Goodman TL. Combined intravenous and oral mesna in outpatients treated with ifosfamide. *Cancer Chemother Pharmacol.* 1997;40(5):371–375.
666. Markman M, Kennedy A, Webster K, et al. Continuous subcutaneous administration of mesna to prevent ifosfamide-induced hemorrhagic cystitis. *Semin Oncol.* 1996;23(3 Suppl. 6):97–98.
667. Wahlberg E, Karlberg T, Kouznetsova E, et al. Family-wide chemical profiling and structural analysis of PARP and tankyrase inhibitors. *Nat Biotechnol.* 2012;30(3):283–288.
668. Plummer ER, Calvert H. Targeting poly(ADP-ribose) polymerase: a two-armed strategy for cancer therapy. *Clin Cancer Res.* 2007;13(21):6252–6256.
669. Griffin RJ, Pemberton LC, Rhodes D, et al. Novel potent inhibitors of the DNA repair enzyme poly(ADP-ribose)polymerase (PARP). *Anticancer Drug Des.* 1995;10(6):507–514.
670. O’Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med.* 2011;364(3):205–214. Epub 2011 Jan 5.
671. Liedtke C. Iniparib in Phase III—significant setback for patients with triple negative breast cancer. *Breast Care.* 2011;6(4):321–322.
672. Fogelman DR, Wolff RA, Kopetz S, et al. Evidence for the efficacy of Iniparib, a PARP-1 inhibitor, in BRCA2-associated pancreatic cancer. *Anticancer Res.* 2011;31(4):1417–1420.
673. O’Shaughnessy J, Telli M, Swain S, et al. Phase 3 study of iniparib (I) plus gemcitabine (G) and carboplatin (C) in metastatic triple-negative breast cancer (MTNBC)—results of an exploratory analysis by prior therapy. *Eur J Cancer.* 2011;47(suppl. 1):S338.
674. Liu X, Shi Y, Maag DX, et al. Iniparib nonselectively modifies cysteine-containing proteins in tumor cells and is not a Bona Fide PARP inhibitor. *Clin.* 18(2):510–523. Epub 2011 Nov 29.
675. Patel AG, De Lorenzo SB, Flatten KS, et al. Failure of iniparib to inhibit poly(ADP-Ribose) polymerase *in vitro.* *Clin Cancer Res.* 2012;18(6):1655–1662.
676. Delaney CA, Wang LZ, Kyle S, et al. Potentiation of temozolomide and topotecan growth inhibition and cytotoxicity by novel poly(adenosine diphosphoribose) polymerase inhibitors in a panel of human tumor cell lines. *Clin Cancer Res.* 2000;6(7):2860–2867.
677. Calabrese CR, Almasy R, Barton S, et al. Anti-cancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361. *J Natl Cancer Inst.* 2004;96(1):56–67.
678. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature.* 2005;434(7035):917–921.
679. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature.* 2005;434(7035):913–917.
680. Plummer R, Jones C, Middleton M, et al. Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors. *Clin Cancer Res.* 2008;14(23):7917–7923.
681. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009;361(2):123–134. Epub 2009 Jun 24.
682. Rajan A, Carter CA, Kelly RJ, et al. A phase I combination study of olaparib with cisplatin and gemcitabine in adults with solid tumors. *Clin Cancer Res.* 2012;18(8):2344–2351. Epub 012 Feb 27.
683. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet.* 2010;376(9737):235–244. Epub 2010 Jul 6.
684. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet.* 2010;376(9737):245–251. Epub 2010 Jul 6.
685. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet.* 2011;12(9):852–861. Epub 2011 Aug 19.
686. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366(15):1382–1392.

15

Immunotherapy of Gynecologic Malignancies

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The natural clinical history of ovarian cancer makes it particularly suited for the evaluation of immune-based strategies. Although the majority of patients are diagnosed with advanced disease, 70% are in a complete clinical remission following initial cytoreductive surgery and platinum and taxane-based primary chemotherapy (1). However, only 30% of optimally debulked stage III patients will remain disease-free with a median progression-free interval of approximately 24 months (2). Despite the high relapse rate, many patients return to a complete or partial clinical remission following additional chemotherapy, but ever-shortening intervals of response are seen (3). Despite this chronic course of relapse and response, the median survival of optimally debulked patients exceeded 60 months in a study evaluating intraperitoneal (IP) therapy as part of primary treatment (4). Neither higher doses nor protracted schedules, nor non-cross-resistant consolidation chemotherapy has provided additional benefit. Ovarian cancer patients with minimal disease burdens are therefore appropriate candidates for the evaluation of immune-based strategies, which typically have excellent side-effect profiles.

With regard to other gynecologic malignancies, the majority of immune strategies being evaluated in patients with cervical cancer target human papillomavirus, and this subject is covered separately in the appropriate chapter (5). The evaluation of immune-based approaches for the treatment of endometrial cancer is limited but interest is growing (6). Targets such as human trophoblast cell surface marker (TROP-2), Wilms Tumor Gene (WT-1), and a variety of cancer testis antigens have been shown to be expressed in endometrial cancers which has prompted early stage trials with dendritic cell vaccines and adoptive cellular therapy as two examples (7,8). The bulk of the clinical information available to date with regards to immunotherapy when one excludes cervical carcinoma, however, remains in patients with ovarian cancer.

CANCER IMMUNOLOGY: OVERVIEW

The immune system evolved to fight foreign invaders such as bacteria, viruses, and parasites. However, strong evidence suggests that it also plays a crucial role in controlling or rejecting incipient cancers. William B. Coley first observed regression in patients with sarcoma contracting “accidental erysipelas” as early as 1893 (9). Since patients with competent immune systems still develop cancers, and spontaneous remission of tumors is rare, enthusiasm for the effectiveness of immune system control has waxed and waned over the decades. The fact that animal models with a variety of deficiencies in immunologic components consistently develop carcinoma has allowed the concept of immunosurveillance to be sustained and developed (10,11).

Observations in patients with ovarian cancer strongly support a role for immune system involvement in patient outcome. For example, the 5-year overall survival in epithelial ovarian cancer has been correlated to the presence or absence of tumor infiltrating lymphocytes (TIL) (38% vs. 4.5%, $p < 0.001$) (12). A second study also showed improved survival in patients with increased frequencies of intraepithelial CD8+ TIL (55 months vs. 26 months; HR = 0.33; 95% CI, 0.18–0.60; $p = 0.0003$) (13). In contrast, patients with increased numbers of immune suppressive CD4+CD25HI regulatory T-cells (Tregs) have reduced survival (14). The process is made more complex when we recognize that not only can the immune system protect the host against tumor development, but it is thought to select cancer cells of lower immunogenicity which can escape early immunity due to changes in gene expression. This actually leads to an outgrowth of tumors with the capacity to escape recognition and this process has been termed immunoediting (15). The immunoediting or “immune sculpting” process, therefore, is responsible for shaping the immunogenicity of the tumors that will eventually form. Considering the effectors of the immune system in the context of both of these processes is important in order to develop immune directed therapies with the greatest chance of success (16,17).

The mechanism by which tumors escape from immune surveillance is complex. An alteration in the function of almost every process discussed herein to facilitate immune activation has been postulated to participate in the ways tumors can evade immune detection. In some cases, antigen presentation is down regulated, or gene deletions or rearrangements may cause reduced expression of the MHC-I complex thus preventing T-lymphocyte activation (18,19). Tumors can also secrete proteins that inhibit T-cell effector action or that promote the development of regulatory T-cells that suppress immune function (20). A recent observation showed that certain melanomas can actually remodel their stromal microenvironment so it resembles lymphoid tissue which recruits regulatory cells to promote tolerance and allow tumor progression (21). Other mechanisms include the downregulation of intracellular adhesion molecules (22), changes in molecules responsible for apoptosis signaling (23), or the development of peripheral tolerance (24). Based on the increasing number of interacting mechanisms with putative activity that allow immune escape, approaches directed against multiple mechanisms will likely be needed in order to eradicate immune tolerant tumor cells (25).

Innate Immunity

The immune system is broadly divided into 2 arms, innate and active immunity, but there are multiple examples of cross communication between them. Recent data, for example, show that neutrophil survival is influenced by T cell responses (26).

Innate immunity is present at birth and does not require adaptation to react against microorganisms or tumors. It includes physical barriers (mucous membranes, skin), chemical components (complement, hydrolytic enzymes), and multiple other cellular components. For example, natural killer cells are lymphocytes that are programmed to recognize and destroy tissues that have been altered or stressed, e.g., by viruses or by malignant transformation (27). They do not have antigen specific receptors but instead have inhibiting receptors that can recognize MHC class I molecules on normal cells, which prevents their activation (28). MHC I expression is aberrant or absent on many virus and tumor infected cells (29). Another component includes macrophages, which play many roles in immunity and inflammation, including production of a multitude of soluble secreted proinflammatory proteins, which are growth factors for other cells of the immune system, for neovasculature, and for cancer cells. These growth factors include *cytokines* and *chemokines*, and they support the growth, movement, and survival of immune and inflammatory cells. Macrophages play important roles in tissue remodeling during wound healing, mediating inflammatory responses, sampling molecules from the environment through internalization, and presenting antigens to stimulate T cells. Macrophages can also play a counterproductive role through production of molecules that promote tumor growth and angiogenesis (e.g., vascular endothelial growth factor [VEGF] and basic fibroblast growth factor [FGF]) (30). Macrophages can also inhibit immune responses through production of cytokines and other molecules that down-regulate immunity, such as prostaglandins E₂, arginase I, and transforming growth factor- β . Thus, the role of macrophages in tumors is complex: they provide an additional means of communication between traditionally defined innate and acquired immunity effectors (31). Dendritic cells have some properties that are similar to macrophages, including production of cytokines and sampling of molecules from the environment. Most importantly, dendritic cells are one of the key links between the innate immune system and the adaptive or acquired immune system through presentation of antigens (professional antigen-presenting cells) to initiate T-cell activation.

Adaptive Immunity

Adaptive immunity is characterized by adaptation to antigens, for example, antigens of infectious pathogens (or potentially by cancer). This arm of the immune system is not mature or activated at birth, but rather adapts through maturation in response to antigens of pathogens. It is characterized by receptors encoded by the immunoglobulin (Ig) gene family. These receptors have the capacity to rearrange, creating enormous diversity (>10 different receptors) (11–12). This provides a system to generate enormous specificity that recognizes and responds to a wide range of antigens that have not previously been encountered.

The two major cell types of acquired immunity are *T lymphocytes* (T cells) and *B lymphocytes* (B cells). T cells have the capacity to recognize antigens sequestered in different compartments within cells, for instance, antigens generated in the cytoplasm or nucleus by viral infections (32). T cells recognize antigens as short peptides, 8 to 16 amino acids in length. These peptides must be complexed with and presented by specialized antigen-presenting molecules, the major histocompatibility complex (MHC) molecules, to T-cell receptors. In humans, MHC molecules are the human leukocyte antigens (HLAs) expressed on virtually every cell in the body. On the other hand, B cells produce secreted *antibodies* that can recognize soluble and cell surface molecules. Both T cells and B cells initially develop with a limited range of receptors for immune recognition. However, in response to antigen (e.g., from a virus or cancer cell) presented by a professional antigen-presenting cell, T cells or B cells

that have receptors with the best “fit” to the antigen itself (for B cells) or antigen/MHC complex (for T cells) are stimulated to proliferate and this subpopulation is quickly expanded (33).

Humoral Immunity

B cells recognize antigens usually in their natural configuration (32). An individual host has a repertoire of B cells that are capable of generating antibodies against the full range of pathogens encountered in the environment. To do this, the total population of B lymphocytes expresses a diverse repertoire of immunoglobulins. Each B cell expresses immunoglobulin against a single antigenic determinant, with the immunoglobulin expressed at the cell surface of the B cell where it acts as a specific receptor to transduce signals in response to that antigen (34). Once activated, the B cell is to create an individual monoclonal antibody (mAb). The diversity of specificities in different B cells is generated by rearrangements of the immunoglobulin genes, and new antibody specificities continue to be generated in response to new antigens (35). During development, B cells with high avidity immunoglobulins against ubiquitous self-antigens are eliminated. This elimination of B cells reactive with autoantigens is not absolute, however, as a broad array of antibodies against autoantigens is found in the blood of humans. Peripheral blood B cells consist of naïve and relatively short-lived B cells, long-lived memory B cells resulting from maturation in response to antigenic stimulation, and a small population of B cells expressing germ-line immunoglobulins that have not undergone rearrangement (which are found in the CD5+ B-cell population) (13).

B cells are mobile and after development in the bone marrow they migrate through the peripheral blood to B-cell-rich areas in lymphoid organs, e.g., the follicles of lymph nodes, spleen, and gastrointestinal tract. Many B cells continue recirculating in the blood. If cognate antigen is encountered in lymphoid organs, the B lymphocyte migrates to the T-cell-rich areas where appropriate T-cell help can be provided to promote increased antibody diversity and increased affinity through immunoglobulin gene rearrangements (36). This T-cell help does not have to be induced by the same antigen. Chemical conjugation of the antibody-recognized antigen to highly immunogenic bacterial or xenogeneic proteins or, alternatively, expression of the antigen in bacterial or viral vectors, is widely used approaches to ensure adequate T-cell help in vaccines. The result of T-cell help is generation of plasma cells, the most mature form of B cell with the highest capacity for antibody production. In addition, T-cell help promotes formation of germinal centers in lymphoid organs where hypermutation in immunoglobulin genes and class and subclass switching occur to generate antibodies with higher affinities for antigen. Class switching refers to changes in antibody class during an immune response, with the IgM class of antibodies appearing first, generally followed by antibodies of the IgG class (different subclasses of IgG antibodies have different blood half-lives and different capacities for effector functions, such as fixation of complement or binding to Fc receptors). The consequence is plasma cells secreting increasingly higher affinity IgG antibodies as the immune response matures over time (37). In addition, some B cells that generally recognize nonprotein antigens, such as carbohydrate or glycolipid antigens, can be stimulated to proliferate in the absence of T-cell help. The immunoglobulin variable region (called the Fv region) determines antibody specificity and is located in the Fab domain of immunoglobulins. This region mediates effective binding to antigens. However, the constant region (Fc), where antibody class and subclass are determined, is equally critical. Binding of antibody to antigen results in a conformational change in the Fc portion, leading to activation of several effector mechanisms, including complement activation (discussed below). IgM antibodies are synthesized early in the response. If T-cell help is

available, antibody responses mature through immunoglobulin gene rearrangements into the higher affinity IgG classes. These are capable of improved binding to antigen as well as receptors on the bone marrow-derived cells for the Fc domain, expanding potential effector functions. The responses to most nonprotein antigens are IgM class and generally do not mature to IgG responses. The IgM pentamer structure is specialized to increase avidity of binding to multimeric antigens and to efficiently activate effector functions such as complement (38). Activation of complement, which includes blood components with different enzymatic properties, results in opsonization (coating of pathogens by complement components), recognition by complement receptors on macrophages, monocytes, neutrophils, and dendritic cells, with subsequent activation of these cells leading to phagocytosis and/or killing. In addition, complement can form a membrane attack complex, which creates holes in membranes of target pathogens and cancer cells, producing complement-dependent cytotoxicity (CDC) (39,40). IgG antibodies are synthesized following immunoglobulin gene rearrangements, with switches in Fc domains, as the B cell matures in response to T-cell help. IgG antibodies usually have higher affinity, and can be found in the extracellular space as well as in the blood. IgG1 and IgG3 antibodies in humans are especially effective at activating complement and also at sensitization of pathogens for killing by NK cells, macrophages, and other cells with complement receptors and immunoglobulin Fc receptors (41).

Opsonization for ingestion and destruction by phagocytes can occur through complement activation, but also occurs directly as a consequence of engagement of Fc receptors on phagocytic cells. Antibodies complexed to antigen bind to Fc receptors, which can lead to activation signals through activating Fc receptors (e.g., FcRIII), but activation can be countered by IgG binding to the inhibitory Fc receptor, FcRIIB. Fc receptors, which are bound effectively by IgG1 and IgG3 subclasses of human antibodies, are expressed on monocytes, macrophages, NK cells, neutrophils, mast cells, and other cells. Cross-linking of Fc receptors leads to activation of the cells, in some cases leading to antibody-dependent cell-mediated cytotoxicity (ADCC) of tumor cells through production of cytotoxic molecules, such as perforin and granzyme by NK cells and reactive molecular species by macrophages (42–44). Monoclonal antibodies are commonly used for cancer therapy. Antitumor effects can be mediated in part by antibody binding to critical molecules on the surface of tumor cells, for example by inhibiting tumor cell attachment or growth receptors. However, generally interactions of antibody with cell antigen are not very effective unless Fc receptor-mediated effector mechanisms are also activated.

Cellular Immunity

T lymphocytes recognize processed (digested) molecules that complex with MHC molecules within antigen-presenting cells. The antigen/MHC molecules are then trafficked to the cell surface for recognition by T-cell receptors, which are encoded by genes of the immunoglobulin family. Similar to generation of antibodies, great diversity of T-cell receptors is generated by rearrangements of these immunoglobulin family genes. Each monoclonal T-cell receptor must bind to its cognate antigen/MHC complex (CD4 cells bind to MHC class II molecules, and CD8 cells bind to MHC class I molecules) presented on the surface of antigen-presenting cells (45,46). Signaling from the T-cell receptor following engagement of antigen/MHC complex is insufficient to activate the T cell. Additional signals are required (co-stimulatory signals or “signal 2”). The most important co-stimulatory signal in T cells comes from the T-cell surface molecule CD28, which engages B7 molecules (CD80 and CD86) on antigen-presenting cells (47–49). Engagement of T-cell receptor by antigen/MHC in conjunction with CD28 engagement

of B7 is sufficient to activate naïve T cells. Within several days following T-cell activation, a second molecule, CTLA-4, appears on the T-cell surface to provide a brake to the T-cell response. CTLA-4 also binds B7 molecules, but with much higher affinity, therefore displacing CD28 activation signals. CTLA-4 signaling leads to down-regulation of the T-cell response. The manipulation of CTLA-4 activity has recently been shown to have therapeutic efficacy with recent data showing tumor responses in patients with melanoma (50,51). A variety of other co-stimulatory molecules are up-regulated on the surface of activated T cells, including OX40 and 4-1BB, which promote survival of T cells and help generate long-lived T-cell memory responses (52,53). Once T cells are activated by professional antigen-presenting cells (primarily dendritic cells), they gain a variety of effector functions, including the production of cytokines and cytotoxic molecules, which lead to death of target cells.

Antigen-Presenting Cells

Dendritic cells are the prototype professional antigen-presenting cells and are the critical link between innate immunity and acquired immunity. These are phagocytic cells that sit on epidermal surfaces, including skin and mucosal membranes, constantly sampling their environment to search for infectious organisms. Although dendritic cells continuously ingest molecules from their environment, uptake of antigen is insufficient to activate dendritic cells. Rather, dendritic cells have a set of receptors, most notably the toll-like receptors (TLRs), which can recognize lipid-containing molecules and CpG-rich DNA and poly-U RNA sequences produced specifically by microbial organisms. Engagement of TLR signals for activation of the dendritic cell, with increased expression of MHC and B7 molecules, and movement of cells with captured antigen to draining lymph nodes. It is in draining lymph nodes that dendritic cells activate appropriate T cells that recognize that particular antigen presented by MHC molecules. Subsequently, activated T cells can then travel from the draining lymph node to distant sites of infection or tumor to carry out the effector functions. One of the central problems for cancer immunology is that dendritic cells may ingest and process cancer antigens, but without activation through TLRs or other receptors, the dendritic cells remain incapable of activating T cells (because of insufficient expression of co-stimulatory molecules, such as B7) and do not move to draining lymph nodes. In fact, insufficiently activated dendritic cells presenting antigens can induce energy, a form of immune tolerance where T cells become paralyzed and incapable of responding to cognate antigens. This is one of the mechanisms used to maintain immune tolerance to self to prevent autoimmunity, but also presents a major hurdle for cancer immunity. Cancer cells do not have any readily apparent mechanism to activate dendritic cells, although several self molecules, including heat shock protein, hyaluronate, and uric acid crystals have been suggested to cause activation.

Helper and Regulatory T Cells

Several types of T cells are activated by dendritic cells, and which type is influenced by whether antigens are presented by MHC class I or MHC class II molecules on antigen-presenting cells. MHC class I molecules complexed with antigen stimulate CD8+ T cells that are cytotoxic and kill target cells (infected cells or tumor cells). Antigens presented by class II MHC molecules stimulate CD4+ helper T cells. Helper T cells produce chemokines and cytokines to help recruit and orchestrate other components of the immune system. Helper T cells come in several types and different cytokines in the milieu determine what type of T cell is generated. Each type of helper T cell mediates

different types of immune responses with different characteristics. Th1 T cells produce interferon (IFN)- γ to activate cytotoxic T cells and macrophages for *cellular immune responses*. On the other hand, Th2 helper T cells produce interleukin (IL)-4 and other cytokines that favor antibody responses, or *humoral immunity*. The newly discovered Th17 CD4⁺ T cell produces IL-17 to mediate inflammatory autoimmune diseases, such as arthritis, colitis, and encephalitis, and may play a role in cancer pathogenesis, either by promoting cancer progression or by destroying tumors. Another type of CD4⁺ T cell restricted by MHC II presentation negatively regulates immune responses. These are regulatory T cells, or Tregs. Tregs recognize self antigens, are dependent on IL-2, and produce inhibitory molecules such as IL-10 and transforming growth factor- β . Th1 cellular immunity may be particularly effective at attacking tumors in tissues, while humoral immunity may have an advantage in controlling circulating metastatic tumor cells. Infiltration of ovarian cancers and other cancers by Treg cells is associated with a poorer prognosis (50,54).

CANCER IMMUNITY AND IMMUNOTHERAPY

Careful studies over the past 3 decades have shown that the immune system can recognize and destroy cancers, usually involving interactions between multiple arms of the immune system. For instance, simple recognition by T cells, antibodies, or NK cells is usually not sufficient to reject cancers. Cytotoxic T cells and NK cells produce soluble and cell surface molecules that induce death of target tumor cells. Helper T cells can produce cytokines and chemokines that not only recruit cytotoxic T cells or B cells to make antibodies, but also inflammatory cells which mediate tissue destruction. Antibodies can activate NK cells, macrophages, or other cells that have receptors for the antibodies' Fc domain, leading to activation of the recruited cells, a mechanism implicated in the antitumor effects of monoclonal antibody therapies. Antibodies can also activate complement proteins in the blood that can directly kill tumor cells and activate inflammatory cells at the tumor site.

The abundant evidence that the immune system can recognize antigens on tumor cells and that immunity is sufficient to destroy tumors, provides the impetus to continue and develop strategies for *immunotherapy*. These approaches can be broadly divided into three groups. First, *immune modulation* uses more broad approaches to treat cancer. Traditional examples include cytokines such as IL-2, IL-12, or interferons, and more recently more targeted approaches such as those interfering with CTLA-4 or PD-1 (51). Secondly, *passive therapy* refers to the transfer of specific components from the acquired immune system to the host with cancer. The best examples are monoclonal antibodies directed against antigens expressed on the surface of cancer cells such as rituximab against the CD20 antigen, or trastuzumab (Herceptin) directed towards the HER 2 receptor in breast cancer. It should be noted that although the antitumor effects of trastuzumab in part probably involve inhibition of signaling by the HER2 tyrosine kinase oncogene, evidence strongly supports a major role for immune activation of Fc receptor-positive cells by both rituximab and trastuzumab (55). Another example of passive immunotherapy is adoptive cellular therapy, where cells from the blood or bone marrow donor are purified, cultured, and/or manipulated outside the body and reinfused into the same patient (autologous) or a different patient (allogeneic). Cellular therapy has particularly focused on T cells and more recently on NK cells. Finally, *active immunization* refers to vaccines that trigger the patient to make an immune response. Both passive and active immunotherapy must be directed against specific antigens on cancer cells, and the notion of an

Table 15.1 Antigenes for Immunotherapy

Antigen Category	Representative Examples
Differentiation antigens	Tyrosinase (62), Melan-Mart-1(302), gp-100 (303)
Mutational antigens	CD4 (63), β -catenin (304), caspase (305)
Amplification antigens	HER2/neu (64), P53 (306)
Splice variant antigens	NY-CO-37/PDZ 45 (65), ING1 (307)
Glycolipid antigens	MUC1 (66)
Viral antigens	HPV (67)
Cancer testis antigens	MAGE (68), NY-ESO-1 (308), LAGE-1 (309)

integrated immune response with effectors to include antibodies and T cells as well as some component of immunomodulation is increasingly becoming the goal of immunotherapeutic strategies (56).

With regards to potential targets, ongoing advances utilizing newer technologies including serological analysis of recombinant cDNA expression libraries (SEREX) (57,58), robust applications of bioinformatics (59) and seromic profiling techniques (60) have allowed the further characterization of tumor associated antigens in multiple tumor types. There are over 2000 candidate tumor associated antigens and they are generally classified as follows: (61) (a) differentiation antigens (62), (b) mutational antigens (63) (that are altered forms of proteins), (c) amplification antigens (64), (d) splice variant antigens (65), (e) glycolipid antigens (66), (f) viral antigens (67), and (g) cancer-testis (CT) antigens (68). Representative examples of each group are seen in Table 15.1.

In addition to selecting the appropriate targets, it is necessary to select the strategy to be used for immunotherapy. Multiple approaches have been considered from giving the effector cells directly to include antigens of a variety of types given alone or with adjuvants, modified or unmodified tumor cell lysates can be administered (autologous or allogeneic), dendritic cells can be primed with a variety of agents, tumor hybrids with antigen-presenting cells can be made, or DNA alone or in a recombinant fashion can be administered. A sample of cancer vaccine strategies are listed in Table 15.2.

Table 15.2 Examples of Vaccine Approaches

- I. Antigens alone with or without adjuvants
 - Peptides
 - Protein
 - Gangliosides
 - Immunoglobulin idiotypes
- II. Dendritic cells
 - Peptides, immunoglobulin idiomorph
 - Tumor lysates
 - DNA or RNA
 - Protein
- III. Tumor cells unmodified or modified
 - Autologous
 - Allogeneic
 - Mixed autologous-allogeneic
- IV. Tumor-APCs hybrid
- V. DNA alone (naked DNA), recombinant viruses (adenovirus, vaccinia, and others)

A critical component of any immune approach is a consideration of immune escape. Tumors escape destruction by the immune system via a variety of active, regulatory mechanisms. These include downregulation of MHC and tumor antigen loss (69), stimulation of the inhibitory receptors on T-cells such as CTLA-4 (70), PD-1 and LAG-3 (71), tumor overproduction of indoleamine 2,3-dioxygenase (IDO) (72), induction of increased tumor infiltration by regulatory CD4⁺CD25⁺ T cells (Tregs) (73) and also certain types of natural killer T (NKT) cells that inhibit tumor immune destruction (74). Overcoming these mechanisms is the goal of immunomodulation.

IMMUNOMODULATION

Multiple potential difficulties remain in developing new immunotherapy approaches, including insufficient activation of dendritic cells by cancer cells, inhibition of responses by Treg cells, and both intrinsic and extrinsic mechanisms that down-regulate T-cell responses, e.g., signaling through CTLA-4. These checkpoints all participate to dampen immune responses against cancer. Modulating immune check points by activation of effector cells, depletion of Tregs or activation of professional APCs could substantially improve the therapeutic efficacy of vaccines or adoptively transferred T cells. The development of functional antibodies is now enabling effective immunomodulation as shown in Figure 15.1. Passive therapy with monoclonal antibodies or with adoptive cellular treatments may also be able to bypass some of these checkpoints.

Dendritic Cell Activation

The main mechanism of immune stimulation by CD 40 ligands is activation of DCs resulting in increased survival, upregulation of costimulatory molecules, and secretion of critical cytokines to T cell priming such as IL-12. This promotes antigen presentation, priming and cross priming of CD4⁺ and CD8⁺ effector T cells (75). However, agonistic anti-CD40 antibody

is best used in combination with vaccines or Toll-like receptor agonists (75,76), because alone it can accelerate the deletion of tumor-specific cytotoxic lymphocytes (77). Additional value of CD40 ligation is provided by the fact that ovarian cancers, like many tumors, express the CD40 receptor (78–81) and respond to CD40 agonists with apoptosis and growth inhibition *in vitro* and *in vivo* (80,82,83).

Effector T-cell Activation

T-cell activation is triggered through the T-cell receptor by recognition of the cognate antigen complexed with MHC. This activation is regulated by complex signals downstream of CD28 family immune receptors, which includes costimulatory (CD28 and ICOS) and inhibitory receptors (CTLA-4, PD-1 and BTLA). PD-1 and CTLA-4 are induced on T cells following a TCR signal, and result in cell cycle arrest and termination of T-cell activation. The use of blocking CTLA-4 or PD-1 mAbs can sustain the activation and proliferation of tumor-specific T cells, preventing anergy or exhaustion and thereby allowing the development of an effective tumor-specific immune response.

CTLA-4 Blockade

CTLA-4 is the best characterized among the inhibitory B7 receptors. As with CD28, CTLA-4 also binds CD80 and 86 expressed by APCs, but provides inhibitory signals to the T cell, serving as a negative feedback loop. In animal models, CTLA-4 proved critical in the normal functioning immune system. CTLA-4 knockout mice develop uncontrolled lymphoproliferation with early lethality. Furthermore, administration of CTLA-4 blockade significantly enhanced antitumor immunity in a variety of mouse models and with various therapeutic combinations including vaccine, TLR agonist, chemotherapy and radiation therapy. The mechanism by which CTLA-4 blockade induces tumor regression is not fully understood. Although Treg constitutively express CTLA-4, CTLA-4 blockade had no effect on the number or function of Treg in cancer patients. It seems that CTLA-4 blockade activates directly CD4⁺ and CD8⁺ T effector cells

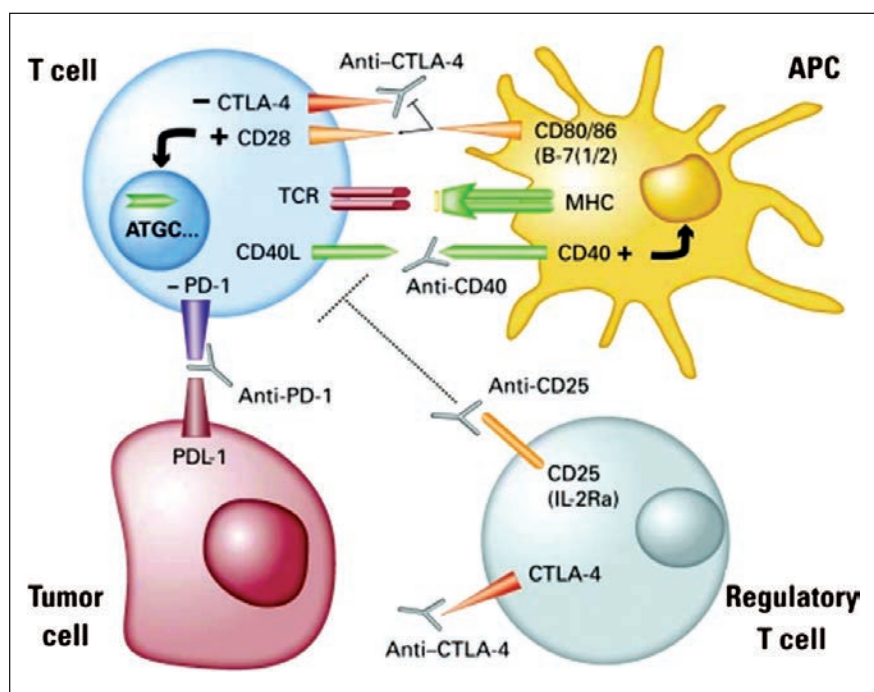


FIGURE 15.1 The modulation of immune checkpoints.

Source: From Kandalaft, LE, Powell DJ Jr, Singh N, et al. Immunotherapy for ovarian cancer: what's next? JCO 2011;29:925–333, with permission.

by removing an inhibitory checkpoint on proliferation and function (84). The combination of direct enhancement of T cell function and inhibition of Treg activity is essential for mediating the full therapeutic effects of anti-CTLA-4 antibodies during cancer immunotherapy (85).

Based on these data, several clinical studies have been undertaken to assess the efficacy of a CTLA-4 antagonist antibodies in the setting of human cancer. The majority of clinical data to date have emerged from studies in patients with melanoma (reviewed in (86)). Phase II studies with ipilimumab monotherapy showed objective responses at a dose of 3 to 9 mg/kg every 3 weeks, with 10 mg/kg showing the best risk-benefit profile. Ipilimumab (3 mg/kg every 4 weeks x 4) administered in combination with *chemotherapy* (dacarbazine) resulted in enhanced objective response rates without added toxicity. Ipilimumab has also been combined successfully with IL-2 (720,000 U/kg every 8 hours x 15 (OR rate of 22% - 3 CRs) or melanoma vaccine (OR rate of 13% - 2 complete responses). In addition, tremelimumab has also produced OR and CRs in melanoma patients. To date, CTLA-4 antibody has not shown superiority over standard chemotherapy trial in treatment-naïve melanoma patients in a phase III randomized clinical, which was discontinued after interim analysis. In melanoma patients, the most common grade 3 to 4 adverse events were colitis/enterocolitis (increased frequency of diarrhea/stools), dermatitis, and hypophysitis.

Eleven patients with ovarian carcinoma, previously vaccinated with GM-CSF modified, irradiated autologous tumor cells (GVAX), received ipilimumab (1 month to 3 years following GVAX). Significant antitumor effects were observed in a minority of the patients. One patient achieved a dramatic fall in CA-125 levels several months after an initial dose of ipilimumab; although the response was not maintained, a second infusion resulted in a more rapid decline in CA-125 values. Nine additional infusions of the anti-CTLA-4 antibody spaced at 3- to 5-month intervals over nearly 4 years have maintained profound disease control, with grade 1 rash as the only adverse event. An objective radiographic response was noted in parallel with the reduction in CA-125. Moreover, this patient's course was initially characterized by a remarkable periodicity to the rise and fall of CA-125 levels, but this gradually dampened as a function of time and/or prolonged therapy, demonstrating a lack of acquired resistance to ipilimumab commonly observed with cytotoxic chemotherapy (87). In contrast to the melanoma cohort, a single dose of 3 mg/kg Ipilimumab triggered 2 cases of grade 3 gastrointestinal inflammation among the 9 ovarian carcinoma patients, consistent of significant diarrhea. Endoscopic biopsies revealed mucosal damage associated with abundant granulocytes, macrophages, CD4+ and CD8+ T cells, and FoxP3+ Treg. The remaining seven patients showed only minor inflammatory toxicities including papular rash, or urticarial-like reactions at sites of prior vaccination (87). Tumor regression in these patients correlated with the CD8+/Treg ratio, suggesting that other forms of therapy that target Treg depletion may provide a highly effective form of treatment when combined with the tumor vaccine and CTLA-4 antibody arsenal (87).

PD-1 Blockade

Programmed death receptor-1 is a negative regulator of cell activation, primarily expressed on both B and T lymphocytes, which binds PD-L1 and PD-L2 ligands. PD-L2 is restricted to professional antigen-presenting cells, while PD-L1 is expressed on many tissues, and plays a pivotal role in maintaining peripheral tolerance. Importantly, cancer cells have adopted expression of PD-L1 into their immunosuppressive arsenal (88) and a variety of epithelial cancers express PD-L1 (89–91). It has also recently been shown that ovarian carcinoma cells as well as

tumor-infiltrating tolerogenic DCs and myeloid derived suppressor cells express PD-L1 (92,93). Furthermore, expression levels correlate with disease course. Although PD-1 signaling can occur at very low levels of receptor expression, elevated levels of PD-1 have recently been attributed functional significance. During conditions of chronic antigen persistence (such as in chronic viral infections), antigen specific effector T cells expressing high levels of PD-1 were demonstrated to be functionally exhausted, i.e., unable to proliferate, secrete IL-2, or kill target cells (94). It has been shown recently that tumor infiltrating lymphocytes in metastatic melanoma and other tumors expresses higher levels of PD-1 than CD4+ and CD8+ cells in the peripheral blood of healthy patients and exhibit phenotypic and functional characteristics of exhausted T cells with impaired effector function. These findings suggest that the tumor microenvironment can lead to up-regulation of PD-1 on tumor-reactive T cells and contribute to impaired antitumor immune responses (95). Indeed, constitutive or inducible expression of PD-L1 by tumors conferred resistance to immunotherapy in mice related to failure of antigen-specific CD8+ CTLs to destroy tumor cells but without impairment of CTL function (96).

Following evidence that PD-1 blockade through gene therapy approaches in the tumor microenvironment activates antitumor immunity (97), antibodies blocking PD-L1 or PD-1 were found to profoundly enhance the efficacy of immune therapy (96,98). Anti-PD-1 antibody has been combined with cell-based vaccines and demonstrated increased infiltration, potency and duration of activity of CD8 T cells in the tumor microenvironment in the setting of B16 melanoma and CT26 colon carcinoma in mice.

Despite their similarities, the regulatory roles of CTLA-4 and PD-1 may differ substantially in cancer patients. First, Even though PD-1 and CTLA-4 ligation efficiently block T-cell responses, the homeostatic function of the 2 inhibitory receptors differs. For example, CTLA-4 ligation does not inhibit PI3-kinase signaling, while PD-1 engagement blocks the induction of PI3K activity. PD-1-mediated signaling blocks T-cell activation more effectively than CTLA-4-mediated signaling. In addition, PD-1 signaling may be related to T-cell apoptosis. Second, whereas the ligands for CTLA-4, CD80 and CD86, are primarily expressed by mature antigen-presenting cells, PD-L1 (on tumor cells or myeloid cells) and PD-1 (on effector T cells) are significantly upregulated in the tumor microenvironment. Thus, the effects of PD-1 blockade may be more pronounced in the tumor than in periphery. A phase I study using PD-1 blocking antibody showed the antibody to be safe and well tolerated in patients with hematologic malignancies. No single maximum tolerated dose was defined in this study. Clinical benefit was observed in 33% of the patients with one complete remission (99).

T Regulatory Cell Depletion

CD4+ CD25+ Foxp3+ T regulatory cells are responsible for maintaining peripheral tolerance by inhibiting T-cell activity. A number of Treg-depleting strategies have been investigated (100–104). An example is the use of low dose oral or intravenous cyclophosphamide (105,106). Other strategies for Treg depletion are through targeting the IL-2 receptor alpha chain, also known as CD25. In mouse models, the use of anti-CD25 monoclonal antibody before vaccination led to complete tumor rejection and establishment of long-lasting tumor immunity with no autoimmune complications (107,108). Administration of anti-CD25 antibody linked to a potent pro-inflammatory toxin showed significant but transient reduction in CD4+ CD25+ Treg cells in patients with metastatic melanoma (109). Another clinical approach of targeting CD25 is through Denileukin diftotox, a fusion protein of IL-2 and diphtheria toxin that targets

CD25-expressing cells used in patients with melanoma, ovarian cancer and renal-cell carcinoma (110–113). Although effective in short-term infusions, these conjugates are quite immunogenic and induce neutralizing antibodies, which hamper their long-term application.

Another agent is Daclizumab, which is an FDA-approved humanized IgG1-kappa mAb that binds specifically to CD25 (114). It has been used in autoimmune disorders (115,116), acute graft-versus-host disease (117), and in cancer patients with CD25⁺ T-cell malignancies (118). The advantage of Daclizumab is that it is well tolerated, and has a half-life of 20 days (119). In a recent study, Daclizumab was used in a single dose of 1 mg/m² prior to hTERT peptide vaccine for metastatic breast cancer. Total CD4⁺CD25⁺ and CD4⁺CD25⁺FoxP3⁺ cells remained suppressed for several weeks after a single infusion.

Cytokines

Cytokines play important roles in immune modulation. Many cytokines, including IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, tumor necrosis factor- α (TNF- α), macrophage colony-stimulating factor, and IFNs, have been studied for their roles in tumor treatment. Some cytokines (IL-2 and IFN- α) have been approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of melanoma and renal-cell carcinoma though enthusiasm for use has waned given the systemic toxicity profile (120,121). Ovarian cancer ascites is rich with cytokine expression and the study of the ascitic fluid should help to better understand the immune interactions between tumor and host which is complex. A recent analysis showed ascites to be high in pro-inflammatory cytokines IL-6, IL-8 and the immune suppressive cytokines IL-10, CCL22 and TGF- β in most samples. Interestingly, high IL-6 expression predicted residual disease after debulking and was highest at recurrence (122).

Interferons

Although the full extent of action of IFN in patients with ovarian cancer is unknown, several mechanisms have been proposed: (a) stimulation of NK cells and macrophages, both of which are known to have antitumor properties (21); (b) antiangiogenic effects; and (c) inhibition of expression of dysregulated oncogenes (such as *HER2/neu*) and thereby improving the responsiveness of cisplatin-resistant cells (123). A Gynecologic Oncology Group Study evaluated administration of systemic IFN- α to patients with advanced ovarian cancer where patients with measurable disease showed a low response rate of approximately 10% (124). The role of intravenous IFN- α as a maintenance treatment after initial surgical resection and chemotherapy was also evaluated by a randomized phase III study and showed no benefit (125). Systemic IFN- α was also associated with frequent dose-limiting toxicity. Because of the poor response rate and frequent toxicity of systemic administration, further studies were focused on IP administration of IFN- α . Multiple clinical trials with IP IFN therapy were carried out leading to a randomized trial of adjuvant intraperitoneal α -interferon in stage III ovarian cancer patients who had no evidence of disease after primary surgery and chemotherapy by the Southwest Oncology Group (126). The trial was closed early but there was no difference between the study arms with regard to progression-free survival ($p = 0.56$). In cervical cancer, monotherapy with IFN- α had minimal activity (127). Studies evaluating intralesional interferon in HPV associated diseases (cervix and vulvar cancer) have waned as directly targeted immunologic approaches against the virus have emerged. Nonetheless, a recent study utilizing intralesional IFN = α 2 b in high grade cervical intraepithelial neoplasia showed a 60% response rate. Treated patients also expressed more Th1 (IFN- γ , TNF- α , IL-2) cytokines,

with a significant reduction in the viral load of high-risk HPV ($p = 0.0313$) (128).

Interleukin-2

IL-2 is a T-cell growth factor that plays a central role in the immune system with data showing IL-2-induced CD4⁺ T cell expansion in patients with HIV infection (129) as well as clinical responses in renal cell cancer and malignant melanoma resulting in an indication for treatment by the U.S. Food and Drug Administration for these tumors (120,121). It has been shown to activate tumor-associated macrophages and upregulate IFN-stimulated genes (130). Based on the toxicity of intravenous IL-2 administration, studies in ovarian cancer focused on IP administration. A phase I-II study (131) of IP IL-2 in patients with laparotomy-confirmed persistent or recurrent ovarian cancer after ≥ 6 courses of prior platinum-based chemotherapy had shown an overall response rate of 25.7%, with an overall 5-year survival probability of 13.9%. A more recent study shows that IP IL-2 administration in patients with ovarian cancer increases CD4⁺CD25⁺ high T-cells which highly express FOXP3 and suppress Treg cells. This suggests that IL-2 has a critical role in maintaining the Treg pool as well as enforcing Treg cell tumor trafficking in humans and may lend itself to combination studies of other agents targeting different immune checkpoints (132,133). A disadvantage of frequent administration of intravenous high-dose IL-2 is the occurrence of dose-limiting side effects. Therefore, delivery of IL-2 from an expression plasmid has been evaluated for the treatment of ovarian cancer. IP treatment of ovarian tumors with an IL-2-expressing plasmid resulted in an increase in local IL-2 levels, a change in the cytokine profile of the tumor ascites, and a significant antitumor effect in a mouse model (134). A recent *in vitro* study in colorectal cancer showed the ability of plasmids expressing murine IL-2 to enhance the antitumor activity of viral vector immunization against a cancer mucosa antigen showing the tolerability and possibility of combining plasmid-derived IL-2 production with other immunotherapeutic strategies as well (135).

Interleukin-12

IL-12 is a cytokine mainly produced by activated monocytes, tissue macrophages, and B cells. It can induce IFN- γ and together with IL-2 becomes a potent activator of cytotoxic T lymphocytes and NK cells (136,137). Whereas IL-4 and IL-10 mediate the development of Th2-type immunity, IL-12 initiates the differentiation to the Th1 phenotype. In addition, IL-12 production can be negatively or positively regulated by cytokines. For example, IL-10 and IL-4 have been shown to inhibit the production of IL-12 (138), whereas IL-2 and IFN- α enhance its production. In addition, IL-12 has potent antimetastatic and antitumor effects in several murine tumor models, as well as in human tumor cells *in vitro* and *in vivo* (139). Ascitic IL-12 had been shown to be an independent prognostic factor for adverse outcome in ovarian cancer (140) though later there was uncertainty over this finding as a result of a possible statistical flaw (141). A phase II GOG clinical trial (142) evaluated intravenously administered recombinant human IL-12 in patients with recurrent or refractory ovarian cancer. Myelotoxicity and capillary leak syndrome were the major adverse events. Partial response rate was on 3.8% with no complete responders. Recent focus has shifted to evaluating the administration of IL-12 expressing DNA. Two studies have evaluated this strategy in patients with malignant melanoma with patients showing response of greater than 30% in 5 of 12 patients receiving intratumoral injections; or CR in 2 of 19 and PR or SD in 8 of 19 patients using electroporation of plasmid coding IL-12. More investigation in this area including other tumor types is warranted and ongoing (143,144).

ANTIBODY MEDIATED THERAPY OF CANCER

Antibodies are the primary mechanism for eliminating infectious pathogens from the bloodstream. The effect of most commonly used vaccines against infectious agents is thought to be primarily a consequence of antibody induction with subsequent complement mediated inflammation and cytotoxicity (145). In addition, tumor antigen-specific autoantibodies are found in the sera of patients with solid tumors and generally increase with tumor burden (146,147). As one example, the presence of p53 autoantibodies was detected in 41.7% of patients with serous cancer, and detectable p53 antibodies were associated with improved overall survival ($p = 0.04$; HR = 0.57; 95% CI, 0.33, 0.97) (148). It is unknown whether this finding represents a biomarker for prognosis, or if the antibodies exert immunologic control of tumor. Another example is found in the presence of natural antibodies (i.e., prior to vaccination or administration) in paraneoplastic syndromes. In a series of 100 patients with small cell lung cancer, patients with autoantibodies causing the Lambert-Eaton myasthenic syndrome had improved survival (19.6 months) versus those who were antibody negative (8.9) (149). In platinum resistant ovarian cancer patients, another study showed that anti-MUC1 IgM antibodies correlated with overall survival at both early ($p = 0.052$) and late ($p = 0.009$) time points (150). These results provide the possibility that functionally effective antibodies may confer a survival advantage. The possibility that these represent a biomarker for better outcome instead cannot be excluded from this data. The ability of antibodies to mediate protection from tumor recurrence has also been suggested in experimental animal models (151). The administration of monoclonal antibody 3F8 against GD2 or induction of GD2 antibodies by vaccination after challenge with EL4 lymphoma (which expresses GD2) showed prolonged survival in mice receiving antibody ($p < 0.004$) or vaccination ($p < 0.008$) (151). Trials in gynecologic cancers have included the administration of murine or humanized antibodies directly targeting tumor associated antigens, indirect approaches utilizing anti-idiotypic antibodies, or antibodies conjugated to radionuclides, cytokines, or other immunotoxins. The greatest success in the antibody mediated treatment of cancer to date has come from a series of monoclonal antibodies against antigens expressed at the cell surface of cancer cells with clinical efficacy in both the advanced disease and adjuvant settings. Monoclonal antibodies are produced by hybridoma cells. They have evolved from simple murine derived antibodies with recombinant

engineering techniques to now permit monoclonal antibodies of various sizes, configuration, valence, and target effector functions (152). Examples with proven efficacy continue to grow to include an ever increasing list such as rituximab, ibritumomab, and tositumomab for B-cell lymphomas; gemtuzumab for acute myelocytic leukemias; alemtuzumab for chronic lymphocytic leukemias; cetuximab for colorectal and head and neck squamous cell carcinomas; and trastuzumab for breast cancer (152,153). A variety of mechanisms of action have been postulated: (a) monoclonal antibodies can mediate effector cells by having an activating or suppressive function in pathways such as with CTLA-4 (51), (b) they may target tumor supportive molecules such as VEGF with bevacizumab (154), or (c) they may recognize tumor specific receptors and by binding may activate or repress signaling pathways. Preclinical studies suggest that antibodies may have the most efficacy in the adjuvant setting. Since many gynecologic cancer patients are initially rendered free of detectable disease by surgery and/or chemotherapy after initial diagnosis, the administration of effective mAbs or vaccines with antibodies as part of the effector repertoire would have broad applicability. There are a variety of potential antigen targets for antibodies on gynecologic cancers. Screening for this purpose was traditionally limited to surface antigens since antibodies recognize antigens primarily at the cell surface. A previous study screened a series of 40 mAbs against 25 antigens common antigens that are potential targets for antibody mediated immunotherapy as listed in Table 15.3 (66,155,156). The antigens expressed by ovarian and endometrial cancers are similar, and quite different from those expressed by melanomas, and similar to, although not the same as, those expressed by prostatic cancers. The 18 excluded antigens (including CEA and *HER2/neu*) were expressed in 1 or 0 of 5 specimens. The expression of these antigens on normal tissues is essentially restricted to apical epithelial cells at luminal borders, a site that appears not to be accessible to the immune system. In addition to these overexpressed tumor associated antigens, other targets have included over-expressed growth-factor receptors (e.g., *HER2/neu* [erbB2], epidermal growth-factor receptor [EGFR], vascular endothelial growth factor [VEGF]); and mutated tumor-suppressor genes (e.g., p53 and *BRCA-1*). Binding of mAb to these antigens may have antitumor effect generated through a variety of possible mechanisms including: (a) antibody-mediated recruitment of human effector mechanisms *in situ*, ADCC against the tumor cells; (b) development of tumor-specific cytotoxic T lymphocytes (CTLs); (c) activation of the complement system; (d) stimulation of granulocytes cytotoxic to the cancer cells; and (e) induction of an anti-idiotypic antibody that can elicit active immunity.

Table 15.3 Potential Antigens for Antibody Directed Therapy

Tumor	Antigen (mAb) ^a									
	sTn (CC49)	sTn (B72.3)	TF (49H.8)	Le ^x (3S193)	Le ^y (BR96)	GM2 (696)	Globo H (Mbr1)	MUC-1 (HMFG2)	KSA (GA7333)	MUC-16/ (CA-125)
Ovarian	4/5	3/5	5/5	4/5	99/133 ^b	5/5	18/19	5/5	5/5	53/62 ^c
Endometrial	4/5	2/5	4/5	3/5	2/5	5/5	4/5	3/5	5/5	—
Melanoma	0/5	0/5	0/5	0/5	0/5	10/10	0/10	0/5	0/5	0/4
Small-cell Lung	0/5	0/5	0/5	2/5	1/5	6/6	4/6	2/5	4/5	0/2
Prostate	4/5	3/5	1/5	3/5	3/5	5/5	2/5	1/5	5/5	0/5

^aAll the tumor tissues were stained by avidin-biotin complex immunoperoxidase methods (155). Figures are the number of tumor specimens with >50% positive tumor cells by immunohistochemistry.

^bFrom Federici MF, et al. Selection of carbohydrate antigens in human epithelial ovarian cancers as targets for immunotherapy: serous and mucinous tumors exhibit distinctive patterns of expression. *Int J Cancer* 1999;81(2):193–198.

^cFrom Kabawat SE, et al. Immunopathologic characterization of a monoclonal antibody that recognizes common surface antigens of human ovarian tumors of serous, endometrioid, and clear cell types. *Am J Clin Pathol* 1983;79(1):98–104.

The extensive expression of CA-125 in over 80% of serous and endometrioid ovarian cancers has been well documented since the early 1980s (157). Following the successful cloning of CA-125 and identifying it as a complex mucin, it has been termed MUC-16 (158,159). Multiple efforts to target MUC-16 as a logical target for immunotherapy are underway.

Antibody Conjugates

In an attempt to add to the efficacy of unconjugated antibodies, efforts have been made to optimize the antitumor activity by conjugating with radionuclides, toxins, cytotoxic drugs, or second antibodies. The choice of conjugates and specific antibodies is influenced by features such as antigen internalization, lysosomal degradation, shedding, and heterogeneity of expression. The mechanism can be complex in that for some internalization is a prerequisite for cellular toxicity; while in others it may result in reduced efficacy and increased host toxicity due to intracellular catabolism (160).

Radionuclides

A variety of radionuclides have been conjugated with antibodies for imaging and treatment. The optimal radionuclide for cancer therapy is dependent on many factors (161). Radioconjugates with β (i.e., ^{131}I and ^{90}Y) and α (i.e., ^{211}At and ^{212}Bi) emitters have been proposed for regional therapy of peritoneal implants (162). Estimates of dosimetry suggest that adequate therapy (i.e., 20 Gy) could be delivered to tumors with a depth less than 300 μg using ^{211}At , less than 0.1 cm using ^{131}I , and less than 1 cm using ^{90}Y when conjugated to antibodies. The relatively low radiation dose makes the intraperitoneal delivery route attractive in order to put the source close to the tumor implants in the case of ovarian cancer. Delivery of effective radiation dose is greatly influenced by the extent of tumor binding, depth of tumor penetration, catabolism, and relative distribution between tumor and normal tissues. Antibody-radionuclide conjugates have been successfully developed for non-Hodgkin's lymphoma resulting in drug approvals with CD20 targeted agents (163). Randomized clinical data in ovarian cancer are sparse with two larger studies having been reported. A randomized trial of 251 patients with Stage 1a or 1b grade 3, or 1c, or 2 ovarian cancer with no macroscopic residual disease were randomized to intraperitoneal radioactive chromic phosphate (32P) versus cisplatin and cyclophosphamide chemotherapy. The cumulative incidence of recurrence at 10 years was 35% (95% CI, 27%–45%) versus 28% (95% CI, 21%–38%) favoring chemotherapy ($p = \text{ns}$). The toxicity profile of 32P was worse (164).

The SMART study was a large randomized study which evaluated intraperitoneal yttrium-90-labeled HMFG1 murine monoclonal antibody in patients with ovarian cancer after a surgically defined complete remission. The MUC-1 antigen that ^{90}Y -muHMFG1 is directed towards is well established as an immunotherapy target and is overexpressed on 90% of adenocarcinomas including that of ovarian cancer. The phase II data supporting the use of ^{90}Y -muHMFG1 administered intraperitoneally in patients in first remission was promising with a Cox model estimate of 10 year survival at 70% compared to 32% of case matched controls ($p = 0.003$) (165). Patients were stratified using a second surgical assessment where disease status at second look remains a powerful predictor of ultimate progression-free and overall survival (166). Despite the strong preclinical and clinical data supporting this approach, at a median followup of 3.5 years, relapses occurred in 98 versus 104 patients ($p = \text{ns}$). While there is no randomized evidence supporting efficacy of radioconjugates in gynecologic malignancies to date, the number of candidate agents for investigation continues to increase and earlier phase trials are ongoing.

Immunotoxins, Drugs, and Cytokines

Drugs, toxins, and cytokines conjugated to mAbs have been evaluated in numerous cancers. Immunotoxins incorporate an antibody-binding domain and a toxin joined by a chemical cross-linker, peptide, or disulfide bond. The specific targeting afforded by mAbs and the relative potency of the toxin moiety present potential therapeutic advantages. Early conjugates, which have generally not been successful, linked antibodies to standard anticancer drugs such as doxorubicin or vinblastine. It is generally not possible to deliver comparable levels of cytotoxic agents as intravenous administration using this approach. This field is advancing by replacing murine antibodies with humanized versions and conjugating agents that are both specific and functional at lower doses (167). Multiple agents are being evaluated though none have proven efficacy in gynecologic tumors to date.

Other Selected Clinical Trials with Monoclonal Antibodies

Monoclonal Antibodies Targeting CA-125

CA-125, a tumor-specific antigen that is found in 97% of patients with late-stage ovarian cancer, was first described by Bast et al. as an antigen that is elevated in the serum of patients with epithelial ovarian cancer (157). CA-125 has been cloned and identified as the mucin MUC-16 (168), as shown in Figure 15.2. Studies have shown that MUC-16 has a variety of functions and contributes to ovarian cancer cell growth, survival and invasiveness (169). Recent data suggest that expression is extended to digestive tract adenocarcinomas, and moderate expression likewise correlates with poor survival ($p < 0.001$) (170). The sheer size of the MUC-16 complex has made selecting appropriate sequences for incorporation into vaccines difficult, and initial studies focused on antibodies which could be raised against CA-125.

Monoclonal antibodies including anti-idiotypic antibodies have been used as CA-125 targets. The historical rationale for

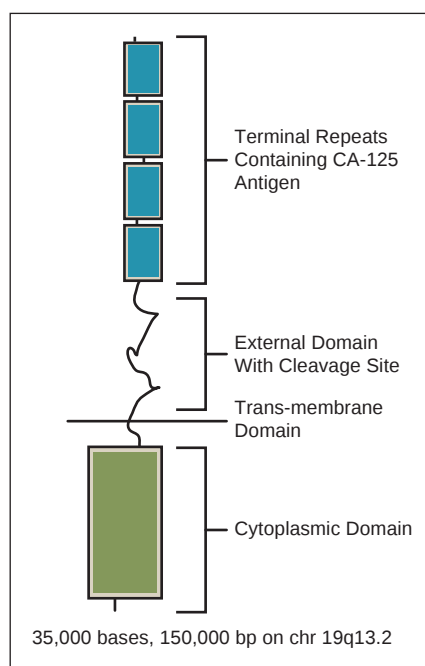


FIGURE 15.2. Proposed MUC-16 structure.

an anti-idiotypic vaccine was an attempt to augment both antibody and T-cell responses by using antibody facsimiles of the native antigens with the goal of overcoming poor immunogenicity. Tumor-associated antigens are traditionally weakly immunogenic as the large majority of them in humans are nonmutated self-antigens. This approach attempted to present the desired epitope to the now tolerant host in a different molecular environment but the problem with many tumor antigens is that they are ill-defined chemically and difficult to purify and produce (171). The “immune network hypothesis” set out to transform epitope structures into idiotypic determinants expressed on the surface of antibodies. It was originally proposed in the 1970s (172), and assumes that immunization with a given antigen will generate the production of antibodies against this antigen (termed Ab1). Ab1 can generate anti-idiotypic antibodies against Ab1, termed Ab2. Some of the anti-idiotypic antibodies (Ab2 β) express the internal image of the antigen recognized by the Ab1 antibody and can be used as surrogate antigens. Immunization with Ab2 β can cause the production of anti-anti-Id antibodies (termed Ab3) that recognize the corresponding original antigen identified by Ab1 (285,286). (Since Ab3 can have Ab1-like reactivity, it is also called Ab1' to distinguish it from the original Ab1.) Two mAbs against CA-125 have been extensively evaluated and recently reported in a series of clinical trials.

Oregovomab

Oregovomab (MAb B43.13) is an IgG1k subclass murine monoclonal antibody that binds with high affinity (1.16 X 1010/M) to circulating CA-125. CA-125-specific antibodies, T helper cells, and cytotoxic T cells are produced demonstrating both a humoral and cellular response (173–175). Retrospective and prospective phase II trials have associated a longer overall survival with immune response (176,177). A randomized placebo controlled trial of 145 patients with stage III or IV epithelial ovarian cancer receiving IV oregovomab in first clinical remission showed a median time to progression from randomization post front-line therapy of 13.3 months for patients receiving oregovomab versus 10.3 months for those receiving placebo ($p = 0.71$). In a subgroup of patients (*maximum* of 2 cm residual at debulking, CA-125 at *maximum* of 65 U/ml before third cycle, and CA-125 at *maximum* of 35 U/ml at entry), time to progression for patients receiving oregovomab versus placebo was 24 months versus 10.8 months (HR, 0.543; 95% CI, 0.287–1.025) (178). Appropriately, using the eligibility criteria of the subgroup as hypothesis generating, the investigators prospectively enrolled 354 patients in first clinical remission in a recently reported phase III trial. Median time to progression was 10.3 months (95% CI, 9.7–13.0 months) for the oregovomab group, and 12.9 months (95% CI, 10.1–17.4 months) for the placebo group ($p = 0.29$), showing no benefit to oregovomab immunotherapy (179).

Abagovomab

Abagovomab is an anti-idiotypic antibody produced by a mouse hybridoma and generated against OC125 (180). It recognizes the tumor associate antigen CA-125. The induction of a specific immune response (both humoral and cellular) was confirmed in preclinical studies, and a phase I-II trial with 119 patients showed an association between prolonged survival in ovarian cancer patients who demonstrated an Ab3 antibody response (68%) to vaccination versus those that did not (23.4 months versus 4.9 months). No significant adverse events were noted (181,182). Subsequent phase I studies confirmed safety, efficacy of the subcutaneous route, and suggested that longer vaccination sequences produced more robust immune responses (182,183). These data provided the rationale for a phase III randomized trial. Patients with FIGO stage III or IV ovarian cancer in

complete clinical remission after primary surgery and platinum/taxane based chemotherapy were randomized 2:1 in a phase III, double blinded, placebo controlled, multicenter study. Abagovomab 2 mg or placebo was given as 1 ml sc every 2 weeks for 6 weeks (induction phase), then every 4 weeks (maintenance phase) until recurrence or up to 21 months after randomization of last patient. Primary endpoint was recurrence free survival; secondary end-points were overall survival and immunological response. The characteristics of 888 patients were: mean age, 56.3 years; ECOG PS *maximum* of 1 in more than 99%; serous papillary subtype in 81.5%; FIGO stage III in 85.9%; CA-125 ≤ 35 U/ml after the third cycle FLCT in 80.9% of patients. The mean exposure to study treatment was 449.7 ± 333.08 days. The hazard ratio of recurrence free survival for treatment group using (≤ 1 cm, > 1 cm) tumor size categorization was 1.099 (95% CI, 0.919–1.315; $p = 0.301$). The hazard ratio of overall survival for the treatment group using tumor size catheterization (≤ 1 cm, > 1 cm) was 1.150 (95% CI, 0.872–1.518, $p = 0.322$). The most frequently reported type of adverse event was an injection site reaction reported in 445 (50.2%) patients overall followed by injection site erythema and fatigue which are reported in 227 (25.6%) and 212 (23.9%) patients overall respectively. By the final study visit, the median Ab3 levels were 493,000.0 ng/ml which indicated a robust immunologic response. In conclusion, Abagovomab given as repeated monthly injections was safe and induced a measurable immune response but its use did not result in a prolonged progression-free survival (184).

There was a traditional notion that combining immunotherapy and chemotherapy may not be desirable due to the possible immunosuppressive nature of cytotoxic chemotherapy. However, emerging data continues to show that chemotherapy selectively eliminates immunosuppressive lymphocyte populations, and thereby may beneficially alter the characteristics of an immune response (101). A study with concurrent oregovomab and chemotherapy in recurrent epithelial ovarian cancer supports the idea that favorable specific immune responses could be generated in the presence of concurrent chemotherapy (185). The idea of combining chemotherapy and immunotherapy remains one to be clinically evaluated.

Monoclonal Antibodies Targeting ERBB1 (EGF), ERBB2 (HER2/neu), and VEGF

The epidermal growth factor receptor (EGFR) has been a frequent target for cancer treatment development in the past decade. The EGF tyrosine kinase inhibitor gefitinib had a minimal objective single agent response rate of 4% in unscreened patients with ovarian cancer (9% in EGF + patients). The patient with the only objective response had a mutation in the catalytic domain of EGFR, and the frequency of mutation in this study was 1/32 or 3% (186). The anti-EGFR antibody matuzumab, was also tested in patients with recurrent, EGFR-positive ovarian, or primary peritoneal cancer in a multi-institutional single-arm phase II trial of 75 patients, and showed no significant clinical activity as a monotherapy. These data suggest that anti-EGF targeted therapy as a single agent in ovarian cancer is relatively inactive, but dual inhibitors and combination therapy with chemotherapy are still being investigated (187).

HER2 overexpression appears inversely correlated with overall survival in patients with ovarian cancer when considered in univariate and multivariate analysis among other usual prognostic factors (188). The most significant treatment experience in patients with recurrent or refractory ovarian or primary peritoneal cancer in a Gynecologic Oncology Group Study screened 837 tumor samples for HER2 expression, and showed the required 2+/3+ expression occurred in only 95 (11.4%) patients (189). Forty-five patients were entered into the study with an overall response rate of 7.3% with a median progression-free

interval of 2.0 months. Based on infrequent HER2 expression, and the low rate of objective responses, the clinical value of single-agent trastuzumab appears limited in these patients. The potential role on combination with chemotherapy is unknown but the broad applicability will be limited by the frequency of expression. Pertuzumab is a recombinant humanized monoclonal antibody binding to the HER 2 dimerization domain which stoically blocks the pocket required for dimerization (190). A randomized phase II trial evaluated pertuzumab in platinum sensitive disease with a comparison of platinum based therapy with or without pertuzumab. Results are pending publication. Studies are simultaneously looking to characterize the affected molecular pathways particularly in patients with response as colateral signaling may play an important role in further tumor growth (191).

The growth and metastasis of malignant neoplasms require the presence of an adequate blood supply, and recent data have confirmed the therapeutic potential of multiple antivascular strategies. The role of bevacizumab and other antivascular agents are discussed in the appropriate chapters regarding the treatment of patients with ovarian cancer.

Monoclonal Antibodies Targeting EPCAM (Antiepithelial Cell Adhesion Molecule)

The tri-functional antibody catumaxomab (EPCAM X anti-CD33) has been evaluated in patients with malignant ascites (192). The phase II/III trial randomized patients to standard paracentesis or paracentesis with antibody delivered via the intraperitoneal route. Puncture free survival was longer in the catumaxomab group (median 46 days) than the control group (median 11 days) with hazard ratio = 0.254, $p < 0.0001$. There was a correlation between humoral response and clinical outcome (193). Additional study is ongoing.

Monoclonal Antibodies Targeting Antigens in Cervical and Endometrial Cancer

There are no approved antibody strategies targeting antigens in cervical or endometrial cancer to date. Vascular endothelial growth factor targeted approaches are ongoing in patients with cervical carcinoma and endometrial cancer, and these are discussed in the appropriate chapters. Epidermal growth factor targeted approaches have also been evaluated in patients with cervical cancer. The epidermal growth factor receptor is overexpressed in 85% of patients with invasive cervical cancer (194). Cetuximab is a chimeric IgG1 mAb that antagonizes normal ligand receptor interactions. A phase II trial by the Gynecology Oncology Group evaluated single agent cetuximab in 38 patients. No clinical responses were detected (195). Cetuximab was also evaluated in 76 patients in combination with cisplatin chemotherapy in treated and chemotherapy naïve patients. Response rates of 9% and 16% respectively were seen with no evidence for a benefit of cetuximab over cisplatin alone (196).

(phenotype and polarization) of antibody and T-cell responses; and (c) developing combinatorial approaches with adoptive T cell or immunomodulation therapy to maximize activation and function of vaccine-primed effector cells *in vivo*.

Vaccines Designed Primarily to Generate Antibody Responses

Most current vaccines seek to generate cellular responses (often with an accompanying humoral or integrated response). However, based on the cell surface target antigen selection process appropriate for antibody recognition described above, and advances in the chemical and enzymatic synthesis of carbohydrate and glycopeptide antigens and optimization of adjuvant use, the exploration of a variety of synthetic antigen vaccines with antibody production as the endpoint was feasible (203–205). After defining targets to include GM2, Globo-H, Lewis^x, sialyl Tn (STn), Tn, Thompson Friedreich antigen (TF), and mucin 1 (MUC-1) (66,155,156,206), a series of phase I univalent trials were performed. The most immunogenic approach was identified to include chemical conjugation of the antigen to a highly immunogenic carrier protein (keyhole limpet hemocyanin (KLH) plus the use of a potent immunological adjuvant such as the saponin QS-21 or OPT-821 (207). Preclinical data supported the hypothesis that polyvalent vaccines would likely be required due to tumor cell heterogeneity, heterogeneity of the human immune response, and the correlation between overall antibody titer against tumor cells and antibody effector mechanisms (208). Preclinical models further showed that a heptavalent KLH conjugate plus QS-21 vaccine induced antibody titers comparable to those induced by monovalent vaccines containing Tn, STn, TF, MUC-1 and Globo-H. Lower titers were produced against Lewis^x and GM2 (209). Some antigens have required modification for optimal immunogenicity resulting in trimers or clusters (c) of Tn, STn, and TF rather than unmodified monomers (210,211). A pilot trial of a heptavalent vaccine-KLH conjugate plus QS-21 in patients with epithelial ovarian, fallopian tube, or peritoneal cancer in either a first (following persistence and additional treatment), second, or third remission (212). The administered heptavalent vaccine contained GM2 (10 µg), Globo-H (10 µg), Le^x (10 µg), Tn-MUC1 (3 µg), Tn(c) [clusters] (3 µg), STn(c) (3 µg) and TF(c) (3 µg) individually conjugated to KLH and mixed with adjuvant QS21 (100 µg). Vaccinations were administered at weeks 1, 2, 3, 7, and 15. ELISA assays were tested against the following target antigens: Tn-MUC1-32mer, GM2, Globo-H ceramide, Le^x ceramide, desialated ovine submaxillary mucin (DOSM) expressing Tn, OSM expressing STn, and desialated porcine submaxillary mucin (DPMSM) expressing TF. IgM and IgG antibody titers were measured by ELISA as described previously (213–215). Fluorescent-activated cell-sorting (FACS) was performed as previously described to demonstrate antibody binding to the cell surface of the cell line MCF-7. MCF-7 was chosen as it is known to express each of the 7 antigens (213–215). Side effects were limited to fever and local injection site reactions which were self limited. After immunization median IgM titers were as follows: Tn-MUC-1 1:640 (IgG 1:80), Tn 1:160, TF 1:640, Globo-H 1:40, and STn 1:80. Eight of nine patients developed responses against at least three antigens. FACS and CDC analysis showed substantially increased reactivity against MCF7 cells in 7/9 patients, with some increase seen in all patients (212). This has led to Gynecology Oncology Group Trial 255 (NCT00693342) which is a randomized trial in ovarian cancer patients with second or third complete clinical remission receiving either the adjuvant alone (OPT-821) versus the multivalent antigen construct + OPT-821. The endpoint is the proportion of patients' disease free at 12 months (35% vs. 50%) and accrual is currently ongoing with a target accrual of 154 patients.

CANCER VACCINES

Vaccines remain a backbone in the approach to ovarian cancer immunotherapy (197–201). Similar to experiences in other immunogenic tumors (202), vaccines have shown limited efficacy as monotherapy in patients with advanced recurrent disease. Clearly, much work is required to improve their performance. Current efforts to improve vaccines are directed broadly towards (a) optimizing the choice of antigens; (b) improving vaccine delivery systems to maximize the magnitude and quality

Vaccines Primarily Designed to Produce Cellular or Integrated Responses

There are a wide range of options for augmenting the immunogenicity of the antigenic targets for T-cell immunity and this remains the primary goal for tumor immunotherapy (216,217). This now includes the possibility of genetically modifying T cells by themselves to express both tumor associated antigens and dendritic cell activating molecules (217). For the antigens, the options include (a) the full proteins or MHC-restricted peptides modified by amino acid substitutions to increase immunogenicity; (b) genes or mini-genes for these proteins or peptides used as DNA vaccines; or (c) genes expressed in viral or bacterial vectors. Co-stimulatory molecules, cytokines, or molecules targeting antigens to particular processing compartments can be incorporated into these vaccines. DNA vaccines are appealing in this regard because of ease of production, versatility, and adaptability to such combinations (198). Most of these approaches can also be applied to expressing these antigens in antigen-presenting cells, such as dendritic cells, that are then used to vaccinate the patient. Furthermore, since many tumor-rejection antigens detected by T cells in experimental animals are individually unique (mutated), a variety of individualized vaccines are being tested. Whole-cell vaccines can be prepared from a specific patient (if accessible tumor is available) and immunogenicity may be increased by the use of an immunologic adjuvant and transduction with genes for cytokines or co-stimulatory molecules, or treatment with haptens such as dinitrophenyl (DNP) (218). Other approaches attempting to increase the immunogenicity of unique and shared antigens include the use of heat shock proteins that may carry the full range of cancer peptides, and DNA or messenger RNA vaccines that may be obtained from smaller biopsy specimens (219).

An ever increasing number of antigen targets for vaccines producing cellular or integrated responses is being identified. Common antigens shared by ovarian or endometrial cancers from different patients are KSA, MUC-16, WT1, CEA, MUC-1, HER2/neu, and cancer-testis antigens (including the MAGE family) and NY-ESO-1. None of these cancer antigens defined as targets for T cells to date is a perfect candidate for the majority of patients due to (a) overexpression on less than 50% of ovarian or endometrial cancers (HER2/neu, CEA, and the cancer-testis antigens) and (b) wide expression (though at lower levels) on normal tissues (KSA, CEA, HER2/neu, MUC-1) (220). MUC-16 for ovarian cancers and human papillomavirus (HPV)-related antigens for cervical cancer are especially strong candidates at this time because of their widespread expression on the respective cancers and restricted expression on normal tissues.

Molecular analysis of endometrial carcinomas has identified a variety of proteins that may serve as target antigens for vaccine-based therapy. For example, over-expression of HER2/neu has been correlated with advanced disease and poor outcome in both adenocarcinoma and uterine papillary serous carcinoma (221). More recent reports have implicated alterations in the hMLH1, p16 (ink4a) (p16), and *PTEN* genes as promoters of carcinogenesis, as well as over-expression of the *SART-1* gene, which encodes the SART-1 tumor antigen that is recognized by HLA-A26-restricted cytotoxic T lymphocytes (32% of tested specimens) (6).

Dendritic-Cell Approaches

Dendritic cells (DC) are phenotypically distinct, potent antigen-presenting cells well suited for vaccine strategies (222). They are found throughout the body, particularly at the portals of entry for infectious organisms, such as in the epidermis and other epithelial surfaces. Cancers may be ineffective at attracting DCs, may attract the wrong type of DCs, or may attract immature

DCs that induce tolerance. It has been observed that ovarian carcinoma cells express high levels of the chemokine SDF-1 that attracts a subset of DC precursors with capacity to differentiate into plasmacytoid DCs, which are implicated in immune suppression through induction of IL-10 by T cells. Myeloid DCs, which are more effective at inducing immune responses, were not detected (223). Also, plasmacytoid DCs have been implicated in inducing a set of CD8+ regulatory T cells in ovarian carcinoma (224). DCs from patients with ovarian cancer can be matured *ex vivo* to activate T cells producing IFN- γ in response to autologous tumor cell lysates, but not cytotoxic T cells (225). Ovarian carcinoma cell lines can directly inhibit maturation of DCs (226). These results and many others suggest that DCs from cancer patients can be defective at fully activating T cells. Studies have shown that myeloid DCs from tumor or draining lymph nodes of ovarian carcinoma express B7-H1, a molecule in the B7 family implicated in inhibiting immune responses (92). Blockade of B7-H1 led to marked increases in T-cell responses. Multiple animal studies have demonstrated CTL-mediated protective immunity and even regression of established tumors with the administration of antigen pulsed dendritic cells (227). A variety of approaches have been considered with regard to antigen type and loading techniques to include recombinant or fusion proteins (227), peptides as tumor antigen-derived CTL epitopes (228), DC-tumor cell hybrids (229), HLA-restricted antigens (230), and autologous antigens from tumor cell lysates and apoptotic tumor cells as discussed below. A number of other antigen sources are also possible for DC-based treatment of ovarian cancer.

SELECTED CLINICAL TRIALS

NY-ESO-1 Vaccines

Cancer/testis (CT) antigens: The first human cancer antigen was identified in a melanoma patient by a strategy called the T cell epitope cloning technique. This antigen was named MAGE-1 (melanoma associated gene 1) (231). Subsequently, a family of MAGE related genes (e.g., *MAGE-1*, *MAGE-3*, *BAGE*, *GAGE*) was identified in the same patient and later also in others, which encode antigens that are expressed in melanomas and several other tumors, but not in normal tissues except testis. At present, over 100 CT genes or gene families have been found with the following two distinguishing features: (a) mRNA expression in testis and cancer and (b) no or highly restricted mRNA expression in normal adult somatic cells.

Approximately 50% of the currently known CT genes reside on chromosome X (CT-X), where they constitute over 10% of the coding sequence and appear to be under strong positive selection during evolution. Many questions regarding CT genes remain open, including the biological function of their protein products, and the elucidation of factors that control their expression in normal tissues and cancer. The frequency of CT antigen expression in many cancer types ranges from 5% to 40%, with exceptionally high expression of individual CT antigens in certain cancers, e.g., MAGEC1/CT7 in 70% of myeloma and NY-ESO-1 in 80% of synovial sarcoma.

The reasons for the aberrant expression of CT antigens in cancer are currently unknown. Nevertheless, the fact that the expression of these antigens is restricted to cancers, gametes, and trophoblast suggests a link between cancer and gametogenesis. Although possible mechanisms include global demethylation and histone deacetylation, the induction of a "gametogenic" program in cancer has also been proposed (232). Emerging evidence also suggest that NY-ESO-1 and some additional CT antigens, may be selectively expressed by cancer "stem cells." Therefore, the development of strategies to target CT antigens

Table 15.4 Expression and Immunogenicity of Selected CT Antigens in Ovarian Cancer

CT antigen	mRNA	IHC	ELISA
NY-ESO-1 (233)	43%	43%	25%
SPAG9 (312)	90%	—	67%
OY-TES-1 (313)	69%	69%	10%
LAGE-1 (233)	21%	—	25%
Sp17 (314)	83%	—	—
SSX (315)	26%	—	2.3%
AKAP-3 (316)	58%	—	—
HOM-TES-14 (SCP-1) (317)	15%	0%	—

Source: From Mirandola L, et al. Cancer testis antigens: novel biomarkers and targetable proteins for ovarian cancer. *Int Rev Immunol* 2011;30(2-3):127-137, with permission.

in ovarian cancer could have potential therapeutic benefit. The expression and immunogenicity of selected CT antigens is presented in Table 15.4.

Among CT antigens, NY-ESO-1, initially defined by serologic analysis of recombinant cDNA expression libraries (SEREX) in esophageal cancer, is particularly immunogenic, eliciting both cellular and humoral immune responses in a high proportion of patients with advanced NY-ESO-1 expressing ovarian cancer (233). The immunogenic NY-ESO-1 epitopes recognized by T lymphocytes appear to be clustered around the central part of the NY-ESO-1 protein. A number of NY-ESO-1 based clinical trials have been conducted in ovarian cancer patients, and additional trials are ongoing. Details of studies in progress are as follows:

A pilot clinical trial of NY-ESO-1DP4 p157-170 (NY-ESO-1DP4), a peptide of potentially dual MHC class I and class II specificities, in patients with epithelial ovarian, fallopian tube or primary peritoneal carcinoma whose tumors express NY-ESO-1 or LAGE-1: In this trial, 18 ovarian cancer patients who were NED after therapy for primary or recurrent disease were vaccinated with NY-ESO-1 epitope, ESO₁₅₇₋₁₇₀, a naturally processed helper epitope that is recognized by CD4⁺ T cells in the context of HLA-DP4 (i.e., HLA-DPB1*0401 and *0402) (234). This NY-ESO-1 epitope has HLA-A2 (ESO₁₅₇₋₁₆₅) (235) and HLA-A24 (ESO₁₅₈₋₁₆₆) (236) motifs embedded in its natural sequence. The study tested whether active immunization with ESO₁₅₇₋₁₇₀ would elicit NY-ESO-1-specific CD4⁺ and CD8⁺ T-cell responses in ovarian cancer patients with minimal disease burden. The peptide SLLMWITQC (100 µg) was mixed with 0.5 mL of Montanide ISA-51, given by s.c. injection once every 3 weeks for a total of 5 to 15 doses. There was induction of CD4⁺ T-cell responses in 83% of patients; and CD8⁺ T-cell responses in 60% of HLA-A2⁺ patients; but in none of the five HLA-A24⁺ patients. Although the majority of patients were heavily pretreated, the median time to disease progression/recurrence from start of vaccination was 19.0 months (237).

Phase I study of NY-ESO-1b peptide and montanide ISA-51 vaccination of patients with epithelial ovarian cancer in high-risk first remission: This study enrolled nine patients to assess the primary and secondary end points of toxicity and immunogenicity. Eligible patients were those with high-risk epithelial ovarian cancer (defined by suboptimal initial debulking surgery, failure to normalize CA-125 after 3 cycles of chemotherapy, or positive second-look surgery) in cCR, as documented by CT scan and CA125 after completion of primary surgery and

chemotherapy. The HLA-A*0201-specific NY-ESO-1b peptide SLLMWITQC (position 157-165; 100 µg) mixed with 0.5 mL of Montanide ISA-51 was given by s.c. injection once every 3 weeks for a total of 5 doses (week 1, 4, 7, 10, and 13). Three of 4 patients (75%) with NY-ESO-1-positive tumor showed T-cell immunity by tetramer and ELISPOT. Four of 5 patients (80%) with NY-ESO-1-negative tumor showed T-cell immunity by tetramer and/or ELISPOT. The median progression-free survival was 13 months (238).

Phase II study of recombinant vaccinia-NY-ESO-1 (rV-NY-ESO-1) and recombinant fowlpox-NY-ESO-1 (rF-NY-ESO-1) in patients with epithelial ovarian, fallopian tube or primary peritoneal carcinoma whose tumors express NY-ESO-1 or LAGE-1 antigen: This is the only reported phase II clinical trial of NY-ESO-1 vaccine therapy in ovarian cancer (239). The objective of the study was to test whether a priming immunization strategy with recombinant vaccinia-NY-ESO-1 (rV-NY-ESO-1), followed by booster vaccinations with recombinant fowlpox-NY-ESO-1 (rF-NY-ESO-1) will minimize the risk of progressive disease in advanced ovarian cancer patients, following their first line therapy. Integrated NY-ESO-1-specific antibody and CD4⁺ and CD8⁺ T cells were induced in a high proportion of the patients. The clinical results showed that (a) seronegative patients who remained seronegative but developed CD4 and/or CD8 T-cell responses and (b) seronegative patients who seroconverted and developed CD4 and/or CD8 T-cell responses demonstrated improved OS (median, 52.4 and 48.4 months, respectively) compared with other categories of patients (median, 14.5 months) ($p < 0.0001$).

Ongoing clinical trials to enhance NY-ESO-1 vaccine efficacy (<http://www.clinicaltrials.gov>): In an effort to enhance NY-ESO-1 vaccine efficacy, a number of novel approaches are undergoing clinical evaluation. These include:

(i) *The use of pox-viral vectors expressing NY-ESO-1 and TRICOM, TRIad of COstimulatory Molecules (B7-1, ICAM-1 and LFA-3, NCT00803569):* These 3 molecules are found on antigen-presenting cells. B7.1 (CD80) is a protein that interacts with T-cell ligands CD28 resulting in T-cell stimulation *in vitro*. ICAM-1 (CD56) is an adhesion molecule found on the surface of antigen-presenting cells that binds to the T-cell ligand leukocyte function-associated-antigen (LFA)-1. LFA-3 (human CD58) is a surface protein that binds to CD2 expressed on T-cell, resulting in T-cell stimulation and priming (240). Together, the use of TRICOM in pox-viral constructs has been shown to expand antigen-specific CD8⁺ T cells with superior functional avidity (241-243), leading to better tumor control.

(ii) *The use of novel adjuvant formulations to enhance magnitude of immune response (study of NY-ESO-1 overlapping peptides and immunoadjuvants montanide and Poly-ICLC, NCT00616941):* In this study, ovarian cancer patients in second or third remission were immunized with NY-ESO-1 peptides and a novel adjuvant, poly-ICLC. Polyriboinosinic-polyribocytidylic acid (poly I:C), a synthetic double-stranded RNA (dsRNA), is recognized by TLR3 and other intracellular receptors. It is expected that this approach will generate robust effector T-cell responses with significant potential for tumor control.

(iii) *Combination of NY-ESO-1 vaccination with a strategy to counteract immune escape due to antigen or MHC downregulation (NCT00887779):* In a completed protocol, the demethylating agent, decitabine was combined with chemotherapy and vaccine therapy in order to induce MHC and tumor antigen expression in tumors, and promote “antigenic” dose to effector T-cells.

(iv) *Combination of NY-ESO-1 vaccination with rapamycin as a strategy to generate memory T cells for durable tumor protection (NCT01536054):* In this study, vaccination is combined with rapamycin in various doses and schedules, in order to determine a regimen that best generates memory T-cell responses. The induction of memory T-cell responses is a key to prevent tumor

recurrence, but has been a major challenge for all tumor immunotherapy approaches. Recent studies indicate that inhibition of mTOR activity switches Tbet for Eomesodermin expression and slants CD8⁺ effector cells for memory precursor like phenotype (244–246). Moreover, *in vivo* murine studies have shown that sirolimus augments antigen specific vaccination by inducing a long lasting, tumor protective memory T-cell response. Therefore, this trial will test whether mTOR inhibition will condition vaccine induced T cells for enhanced persistence, antigen recall and tumor efficacy.

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) Secreting Tumor Vaccines

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has a variety of properties desirable for vaccine production including enhancing immune responses by inducing the proliferation, maturation, and migration of dendritic cells and the expansion of both T- and B-cell lymphocytes (247). Its adjuvant response has shown the early elevation of inflammatory molecules such as IL-6, TNF- α , and monocyte chemoattractant protein-1 (MCP-1) followed later by IL-12 and IFN- δ production, among others (247). *In vitro* characterization of a GM-CSF-secreting vaccine was performed by genetically engineering UCI-107 (ovarian cancer cell line) to secrete GM-CSF by retrovirus-mediated gene transduction with the LXS retroviral vector containing the human GM-CSF gene and the neomycin resistance selection marker. A clone (UCI-107 GM-CSF-MPS) was extensively characterized and shown to secrete high levels of GM-CSF over 6 months of study (248). In human trials, a variety of studies have shown that vaccination with irradiated tumor cells engineered to secrete GM-CSF stimulates long-lasting immunity in murine models and in patients with metastatic melanoma. A phase I study evaluated patients with metastatic non-small cell lung carcinoma. A metastatic site was resected, processed to single-cell suspension, infected with a replication-defective adenoviral vector encoding GM-CSF, irradiated, cryopreserved, and then given intradermally at weekly and biweekly intervals. Vaccines were made successfully for 34 of 35 patients. Dendritic cell, macrophage, granulocyte, and lymphocyte infiltrates were elicited in 18 of 25 assessable patients. Five patients had stable disease ranging from 3 to 33 months; and one patient had a mixed response (249). This led to 2 randomized phase III trials (VITAL 1 and VITAL 2) in patients with prostate cancer evaluating the allogeneic GM-CSF secreting prostate cancer vaccine either in comparison to chemotherapy or in combination with chemotherapy (250). Both trials were closed early and futility analysis predicted < 30% chance of meeting primary endpoint. Efficacy has not been demonstrated in patients with gynecologic cancers.

Folate Receptor–Targeted Vaccines

Previous studies have identified the alpha isoform of the folate receptor (FR), which is a 38-kD GPI-anchored protein constitutively expressed at high levels in 90% of nonmucinous ovarian cancer and at low levels in normal tissues (251). The reason for over-expression is unknown, but one hypothesis is that over-expression provides an alternate folate-processing pathway to compensate for deletion of the tetrahydrofolate reductase gene that is deleted frequently in cancer cells (252). FR expression has been shown in preclinical models to confer a growth advantage in FR-transfected cells, which suggests a role for the receptor in the control of cell proliferation (253,254). The preferential over-expression of the folate receptor in malignant tissue has prompted the investigation of this antigen in several

preclinical immunization studies. Neglia et al. (255) evaluated FR- α cDNA after ligation into the VR1012 (Vical) expression vector under transcriptional control of the cytomegalovirus promoter. Purified plasma DNA was injected into BALB/c mice three times at 14-day intervals. At 10 days after the second injection, sera (100%) showed antibody titers against syngeneic C26 cells transduced with FR- α , but not against unmodified C26 cells. Specific cytotoxic T lymphocyte activity against FR- α -transduced C26 cells could be seen in splenocytes from all immunized animals. Challenge by subcutaneous injection with FR- α -transduced C26 cells (administered 10 days after third injection) showed a statistically significant delay in tumor growth (255). Further studies by Peoples et al. showed that both immunodominant E39 (folate-binding protein [FBP]) (194–202), and subdominant E41 (FBP) (246, 248–255), epitopes of human high-affinity FBP are presented by HLA-A2 in both ovarian and breast cancers (256). Tumor-associated lymphocytes stimulated with FBP peptides exhibit cytotoxicity not only against peptide-loaded targets but also against FBP-expressing epithelial tumors of different histologies. These studies provide motivation for proceeding to clinical trials with folate receptor targeted strategies.

The most developed clinical strategy evaluated Farletuzumab (MORAB-003), which is an anti-folate receptor monoclonal antibody derived from the optimization of the LK26 molecule using a whole cell genetic platform. Following optimization, it exhibits an affinity similar to the original murine LK26 antibody (–2 nM) and its tissue binding profile parallels that of the folate receptor antibody (257). A phase I study in 25 patients with platinum resistant ovarian cancer was dose finding, and showed stable disease in nine patients (258). An open label phase II study followed with patients receiving farletuzumab as single agent or in combination with platinum and taxane based therapy suggesting activity in combination with chemotherapy. Development has proceeded to the FAR 131 study (NCT00849667) which is a randomized phase III trial evaluating Morab-003 in combination with paclitaxel and carboplatin in patients with platinum sensitive disease. The final study results will define the activity of this antibody in patients with ovarian cancer. An alternative approach using dendritic cells transfected with mRNA encoded folate receptor is also being evaluated (259).

Muc-1 Targeted Vaccines

MUC-1 is a mucin family member that is generally expressed on the apical surface of epithelial cells (150). Increased serum MUC-1 ($p = 0.003$) and high MUC-1 antibody levels ($p = 0.052$) have been associated with worse prognosis. Autologous dendritic cells pulsed with mannan-MUC-1 fusion protein have been evaluated in phase I trials. T-cell responses to vaccine were seen and toxicity was minimal (260). This approach is currently being evaluated in a phase II/III trial with the product Cvac for patients with ovarian cancer in complete remission following first-line chemotherapy (NCT01521143). The trial is expected to enroll 1000 patients with a primary endpoint of progression-free survival. Secondary endpoints are overall survival, safety, and health related quality of life.

WHOLE TUMOR VACCINES

Several groups have used viruses to increase tumor cell immunogenicity for whole tumor cell vaccination. Objective responses have been seen after intracavitary delivery of a viral oncolysate vaccine generated with ovarian cancer cell lines infected with influenza-A virus (261,262) or with autologous tumor cells infected with Newcastle disease virus (263). A recent study

investigated preclinical use of replication-restricted herpes simplex virus (HSV) 1 to infect autologous tumor cells for vaccine preparation. HSV-infected tumor cells used directly or pulsed on dendritic cells elicited potent antitumor immune response in the mouse, which was superior to the use of UV-irradiated tumor cells (218,264,265). Thus, whole tumor antigen vaccines can produce objective response if immunogenicity is increased through the use of pathogens. An alternative approach to deliver effectively whole tumor antigen is by using dendritic cells (DCs). In a pilot study using mature DCs pulsed with whole autologous tumor lysate, 3 of 6 subjects demonstrated remission inversion, i.e., their progression-free survival postvaccination was longer than the interval between prevaccine recurrence and prior chemotherapy treatment (266).

Although whole tumor vaccines offer distinct advantages, some drawbacks warrant consideration. First, surgical procurement of large number of autologous tumor cells may not be possible in many patients. Alternatives to this limitation exist, including use of allogeneic cell lines or the use of tumor mRNA. RNA electroporation of DCs is a convenient approach to generate a potent tumor vaccine (218). An additional concern with whole tumor vaccination relates to the inclusion of a large number of “self” antigens, which could potentially drive tolerogenic responses, i.e., expand Treg rather than cytotoxic lymphocyte responses. Recent work has demonstrated that DCs can be polarized *ex vivo* with the use of interferons, Toll-like receptor agonists or p38 mitogen-activated protein kinase (MAPK) inhibitors to drive cytotoxic lymphocytes and Th17 effector cells at the expense of Treg activity (267). On the other hand, if immunization is successful, there may be increased concern for breaking tolerance to “self” antigens, leading to immunopathology. To date, pilot studies with whole tumor vaccines have reported no autoimmunity in patients with ovarian cancer.

A major limitation of cancer vaccines presently stems from the inability to elicit a rapid and overwhelming T-cell response, which is required to reject established tumors. A potential solution to this limitation is provided by combinations with immunomodulation therapy previously discussed aiming at breaking peripheral tolerance mechanisms, which may reduce the number of tumor reactive T cells required to reject tumors. For example, a recent study has shown that immunomodulation through blockade of the endothelin B receptor, a VEGF-regulated gene, markedly increases the efficacy of weak vaccines by reversing the inhibitory function of tumor endothelium and enabling homing of tumor-reactive T cells (268,269). Furthermore, depletion of Treg is a likewise critical maneuver to enhance vaccine therapy (107). A pilot study at the University of Pennsylvania is testing this hypothesis by administering partially mature DCs pulsed with autologous tumor cell lysate to subjects with recurrent ovarian cancer in combination with immunomodulation with oral metronomic cyclophosphamide (to deplete Treg) (270) and bevacizumab (to disrupt the blood-tumor endothelial barrier) (269). An additional approach to enhance the efficacy of vaccines may be provided by combination with postvaccine adoptive transfer of *ex vivo* expanded T cells.

ADOPTIVE CELLULAR THERAPY

Effective cancer immunotherapy is dependent on the presence of large numbers of antitumor lymphocytes with appropriate homing and effector functions that enable them to seek out and destroy cancer cells *in vivo*. The adoptive transfer of *ex vivo* expanded tumor-reactive T cells holds the potential of achieving this condition in a short period of time, as shown in Figure 15.3. Clinical trials testing spontaneous or induced polyclonal or oligoclonal T cells conducted in the past two decades have provided crucial lessons that can guide further optimization. The

use of *ex vivo* expanded TILs has yielded the best clinical immunotherapy results to date. The advantages of TIL-based adoptive therapy include the presence of spontaneously occurring T cells with natural avidity against tumor which have escaped thymic deletion; the use of a polyclonal population of T cells, which can limit immunologic escape of tumors; and the natural selection of patients whose tumor microenvironment is already conducive to T-cell homing. Initial studies using TILs in the treatment of metastatic melanoma during the late 1980s and early 1990s demonstrated objective antitumor responses, but they were short-lived. Based on animal studies showing that host lymphodepletion prior to T-cell transfer enhances persistence of T cells and antitumor response, a scheme of incremental lymphodepletion through high dose nonmyeloablating chemotherapy and added whole body radiation was tested. Infused cells were both long-lived, and highly penetrating, showing regression of voluminous metastatic tumors, with up to 16% complete response and 72% overall objective response rates in recent reports with maximal lymphodepletion and radiation. T cell persistence correlated with long lasting responses (103,202). Although these are phase I studies accruing a highly selected cohort of patients with metastatic melanoma with preexisting antitumor immunity, whose tumors yield tumor-reactive TILs, the results clearly demonstrate the power of adoptive immunotherapy and dispel the assumption that immunotherapy can only control small tumors (271). Interestingly, adoptive transfer of CD8⁺ clones expanded *ex vivo* to large numbers and transferred following lymphodepletion did not result in objective tumor response in melanoma, indicating that polyclonal T cells, a mixture of memory and effector cells, and CD4⁺ cells are necessary for tumor rejection (272).

Although TIL-based adoptive therapy has been mainly tested in melanoma, there is evidence that it is also an important opportunity in ovarian cancer. In the early 1990s, ovarian cancers were found to yield reactive TILs after IL-2 culturing *in vitro* that may be amenable to adoptive transfer (273,274). Moreover, pilot clinical trials of adjuvant therapy with adoptive transfer of tumor-derived lymphocytes expanded *ex vivo* with IL-2, following surgical debulking and frontline chemotherapy, showed a marked survival advantage (275,276). Stage III EOC patients treated with consolidation adoptive transfer of expanded TILs after completion of cisplatin-based frontline chemotherapy (n = 13) had 3-year overall survival rate of 100%, while that of a control group of patients (n = 10) receiving only chemotherapy was 67.5% ($p < 0.01$). The 3-year disease-free survival rate of the patients in the TIL group and in the control group was 82.1% and 54.5%, respectively. While these results can be limited by the lack of randomization, they nevertheless support the feasibility of adoptive therapy for ovarian cancer (275).

Optimization of adoptive TIL therapy is a matter of intense investigation and currently directed at: a) optimizing methods to select tumor-reactive TIL and expand them under optimal costimulation conditions that allow preferential expansion of specific T-cell phenotypes; and b) optimizing host and/or tumor conditioning. As shown in the melanoma trials, although infused cells had an effector phenotype (CD27⁻ CD28⁻ CD45RA⁺ CD62L⁻ CCR7⁻), TILs that persistent at two months in association with tumor regression were characterized by a less differentiated phenotype (CD27⁺ CD28⁺ CD45RA⁺ but CD62L⁻ CCR7⁻) and longer telomeres (277–281). These results argue that use of memory rather than effector cells may be more convenient for adoptive transfer (282), which has been confirmed by mouse models (283). Because TILs comprise a large number of tumor-reactive effector cells, identification of culture conditions that preferentially expand memory phenotypes is a priority. Recent technological advances with the development of artificial antigen-presenting cells (aAPCs) expressing a variable repertoire of costimulatory molecules and cytokines has generated new opportunities to provide the desired costimulatory molecules and cytokines

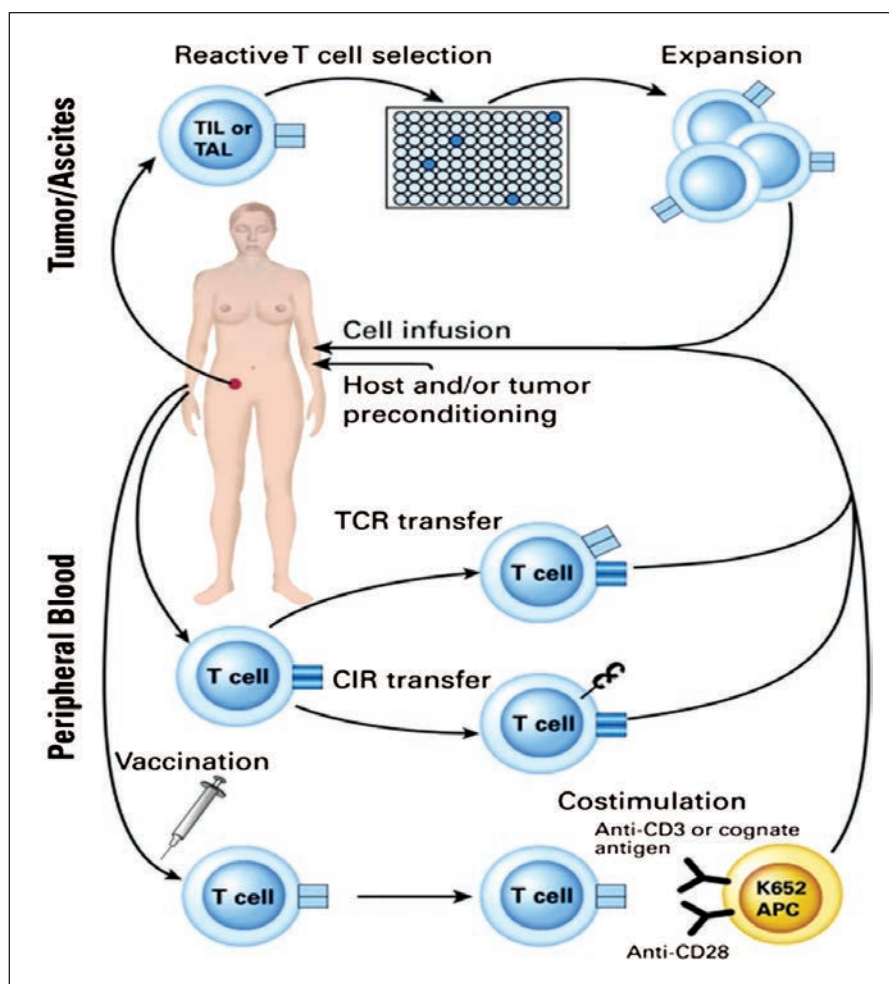


FIGURE 15.3. Cellular therapy.

Source: From Kandalaft, LE, Powell DJ Jr, Singh N, et al. Immunotherapy for ovarian cancer: what's next? *JCO* 2011;29:925–933, with permission.

to re-educate TILs, improving their potency and function *in vivo*. Carl June and colleagues recently described the development of a next generation K562-based aAPC platform capable of expressing multiple gene inserts, including human lymphocyte antigen (HLA)-A2, CD64 (the high-affinity Fc receptor) CD80, CD83, CD86, CD137L (4-1BBL) and CD252 (Ox40L), and a variety of T cell supporting cytokines (284). Cell-based aAPCs have proven to be more efficient at activating and expanding CD8⁺ CD28⁺ T cells, and antigen-specific T cells, than the magnetic bead-based aAPC (284). Importantly, TILs from ovarian cancer patients undergo robust expansion while maintaining their tumor reactivity after K562-based aAPC stimulation (Powell and colleagues, unpublished).

A proportion of patients are not eligible for TIL-adoptive therapy, because tumors are either unresectable or yield no tumor-reactive TILs. One strategy to overcome the daunting task of raising large numbers of tumor-reactive T cells is by engineering T cells to redirect their specificity. This can be accomplished by transducing lymphocytes to express a cloned T-cell receptor (TCR) with high affinity to tumor-associated epitopes. In this case, the cloned heterodimeric TCR is transduced to mixed peripheral blood T cells isolated from the patient, creating a large amount of bispecific T cells, which are polyclonal with respect to their original TCR, but potentially monoclonal for the cloned TCR (if recombination with endogenous TCR is minimized) (285). Alternatively, T cells can be transduced with a chimeric immunoreceptor (see below).

Recently, the clinical feasibility, safety, and preliminary efficacy of redirecting T cells of patients with melanoma using a TCR specific to MART-1, a melanoma antigen, was demonstrated (286). The genes encoding α and β chains of the TCR were cloned from a TIL clone derived from a patient demonstrating a near-complete regression of metastatic melanoma after adoptive cell transfer of TILs. Gene transfer resulted in transfection of 30% of CD8⁺ cells. Adoptive transfer of TCR-transduced cells in 15 patients resulted in durable engraftment at levels exceeding 10% of peripheral blood lymphocytes for at least 2 months after the infusion. High sustained levels of circulating, engineered cells at 1 year after infusion was observed in 2 patients who demonstrated objective regression of metastatic melanoma lesions (286). TCR-based engineering represents a potentially powerful strategy for ovarian cancer therapy as TCRs that recognize HLA-A2 restricted epitopes from known ovarian cancer antigens such as NY-ESO-1, p53, and others are available for clinically testing as well (287–290). Optimization through selection of naturally occurring or recombinant high affinity receptors, engineering to prevent recombination with endogenous TCR, and the use of lentiviral vectors developed in the June lab with transfection efficiency above 90% are poised to improve this approach significantly (291).

An alternative strategy to engineer T cells with redirected specificity is through genetic modification to recognize antigens in an MHC-unrestricted fashion through the use of chimeric immunoreceptors (CIR), fusion genes encoding an extracellular domain that specifically binds to tumor epitopes through a single chain

variable fragment (scFv) antibody, linked to intracellular signaling modules that mediate T cell activation (285,292,293). The tumor binding function of CIR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the V_H and V_L chains joined by a peptide linker of about 15 residues in length. In principle, universal targeting vectors can be constructed, because the scFvs bind to native cell surface epitopes and bypass the requirement for MHC restriction (294,295). Thus, in comparison to TCRs, CIR have 2 major advantages: (a) their HLA-independent recognition of antigen, which makes them broadly applicable regardless of the subject's HLA and regardless of the level of HLA expression on tumor cells, and (b) their signaling, which redirects T-cell cytotoxicity and permits T-cell proliferation and survival upon repeat antigen exposure. A potential drawback stems from their potential immunogenicity, if scFv are nonhuman. This can be averted by using human scFv. CIR will then be the tools of choice for T-cell engineering for cancer immunotherapies.

A large number of CIRs targeting diverse tumors have been developed (reviewed elsewhere) (285,296), however, clinical pilot tests are just beginning. Some of the ovarian tumor antigens and CIR investigated *in vitro* and *in vivo* in T lymphocytes are FBP (297,298), MUC-1 (299), HER2 and mesothelin (300). There has been a single study of adoptive transfer of CIR T cells in ovarian cancer (301). While this study demonstrated safety, the results were disappointing, with no clinically evident tumor responses, most likely due to low expression of the transgenic CIR, and poor persistence of the transferred T cells (301). Persistence can be dramatically improved by using human scFv and by adding costimulatory signaling capabilities to the intracytoplasmic domain of CIRs. Indeed, one issue that needs to be addressed with CIRs is that signaling through the cytosolic domain of the usual scFv-TCR ζ single chain construct does not fully replicate the multichain TCR signaling complex (138,139). This is solved by incorporating additional signaling modules in the cytoplasmic domain of the chimeric receptor. Efficient lentiviral and tissue culture technology now enables highly efficient transduction of primary T cells (291).

CONCLUSIONS

Many patients with cervical, endometrial, or ovarian cancer, who will eventually develop treatment resistant disease, can initially be rendered free of clinically detectable disease by surgery, radiation therapy, and/or chemotherapy for varying periods. This setting where the targets are circulating tumor cells or micrometastasis rather than bulk disease is ideal for treatment with immune based interventions. Significant advances have been made in the field of cancer immunotherapy over the last decade. It has been equally important to identify tumor antigens with immunogenic potential, as well as the application of a variety of strategies to augment the antitumor response. Numerous nonrandomized phase II immune targeted trials have shown a correlation between overall survival and the presence of its respective effectors. However, these benefits have not been confirmed to date in phase III trials in gynecologic malignancies, showing the continued importance of objectively evaluating promising approaches in early phase studies.

The way forward is to proceed with discovery oriented translational research in the form of clinical trials that can quickly assess alternative vaccine strategies, immunological monitoring methods, and tumor escape mechanisms. The key to success will depend on the continued development of organized multidisciplinary groups with the adoption of standardized patient populations (for example, second or third remission), as well as standardized monitoring to enable the comparison of single vaccine variables such as the constitution of an antigen (protein, peptide, viral vectors, or DNA), the method, frequency, and intensity of antigen delivery, and the effect of different adjuvants. In concert, a combination of strategies with the aim of achieving an integrated response (antibody and T-cell effectors) along with immunomodulatory approaches seem most likely to have the potential of demonstrating a meaningful clinical benefit in the future.

REFERENCES

- McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med*. 1996;334:1–6.
- Muggia FM, Braly PS, Brady MF, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol*. 2000;18(1):106–115.
- Markman M, Markman J, Webster K, et al. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. *J Clin Oncol*. 2004;22(15):3120–3125.
- Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354(1):34–43.
- Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med*. 2002;347(21):1645–1651.
- Brooks N, Pouniotis DS. Immunomodulation in endometrial cancer. *Int J Gynecol Cancer*. 2009;19(4):734–740.
- Coosemans A, Wölfl M, Berneman ZN, et al. Immunological response after therapeutic vaccination with WT1 mRNA-loaded dendritic cells in end-stage endometrial carcinoma. *Anticancer Res*. 2010;30(9):3709–3714.
- Bignotti E, Ravaggi A, Romani C, et al. Trop-2 overexpression in poorly differentiated endometrial endometrioid carcinoma: implications for immunotherapy with hRS7, a humanized anti-trop-2 monoclonal antibody. *Int J Gynecol Cancer*. 2011;21(9):1613–1621.
- Coley WB, V. Sarcoma of the clavicle: end-results following total excision. *Ann Surg*. 1910;52(6):776–796.
- Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoeediting: from immunosurveillance to tumor escape. *Nat Immunol*. 2002;3(11):991–998.
- Bui JD, Schreiber RD. Cancer immunosurveillance, immunoeediting and inflammation: independent or interdependent processes? *Curr Opin Immunol*. 2007;19(2):203–208.
- Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003;348(3):203–213.
- Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med*. 2004;10(9):942–949.
- Dietl J, Engel JB, Wischhusen J. The role of regulatory T cells in ovarian cancer. *Int J Gynecol Cancer*. 2007;17(4):764–770.
- Shankaran V, Ikeda H, Bruce AT, et al. IFN- γ and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature*. 2001;410(6832):1107–1111.
- Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoeediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. *Adv Immunol*. 2006;90:1–50.
- Koebel CM, Vermi W, Swann JB, et al. Adaptive immunity maintains occult cancer in an equilibrium state. *Nature*. 2007;450(7171):903–907.
- Meissner M, Reichert TE, Kunkel M, et al. Defects in the human leukocyte antigen class I antigen processing machinery in head and neck squamous cell carcinoma: association with clinical outcome. *Clin Cancer Res*. 2005;11(7):2552–2560.
- Hicklin DJ, Marincola FM, Ferrone S. HLA class I antigen downregulation in human cancers: T-cell immunotherapy revives an old story. *Mol Med Today*. 1999;5(4):178–186.
- Shevach EM. Fatal attraction: tumors beckon regulatory T cells. *Nat Med*. 2004;10(9):900–901.
- Shields JD, Kouritis IC, Tomei AA, et al. Induction of lymphoidlike stroma and immune escape by tumors that express the chemokine CCL21. *Science*. 2010;328(5979):749–752.
- Liu Z, Guo B, Lopez RD. Expression of intercellular adhesion molecule (ICAM)-1 or ICAM-2 is critical in determining sensitivity of pancreatic cancer cells to cytotoxicity by human gammadelta-T

- cells: implications in the design of gammadelta-T-cell-based immunotherapies for pancreatic cancer. *J Gastroenterol Hepatol*. 2009;24(5):900–911.
23. Igney FH, Krammer PH. Immune escape of tumors: apoptosis resistance and tumor counter-attack. *J Leukoc Biol*. 2002;71(6):907–920.
 24. Staveley-O' Carroll K, Sotomayor E, Montgomery J, et al. Induction of antigen-specific T cell anergy: An early event in the course of tumor progression. *Proc Natl Acad Sci USA*. 1998;95(3):1178–1183.
 25. Yigit R, et al. Ovarian cancer creates a suppressive microenvironment to escape immune elimination. *Gynecol Oncol*. 2010;117(2):366–372.
 26. Pelletier M, Micheletti A, Cassatella MA. Modulation of human neutrophil survival and antigen expression by activated CD4+ and CD8+ T cells. *J Leukoc Biol*. 2010;88(6):1163–1170.
 27. Cooley S, Weisdorf DS. Natural killer cells and tumor control. *Curr Opin Hematol*. 2010;17(6):514–521.
 28. Joncker NT, Shifrin N, Delebecque F, et al. Mature natural killer cells reset their responsiveness when exposed to an altered MHC environment. *J Exp Med*. 2010;207(10):2065–2072.
 29. Garrido C, Algarra I, Maleno I, et al. Alterations of HLA class I expression in human melanoma xenografts in immunodeficient mice occur frequently and are associated with higher tumorigenicity. *Cancer Immunol Immunother*. 2010;59(1):13–26.
 30. Veillot V, Carli C, Metz CN, et al. Macrophage migration inhibitory factor elicits an angiogenic phenotype in human ectopic endometrial cells and triggers the production of major angiogenic factors via CD44, CD74, and MAPK signaling pathways. *J Clin Endocrinol Metab*. 2010;95(12):E403–E412.
 31. Qualls JE, Murray PJ. A double agent in cancer: stopping macrophages wounds tumors. *Nat Med*. 2010;16(8):863–864.
 32. Davies DR, Cohen GH. Interactions of protein antigens with antibodies. *Proc Natl Acad Sci USA*. 1996;93(1):7–12.
 33. Mauro C, Fu H, Marelli-Berg F. T cell trafficking and metabolism: novel mechanisms and targets for immunomodulation. *Curr Opin Pharmacol*. 2012;12(4):452–457.
 34. Chan TD, Gardam S, Gatto D, et al. In vivo control of B-cell survival and antigen-specific B-cell responses. *Immunol Rev*. 2010;237(1):90–103.
 35. Boyd SD, Gaëta BA, Jackson KJ, et al. Individual variation in the germline Ig gene repertoire inferred from variable region gene rearrangements. *J Immunol*. 2010;184(12):6986–6992.
 36. Vinuesa CG, Sze DM, Cook MC, et al. Recirculating and germinal center B cells differentiate into cells responsive to polysaccharide antigens. *Eur J Immunol*. 2003;33(2):297–305.
 37. Pone EJ, Zhang J, Mai T, et al. BCR-signalling synergizes with TLR-signalling for induction of AID and immunoglobulin class-switching through the non-canonical NF-kappaB pathway. *Nat Commun*. 2012;3:767.
 38. Wang SY, Weiner G. Complement and cellular cytotoxicity in antibody therapy of cancer. *Expert Opin Biol Ther*. 2008;8(6):759–768.
 39. Walport MJ. Complement. First of two parts. *N Engl J Med*. 2001;344(14):1058–1066.
 40. Walport MJ. Complement. Second of two parts. *N Engl J Med*. 2001;344(15):1140–1144.
 41. Azeredo da Silveira S, et al. Complement activation selectively potentiates the pathogenicity of the IgG2b and IgG3 isotypes of a high affinity anti-erythrocyte autoantibody. *J Exp Med*. 2002;195(6):665–672.
 42. Chan AC, Carter PJ. Therapeutic antibodies for autoimmunity and inflammation. *Nat Rev Immunol*. 2010;10(5):301–316.
 43. Lv M, et al. Novel anti-CD20 antibody TGLA with enhanced antibody-dependent cell-mediated cytotoxicity mediates potent anti-lymphoma activity. *Cancer Lett*. 2010;294(1):66–73.
 44. Natsume A, Niwa R, Satoh M. Improving effector functions of antibodies for cancer treatment: enhancing ADCC and CDC. *Drug Des Devel Ther*. 2009;3:7–16.
 45. Coico R, Sunshine G. *Immunology: A Short Course*. Hoboken: John Wiley and Sons; 2009:391.
 46. Bjorkman PJ, et al. Structure of the human class I histocompatibility antigen, HLA-A2. *J Immunol*. 2005;174(1):6–19.
 47. Trombetta ES, Mellman I. Cell biology of antigen processing in vitro and in vivo. *Annu Rev Immunol*. 2005;23:975–1028.
 48. Cohn M. Does the signal for the activation of T cells originate from the antigen-presenting cell or the effector T-helper? *Cell Immunol*. 2006;241(1):1–6.
 49. Smith-Garvin JE, Koretzky GA, Jordan MS. T cell activation. *Annu Rev Immunol*. 2009;27:591–619.
 50. Hong H, et al. Depletion of CD4+CD25+ regulatory T cells enhances natural killer T cell-mediated antitumor immunity in a murine mammary breast cancer model. *Clin Exp Immunol*. 2010;159(1):93–99.
 51. Hodi FS, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711–723.
 52. MacPhee IA, Yagita H, Oliveira DB. Blockade of OX40-ligand after initial triggering of the T helper 2 response inhibits mercuric chloride-induced autoimmunity. *Immunol*. 2006;117(3):402–408.
 53. Sharma RK, et al. 4-1BB ligand as an effective multifunctional immunomodulator and antigen delivery vehicle for the development of therapeutic cancer vaccines. *Cancer Res*. 2010;70(10):3945–3954.
 54. Li Y, et al. Summary of the primer on tumor immunology and the biological therapy of cancer. *J Transl Med*. 2009;7:11.
 55. Clynes RA, et al. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. *Nat Med*. 2000;6(4):443–446.
 56. Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. *J Clin Oncol*. 2011;29(36):4828–4836.
 57. Kohler ME, Johnson BD, Palen K, et al. Tumor antigen analysis in neuroblastoma by serological interrogation of bioinformatic data. *Cancer Sci*. 2010;101(11):2316–2324.
 58. Sahin U, et al. Human neoplasms elicit multiple specific immune responses in the autologous host. *Proc Natl Acad Sci USA*. 1995;92(25):11810–11813.
 59. Chatterjee M, Wojciechowski J, Tainsky MA. Discovery of antibody biomarkers using protein microarrays of tumor antigens cloned in high throughput. *Methods Mol Biol*. 2009;520:21–38.
 60. Gnjatovic S, et al. Seromic profiling of ovarian and pancreatic cancer. *Proc Natl Acad Sci USA*. 2010;107(11):5088–5093.
 61. Piura B, Piura E. Autoantibodies to tumor-associated antigens in epithelial ovarian carcinoma. *J Oncol*. 2009;581939.
 62. Brichard V, et al. The tyrosinase gene codes for an antigen recognized by autologous cytolytic T lymphocytes on HLA-A2 melanomas. *J Exp Med*. 1993;178(2):489–495.
 63. Wolfel T, et al. A p16INK4a-insensitive CDK4 mutant targeted by cytolytic T lymphocytes in a human melanoma. *Science*. 1995;269(5228):1281–1284.
 64. Cheever MA, et al. Immunity to oncogenic proteins. *Immunol Rev*. 1995;145:33–59.
 65. Scanlan MJ, et al. Characterization of human colon cancer antigens recognized by autologous antibodies. *Int J Cancer*. 1998;76(5):652–658.
 66. Zhang S, et al. Selection of carbohydrate tumor antigens as targets for immune attack using immunotherapy. I. Focus on gangliosides. *Intl J Cancer*. 1997;73:42–49.
 67. Tindle RW. Human papillomavirus vaccines for cervical cancer. *Curr Opin Immunol*. 1996;8(5):643–650.
 68. Boon T, van der Bruggen P. Human tumor antigens recognized by T lymphocytes. *J Exp Med*. 1996;183(3):725–729.
 69. Marincola FM, et al. Escape of human solid tumors from T-cell recognition: molecular mechanisms and functional significance. *Adv Immunol*. 2000;74:181–273.
 70. Hurwitz AA, et al. CTLA-4 blockade synergizes with tumor-derived granulocyte-macrophage colony-stimulating factor for treatment of an experimental mammary carcinoma. *Proc Natl Acad Sci USA*. 1998;95(17):10067–10071.
 71. Matsuzaki J, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. *Proc Natl Acad Sci USA*. 2010;107(17):7875–7880.
 72. Uytendhoeve C, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. *Nat Med*. 2003;9(10):1269–1274.
 73. Shimizu J, Yamazaki S, Sakaguchi S. Induction of tumor immunity by removing CD25+CD4+ T cells: a common basis between tumor immunity and autoimmunity. *J Immunol*. 1999;163(10):5211–5218.
 74. Terabe M, et al. NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway. *Nat Immunol*. 2000;1(6):515–520.
 75. Elgueta R, et al. Molecular mechanism and function of CD40/CD40L engagement in the immune system. *Immunol Rev*. 2009;229(1):152–172.
 76. Scarlett UK, et al. In situ stimulation of CD40 and toll-like receptor 3 transforms ovarian cancer-infiltrating dendritic cells from immunosuppressive to immunostimulatory cells. *Cancer Res*. 2009;69(18):7329–7337.
 77. Kedl RM, et al. CD40 stimulation accelerates deletion of tumor-specific CD8(+) T cells in the absence of tumor-antigen vaccination. *Proc Natl Acad Sci USA*. 2001;98(19):10811–10816.
 78. Melichar B, et al. Expression of CD40 and growth-inhibitory activity of CD40 ligand in ovarian cancer cell lines. *Gynecol Oncol*. 2007;104(3):707–713.
 79. Hakkarainen T, et al. CD40 is expressed on ovarian cancer cells and can be utilized for targeting adenoviruses. *Clin Cancer Res*. 2003;9(2):619–624.
 80. Gallagher NJ, et al. CD40 activation in epithelial ovarian carcinoma cells modulates growth, apoptosis, and cytokine secretion. *Mol Pathol*. 2002;55(2):110–120.
 81. Ciaravino G, et al. Differential expression of CD40 and CD95 in ovarian carcinoma. *Eur J Gynaecol Oncol*. 2004;25(1):27–32.
 82. Toutirais O, et al. Effects of CD40 binding on ovarian carcinoma cell growth and cytokine production in vitro. *Clin Exp Immunol*. 2007;149(2):372–377.
 83. Ghamande S, et al. Recombinant CD40 ligand therapy has significant antitumor effects on CD40-positive ovarian tumor xenografts grown in SCID mice and demonstrates an augmented effect with cisplatin. *Cancer Res*. 2001;61(20):7556–7562.
 84. Korman AJ, Peggs KS, Allison JP. Checkpoint blockade in cancer immunotherapy. *Adv Immunol*. 2006;90:297–339.
 85. Peggs KS, et al. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. *J Exp Med*. 2009;206(8):1717–1725.
 86. Fong L, Small EJ. Anti-cytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. *J Clin Oncol*. 2008;26(32):5275–5283.

87. Hodi FS, et al. Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. *Proc Natl Acad Sci USA*. 2008;105(8):3005–3010.
88. Iwai Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA*. 2002;99(19):12293–12297.
89. Nakanishi J, et al. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother*. 2007;56(8):1173–1182.
90. Thompson RH, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin Cancer Res*. 2007;13(6):1757–1761.
91. Gao Q, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res*. 2009;15(3):971–979.
92. Curiel TJ, et al. Blockade of B7-H1 improves myeloid dendritic cell-mediated antitumor immunity. *Nat Med*. 2003;9(5):562–567.
93. Liu Y, et al. B7-H1 on myeloid-derived suppressor cells in immune suppression by a mouse model of ovarian cancer. *Clin Immunol*. 2008;129(3):471–481.
94. Kaufmann DE, Walker BD. PD-1 and CTLA-4 inhibitory cosignaling pathways in HIV infection and the potential for therapeutic intervention. *J Immunol*. 2009;182(10):5891–5897.
95. Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. *Cancer Immunol Immunother*. 2007;56(5):739–745.
96. Hirano F, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*. 2005;65(3):1089–1096.
97. He YF, et al. Blocking programmed death-1 ligand-PD-1 interactions by local gene therapy results in enhancement of antitumor effect of secondary lymphoid tissue chemokine. *J Immunol*. 2004;173(8):4919–4928.
98. Blank C, et al. Blockade of PD-L1 (B7-H1) augments human tumor-specific T cell responses in vitro. *Int J Cancer*. 2006;119(2):317–327.
99. Berger R, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. *Clin Cancer Res*. 2008;14(10):3044–3051.
100. Berd D, et al. Immunopharmacologic analysis of an autologous, hapten-modified human melanoma vaccine. *J Clin Oncol*. 2004;22(3):403–415.
101. Dudley ME, et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. *Science*. 2002;298(5594):850–854.
102. Machiels JP, et al. Cyclophosphamide, doxorubicin, and paclitaxel enhance the antitumor immune response of granulocyte/macrophage-colony stimulating factor-secreting whole-cell vaccines in HER-2/neu tolerized mice. *Cancer Res*. 2001;61(9):3689–3697.
103. Dudley ME, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol*. 2005;23(10):2346–2357.
104. Klebanoff CA, et al. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. *Trends Immunol*. 2005;26(2):111–117.
105. Berd D, Maguire HC Jr, Mastrangelo MJ. Induction of cell-mediated immunity to autologous melanoma cells and regression of metastases after treatment with a melanoma cell vaccine preceded by cyclophosphamide. *Cancer Res*. 1986;46(5):2572–2577.
106. MacLean GD, et al. Antibodies against mucin-associated sialyl-Tn epitopes correlate with survival of metastatic adenocarcinoma patients undergoing active specific immunotherapy with synthetic STn vaccine. *J Immunother Emphasis Tumor Immunol*. 1996;19(1):59–68.
107. Benencia F, Coukos G. T Regulatory cell depletion can boost DC-based vaccines. *Cancer Biol Ther*. 2005;4(6):628–630.
108. Prasad SJ, et al. Dendritic cells loaded with stressed tumor cells elicit long-lasting protective tumor immunity in mice depleted of CD4+CD25+ regulatory T cells. *J Immunol*. 2005;174(1):90–98.
109. Powell DJ Jr, et al. Partial reduction of human FOXP3+ CD4 T cells in vivo after CD25-directed recombinant immunotoxin administration. *J Immunother*. 2008;31(2):189–198.
110. Dannull J, et al. Enhancement of vaccine-mediated antitumor immunity in cancer patients after depletion of regulatory T cells. *J Clin Invest*. 2005;115(12):3623–3633.
111. Barnett B, et al. Regulatory T cells in ovarian cancer: biology and therapeutic potential. *Am J Reprod Immunol*. 2005;54(6):369–377.
112. Mahnke K, et al. Depletion of CD4+CD25+ human regulatory T cells in vivo: kinetics of Treg depletion and alterations in immune functions in vivo and in vitro. *Int J Cancer*. 2007;120(12):2723–2733.
113. Rasku MA, et al. Transient T cell depletion causes regression of melanoma metastases. *J Transl Med*. 2008;6:12.
114. Waldmann TA. Daclizumab (anti-Tac, Zenapax) in the treatment of leukemia/lymphoma. *Oncogene*. 2007;26(25):3699–3703.
115. Kreijveld E, et al. Following anti-CD25 treatment, a functional CD4+CD25+ regulatory T-cell pool is present in renal transplant recipients. *Am J Transplant*. 2007;7(1):249–255.
116. Nussenblatt RB, et al. Treatment of noninfectious intermediate and posterior uveitis with the humanized anti-Tac mAb: a phase III clinical trial. *Proc Natl Acad Sci USA*. 1999;96(13):7462–7466.
117. Przepiorka D, et al. Daclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for treatment of acute graft-versus-host disease. *Blood*. 2000;95(1):83–89.
118. Lehky TJ, et al. Reduction in HTLV-I proviral load and spontaneous lymphoproliferation in HTLV-I-associated myelopathy/tropical spastic paraparesis patients treated with humanized anti-Tac. *Ann Neurol*. 1998;44(6):942–947.
119. Vincenti F, Nashan B, Light S. Daclizumab: outcome of phase III trials and mechanism of action. Double therapy and the triple therapy study groups. *Transplant Proc*. 1998;30(5):2155–2158.
120. Fyfe GA, et al. Long-term response data for 255 patients with metastatic renal cell carcinoma treated with high-dose recombinant interleukin-2 therapy. *J Clin Oncol*. 1996;14(8):2410–2411.
121. Chang E, Rosenberg SA. Patients with melanoma metastases at cutaneous and subcutaneous sites are highly susceptible to interleukin-2-based therapy. *J Immunother*. 2001;24(1):88–90.
122. Yigit R, et al. Cytokine analysis as a tool to understand tumour-host interaction in ovarian cancer. *Eur J Cancer*. 2011;47(12):1883–1889.
123. Marth C, et al. Interferon-gamma in combination with carboplatin and paclitaxel as a safe and effective first-line treatment option for advanced ovarian cancer: results of a phase I/II study. *Int J Gynecol Cancer*. 2006;16(4):1522–1528.
124. Abdulhay G, et al. Human lymphoblastoid interferon in the treatment of advanced epithelial ovarian malignancies: a Gynecologic Oncology Group Study. *Am J Obstet Gynecol*. 1985;152(4):418–423.
125. Hall GD, et al. Maintenance treatment with interferon for advanced ovarian cancer: results of the Northern and Yorkshire gynaecology group randomised phase III study. *Br J Cancer*. 2004;91(4):621–626.
126. Alberts DS, et al. Randomized trial of adjuvant intraperitoneal alpha-interferon in stage III ovarian cancer patients who have no evidence of disease after primary surgery and chemotherapy: an intergroup study. *Gynecol Oncol*. 2006;100(1):133–138.
127. Wadler S, et al. Lack of efficacy of interferon-alpha therapy in recurrent, advanced cervical cancer. *J Interferon Cytokine Res*. 1995;15(12):1011–1016.
128. Ramos MC, et al. Expression of cytokines in cervical stroma in patients with high-grade cervical intraepithelial neoplasia after treatment with intralesional interferon alpha-2b. *Eur J Gynaecol Oncol*. 2010;31(5):522–529.
129. Sereti I, et al. IL-2-induced CD4+ T-cell expansion in HIV-infected patients is associated with long-term decreases in T-cell proliferation. *Blood*. 2004;104(3):775–780.
130. Weiss GR, et al. Molecular insights on the peripheral and intratumoral effects of systemic high-dose rIL-2 (aldesleukin) administration for the treatment of metastatic melanoma. *Clin Cancer Res*. 2011;17(23):7440–7450.
131. Edwards RP, et al. Comparison of toxicity and survival following intraperitoneal recombinant interleukin-2 for persistent ovarian cancer after platinum: twenty-four-hour versus 7-day infusion. *J Clin Oncol*. 1997;15(11):3399–3407.
132. Wei S, et al. Interleukin-2 administration alters the CD4+FOXP3+ T-cell pool and tumor trafficking in patients with ovarian carcinoma. *Cancer Res*. 2007;67(15):7487–7494.
133. Peng DJ, Liu R, Zou W. Regulatory T cells in human ovarian cancer. *J Oncol*. 2012;34:5164.
134. Horton HM, et al. IL-2 plasmid therapy of murine ovarian carcinoma inhibits the growth of tumor ascites and alters its cytokine profile. *J Immunol*. 1999;163(12):6378–6385.
135. Snook AE, et al. Cytokine adjuvantation of therapeutic anti-tumor immunity targeted to cancer mucosa antigens. *Clin Transl Sci*. 2008;1(3):263–264.
136. Wolf SF, et al. Cloning of cDNA for natural killer cell stimulatory factor, a heterodimeric cytokine with multiple biologic effects on T and natural killer cells. *J Immunol*. 1991;146(9):3074–3081.
137. Trinchieri G. Interleukin-12: a cytokine produced by antigen-presenting cells with immunoregulatory functions in the generation of T-helper cells type 1 and cytotoxic lymphocytes. *Blood*. 1994;84(12):4008–4027.
138. Nash MA, et al. Differential expression of cytokine transcripts in human epithelial ovarian carcinoma by solid tumour specimens, peritoneal exudate cells containing tumour, tumour-infiltrating lymphocyte (TIL)-derived T cell lines and established tumour cell lines. *Clin Exp Immunol*. 1998;112(2):172–180.
139. Whitworth JM, Alvarez RD. Evaluating the role of IL-12 based therapies in ovarian cancer: a review of the literature. *Expert Opin Biol Ther*. 2011;11(6):751–762.
140. Zeimer AG, et al. Ascitic interleukin-12 is an independent prognostic factor in ovarian cancer. *J Clin Oncol*. 1998;16(5):1861–1868.

141. Kudelka AP, et al. Is ascitic fluid interleukin-12 an independent prognostic factor in ovarian cancer? The necessity of correction milligram P values for multiple comparisons. *J Clin Oncol.* 1998;16(9):3208–3209.
142. Hurteau JA, et al. Evaluation of recombinant human interleukin-12 in patients with recurrent or refractory ovarian cancer: a gynecologic oncology group study. *Gynecol Oncol.* 2001;82(1):7–10.
143. Mahvi DM, et al. Intratumoral injection of IL-12 plasmid DNA—results of a phase I/II clinical trial. *Cancer Gene Ther.* 2007;14(8):717–723.
144. Daud AI, et al. Phase I trial of interleukin-12 plasmid electroporation in patients with metastatic melanoma. *J Clin Oncol.* 2008;26(36):5896–5903.
145. Raff HV, et al. Comparison of functional activities between IgG1 and IgM class-switched human monoclonal antibodies reactive with group B streptococci or *Escherichia coli*. *K1. J Infect Dis.* 1991;163(2):346–354.
146. Chapman C, et al. Autoantibodies in breast cancer: their use as an aid to early diagnosis. *Ann Oncol.* 2007;18(5):868–873.
147. Chatterjee M, et al. Diagnostic markers of ovarian cancer by high-throughput antigen cloning and detection on arrays. *Cancer Res.* 2006;66(2):1181–1190.
148. Anderson KS, et al. p53 autoantibodies as potential detection and prognostic biomarkers in serous ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2010;19(3):859–868.
149. Maddison P, Lang P. Paraneoplastic neurological autoimmunity and survival in small-cell lung cancer. *J Neuroimmunol.* 2008;159–162.
150. Budiu RA, et al. Soluble MUC1 and serum MUC1-specific antibodies are potential prognostic biomarkers for platinum-resistant ovarian cancer. *Cancer Immunol Immunother.* 2011;60(7):975–984.
151. Zhang H, et al. Antibodies can eradicate cancer micrometastasis. *Cancer Res.* 1998;58:2844–2899.
152. Bellati F, et al. Monoclonal antibodies in gynecological cancer: a critical point of view. *Clin Dev Immunol.* 2011;890758.
153. Reichert JM, Dhimolea E. The future of antibodies as cancer drugs. *Drug Discov Today.* 2012;17–18:954–963.
154. Burger R, et al. Phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer: a Gynecology Oncology Group Study. *J Clin Oncol.* 2010;28(18s):946s.
155. Zhang S, et al. Selection of Tumor Antigens as targets for immune attack using immunohistochemistry: protein antigens. *Clin Cancer Res.* 1998;4:2669–2676.
156. Zhang S, et al. Selection of tumor antigens as targets for immune attack using immunohistochemistry: II. Blood Group related antigens. *Int J Cancer.* 1997;73:50–56.
157. Bast RC Jr, et al. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest.* 1981;68(5):1331–1337.
158. Yin BW, Dnistrian A, Lloyd KO. Ovarian cancer antigen CA125 is encoded by the MUC16 mucin gene. *Int J Cancer.* 2002;98(5):737–740.
159. O'Brien TJ, et al. The CA 125 gene: an extracellular superstructure dominated by repeat sequences. *Tumour Biol.* 2001;22(6):348–366.
160. Teicher BA. Antibody-drug conjugate targets. *Curr Cancer Drug Targets.* 2009;9(8):982–1004.
161. Teicher BA, Chari RV. Antibody conjugate therapeutics: challenges and potential. *Clin Cancer Res.* 2011;17(20):6389–6397.
162. Meredith RF, et al. Brief overview of preclinical and clinical studies in the development of intraperitoneal radioimmunotherapy for ovarian cancer. *Clin Cancer Res.* 2007;13(18Pt2):5643–5645.
163. Maloney D, et al. Diversity in antibody-based approaches to non-Hodgkin lymphoma. *Leuk Lymphoma.* 2010;51(suppl. 1):20–27.
164. Young RC, et al. Adjuvant treatment for early ovarian cancer: a randomized phase III trial of intraperitoneal 32P or intravenous cyclophosphamide and cisplatin—a gynecologic oncology group study. *J Clin Oncol.* 2003;21(23):4350–4355.
165. Nicholson S, et al. Radioimmunotherapy after chemotherapy compared to chemotherapy alone in the treatment of advanced ovarian cancer: a matched analysis. *Oncol Rep.* 1998;5(1):223–226.
166. Barakat RR, et al. Intraperitoneal chemotherapy for ovarian carcinoma: results of long-term follow-up. *J Clin Oncol.* 2002;20(3):694–698.
167. Chari RV. Targeted delivery of chemotherapeutics: tumor-activated prodrug therapy. *Adv Drug Deliv Rev.* 1998;31(1–2):89–104.
168. Yin BW, Lloyd KO. Molecular cloning of the CA125 ovarian cancer antigen: identification as a new mucin, muc 16. *J Biol Chem.* 2001;276(29):27371–27375.
169. Bafna S, Kaur S, Batra SK. Membrane-bound mucins: the mechanistic basis for alterations in the growth and survival of cancer cells. *Oncogene.* 2010;29(20):2893–2904.
170. Streppel MM, et al. Mucin 16 (cancer antigen 125) expression in human tissues and cell lines and correlation with clinical outcome in adenocarcinomas of the pancreas, esophagus, stomach, and colon. *Hum Pathol.* 2012;43(10):1755–1763.
171. Foon KA, Bhattacharya-Chatterjee M. Are solid tumor anti-idiotypic vaccines ready for prime time? Commentary re: U. Wagner, et al. Immunological consolidation of ovarian carcinoma recurrences with monoclonal anti-idiotypic antibody ACA125: immune responses and survival in palliative treatment. *Clin. Cancer Res.* 2001;7(5):1154–1162. *Clin Cancer Res.* 2001;7(5):1112–1115.
172. Jerne NK. Towards a network theory of the immune system. *Ann Immunol.* 1974;125:373–389.
173. Noujaim AA, et al. Induction of CA125-specific B and T cell responses in patients injected with MAb-B43.13—evidence for antibody-mediated antigen-processing and presentation of CA125 in vivo. *Cancer Biother Radiopharm.* 2001;16(3):187–203.
174. Berek JS, Schultes BC, Nicodemus CF. Biologic and immunologic therapies for ovarian cancer. *J Clin Oncol.* 2003;21(suppl. 10):168–174.
175. Baum RP, et al. Clinical course of ovarian cancer patients under repeated stimulation of HAMA using MAb OC125 and B43.13. *Hybridoma.* 1993;12(5):583–589.
176. Ehlen TG, et al. A pilot phase 2 study of oregovomab murine monoclonal antibody to CA125 as an immunotherapeutic agent for recurrent ovarian cancer. *Int J Gynecol Cancer.* 2005;15(6):1023–1034.
177. Mobus VJ, et al. Immune responses to murine monoclonal antibody-B43.13 correlate with prolonged survival of women with recurrent ovarian cancer. *Am J Obstet Gynecol.* 2003;189(1):28–36.
178. Berek JS, et al. Randomized, placebo-controlled study of oregovomab for consolidation of clinical remission in patients with advanced ovarian cancer. *J Clin Oncol.* 2004;22(17):3507–3516.
179. Berek J, et al. Oregovomab maintenance immunotherapy does not improve outcomes in advanced ovarian cancer. *J Clin Oncol.* 2009;27(3):418–425.
180. Saleh MN, et al. Immunologic response to the dual murine anti-Id vaccine Melimmune-1 and Melimmune-2 in patients with high risk melanoma without evidence of systemic disease. *J Immunother.* 1998;21:379–388.
181. Reinartz S, et al. Immunological properties of a single-chain fragment of the anti-idiotypic antibody ACA125. *Cancer Immunol Immunother.* 2000;49(4–5):186–192.
182. Sabbatini P, et al. Phase I study of abagovomab in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer. *Clin Cancer Res.* 2006;12(18):5503–5510.
183. Pfisterer J, et al. The anti-idiotypic antibody abagovomab in patients with recurrent ovarian cancer. A phase I trial of the AGO-OVAR. *Ann Oncol.* 2006;17(10):1568–1577.
184. Sabbatini P, et al. Abagovomab maintenance therapy in patients with epithelial ovarian cancer after complete response post first-line chemotherapy: preliminary results of the randomized double blind, placebo controlled multi-center MIMOSA trial. *J Clin Oncol.* 2010;28:15s.
185. Braly P, et al. The Immune adjuvant properties of front-line carboplatin-paclitaxel: a randomized phase 2 study of alternative schedules of intravenous oregovomab chemioimmunotherapy in advanced ovarian cancer. *J Immunother.* 2009;32(1):54–65.
186. Schilder RJ, et al. Phase II study of gefitinib in patients with relapsed or persistent ovarian or primary peritoneal carcinoma and evaluation of epidermal growth factor receptor mutations and immunohistochemical expression: a Gynecologic Oncology Group Study. *Clin Cancer Res.* 2005;11(15):5539–5548.
187. Zeineldin R, et al. Targeting the EGF receptor for ovarian cancer therapy. *J Oncol.* 2010;414676.
188. Hogdall EV, et al. Distribution of HER-2 overexpression in ovarian carcinoma tissue and its prognostic value in patients with ovarian carcinoma: from the Danish MALOVA Ovarian Cancer Study. *Cancer.* 2003;98(1):66–73.
189. Bookman MA, et al. Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: a phase II trial of the Gynecologic Oncology Group. *J Clin Oncol.* 2003;21(2):283–290.
190. Franklin MC, et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell.* 2004;5(4):317–328.
191. Sims AH, et al. Defining the molecular response to trastuzumab, pertuzumab and combination therapy in ovarian cancer. *Br J Cancer.* 2012;106(11):1779–1789.
192. Heiss MM, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. *Int J Cancer.* 2010;127(9):2209–2221.
193. Ott MG, et al. Humoral response to catumaxomab correlates with clinical outcome: results of the pivotal phase II/III study in patients with malignant ascites. *Int J Cancer.* 2012;130(9):2195–2203.
194. Kim GE, et al. Synchronous coexpression of epidermal growth factor receptor and cyclooxygenase-2 in carcinomas of the uterine cervix: a potential predictor of poor survival. *Clin Cancer Res.* 2004;10(4):1366–1374.
195. Santin AD, et al. Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011;122(3):495–500.
196. Farley J, et al. Phase II study of cisplatin plus cetuximab in advanced, recurrent, and previously treated cancers of the cervix and evaluation of epidermal

- growth factor receptor immunohistochemical expression: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011;121(2):303–308.
197. Leffers N, Daemen T, Helfrich W, et al. Antigen-specific active immunotherapy for ovarian cancer. *Cochrane Database Syst Rev.* 2010;(1):CD007287.
 198. Chu CS, et al. Immunotherapy opportunities in ovarian cancer. *Expert Rev Anticancer Ther.* 2008;8(2):243–257.
 199. Odunsi K, Sabbatini P. Harnessing the immune system for ovarian cancer therapy. *Am J Reprod Immunol.* 2008;59(1):62–74.
 200. Sabbatini P, Odunsi K. Immunologic approaches to ovarian cancer treatment. *J Clin Oncol.* 2007;25(20):2884–2893.
 201. Hung CF, et al. Antigen-specific immunotherapy of cervical and ovarian cancer. *Immunol Rev.* 2008;222:43–69.
 202. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. *Nat Med.* 2004;10(9):909–915.
 203. Spassova MK, et al. Synthesis of selected LeY and KH-1 analogues: a medicinal chemistry approach to vaccine optimization. *J Org Chem.* 2005;70(9):3383–3395.
 204. Danishefsky SJ, et al. A strategy for the solid-phase synthesis of oligosaccharides. *Science.* 1993;260(5112):1307–1309.
 205. Sorensen AL, et al. Chemoenzymatically synthesized multimeric Tn/STn MUC1 glycopeptides elicit cancer-specific anti-MUC1 antibody responses and override tolerance. *Glycobiology.* 2006;16(2):96–107.
 206. Federici MF, et al. Selection of carbohydrate antigens in human epithelial ovarian cancers as targets for immunotherapy: serous and mucinous tumors exhibit distinctive patterns of expression. *Int J Cancer.* 1999;81(2):193–198.
 207. Livingston PO, Zhang S, Lloyd KO. Carbohydrate vaccines that induce antibodies against cancer. Part I. Rational. *Immunol Immunother.* 1997;45:1–9.
 208. Ragupathi G, Gathuru J, Livingston P. Antibody inducing polyvalent cancer vaccines. *Cancer Treat Res.* 2005;123:157–180.
 209. Ragupathi G, et al. A preclinical study comparing approaches for augmenting the immunogenicity of a heptavalent KLH-conjugate vaccine against epithelial cancers. *Cancer Immunol Immunother.* 2003;52(10):608–616.
 210. Slovin SF, et al. Thomsen-Friedenreich (TF) antigen as a target for prostate cancer vaccine: clinical trial results with TF cluster (c)-KLH plus QS21 conjugate vaccine in patients with biochemically relapsed prostate cancer. *Cancer Immunol Immunother.* 2005;54(7):694–702.
 211. Kagan E, et al. Comparison of antigen constructs and carrier molecules for augmenting the immunogenicity of the monosaccharide epithelial cancer antigen Tn. *Cancer Immunol Immunother.* 2005;54(5):424–430.
 212. Sabbatini P, et al. Pilot study of a heptavalent vaccine-KLH conjugate plus QS-21 in patients with epithelial ovarian, fallopian tube, or peritoneal cancer. *Clin Cancer Res.* 2007;13(14):4170–4177.
 213. Gilewski T, et al. Immunization of metastatic breast cancer patients with a fully synthetic globo H conjugate: a phase I trial. *Proc Natl Acad Sci USA.* 2001;98(6):3270–3275.
 214. Gilewski T, et al. Vaccination of high-risk breast cancer patients with mucin-1 (MUC1) keyhole limpet hemocyanin conjugate plus QS-21. *Clin Cancer Res.* 2000;6(5):1693–1701.
 215. Slovin SF, et al. Immunogenicity of a fully synthetic globo-H hexasaccharide conjugate in man. *Proc Natl Acad Sci USA.* 1999;96:5710–5715.
 216. Trumpfheller C, et al. Dendritic cell-targeted protein vaccines: a novel approach to induce T-cell immunity. *J Intern Med.* 2012;271(2):183–192.
 217. Bear AS, Cruz CR, Foster AE. T cells as vehicles for cancer vaccination. *J Biomed Biotechnol.* 2011;417403.
 218. Benencia F, Courreges MC, Coukos G. Whole tumor antigen vaccination using dendritic cells: comparison of RNA electroporation and pulsing with UV-irradiated tumor cells. *J Transl Med.* 2008;6:21.
 219. Murshid A, et al. Heat shock proteins and cancer vaccines: developments in the past decade and chaperoning in the decade to come. *Expert Rev Vaccines.* 2011;10(11):1553–1568.
 220. Chitale DA, et al. Expression of cancer-testis antigens in endometrial carcinomas using a tissue microarray. *Mod Pathol.* 2005;18(1):119–126.
 221. Santin AD, et al. Overexpression of HER-2/neu in uterine serous papillary cancer. *Clin Cancer Res.* 2002;8(5):1271–1279.
 222. Benencia F, et al. Dendritic cells the tumor micro-environment and the challenges for an effective antitumor vaccination. *J Biomed Biotechnol.* 2012;425–476.
 223. Zou W, et al. Stromal-derived factor-1 in human tumors recruits and alters the function of plasmacytoid precursor dendritic cells. *Nat Med.* 2001;7(12):1339–1346.
 224. Wei S, et al. Plasmacytoid dendritic cells induce CD8+ regulatory T cells in human ovarian carcinoma. *Cancer Res.* 2005;65(12):5020–5026.
 225. Schlienger K, et al. TRANCE- and CD40 ligand-matured dendritic cells reveal MHC class I-restricted T cells specific for autologous tumor in late-stage ovarian cancer patients. *Clin Cancer Res.* 2003;9(4):1517–1527.
 226. Ye F, et al. Ovarian carcinoma cells effectively inhibit differentiation and maturation of dendritic cells derived from hematopoietic progenitor cells in vitro. *Cancer Invest.* 2005;23(5):379–385.
 227. Fujii S, et al. Dendritic cell-based cancer immunotherapies. *Arch Immunol Ther Exp. (Warsz).* 2009;57(3):189–198.
 228. Zom GG, et al. TLR ligand-peptide conjugate vaccines: toward clinical application. *Adv Immunol.* 2012;114:177–201.
 229. Cathelin D, et al. Dendritic cell-tumor cell hybrids and immunotherapy: what's next? *Cytotherapy.* 2011;13(7):774–785.
 230. Markowicz S, et al. Adjuvant vaccination with melanoma antigen-pulsed dendritic cells in stage III melanoma patients. *Med Oncol.* 2012.
 231. van der Bruggen P, et al. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. *Science.* 1991;254(5038):1643–1647.
 232. Old LJ. Cancer/testis (CT) antigens – a new link between gametogenesis and cancer. *Cancer Immun.* 2001;1:1.
 233. Odunsi K, et al. NY-ESO-1 and LAGE-1 cancer-testis antigens are potential targets for immunotherapy in epithelial ovarian cancer. *Cancer Res.* 2003;63(18):6076–6083.
 234. Zeng G, et al. Generation of NY-ESO-1-specific CD4+ and CD8+ T cells by a single peptide with dual MHC class I and class II specificities: a new strategy for vaccine design. *Cancer Res.* 2002;62(13):3630–3635.
 235. Jager E, et al. Identification of NY-ESO-1 epitopes presented by human histocompatibility antigen (HLA)-DRB4*0101-0103 and recognized by CD4(+) T lymphocytes of patients with NY-ESO-1-expressing melanoma. *J Exp Med.* 2000;191(4):625–630.
 236. Yamaguchi H, et al. Identification of HLA-A24-restricted CTL epitope from cancer-testis antigen, NY-ESO-1, and induction of a specific antitumor immune response. *Clin Cancer Res.* 2004;10(3):890–896.
 237. Odunsi K, et al. Vaccination with an NY-ESO-1 peptide of HLA class I/II specificities induces integrated humoral and T cell responses in ovarian cancer. *Proc Natl Acad Sci USA.* 2007;104(31):12837–12842.
 238. Diefenbach CS, et al. Safety and immunogenicity study of NY-ESO-1b peptide and montanide ISA-51 vaccination of patients with epithelial ovarian cancer in high-risk first remission. *Clin Cancer Res.* 2008;14(9):2740–2748.
 239. Odunsi K, et al. Efficacy of vaccination with recombinant vaccinia and fowlpox vectors expressing NY-ESO-1 antigen in ovarian cancer and melanoma patients. *Proc Natl Acad Sci USA.* 2012;109(15):5797–5802.
 240. Levy B, Panicalli D, Marshall J. TRICOM: enhanced vaccines as anticancer therapy. *Expert Rev Vaccines.* 2004;3(4):397–402.
 241. Yang S, et al. Vaccines with enhanced costimulation maintain high avidity memory CTL. *J Immunol.* 2005;175(6):3715–3723.
 242. Hodge JW, et al. A triad of costimulatory molecules synergize to amplify T-cell activation. *Cancer Res.* 1999;59(22):5800–5807.
 243. Yang S, Tsang KY, Schlom J. Induction of higher-avidity human CTLs by vector-mediated enhanced costimulation of antigen-presenting cells. *Clin Cancer Res.* 2005;11(15):5603–5615.
 244. Rao RR, et al. The mTOR kinase determines effector versus memory CD8+ T cell fate by regulating the expression of transcription factors T-bet and Eomesodermin. *Immunity.* 2010;32(1):67–78.
 245. Li Q, et al. A Central Role for mTOR kinase in homeostatic proliferation induced CD8(+) T cell memory and tumor immunity. *Immunity.* 2011;34(4):541–553.
 246. Li Q, et al. Regulating mammalian target of rapamycin to tune vaccination-induced CD8+ T cell responses for tumor immunity. *J Immunol.* 2012;188(7):3080–3087.
 247. Nasi ML, et al. Intradermal injection of granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with metastatic melanoma recruits dendritic cells. *Cytokines Cell Mol Ther.* 1999;5(3):139–144.
 248. Santin AD, et al. Development and characterization of an IL-4-secreting human ovarian carcinoma cell line. *Gynecol Oncol.* 1995;58(2):230–239.
 249. Salgia R, et al. Vaccination with irradiated autologous tumor cells engineered to secrete granulocyte-macrophage colony-stimulating factor augments antitumor immunity in some patients with metastatic non-small-cell lung carcinoma. *J Clin Oncol.* 2003;21(4):624–630.
 250. Higano CS, et al. Phase 1/2 dose-escalation study of a GM-CSF-secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer. *Cancer.* 2008;113(5):975–984.
 251. Miotti S, et al. Growth of ovarian-carcinoma cell lines at physiological folate concentration: effect on folate-binding protein expression in vitro and in vivo. *Int J Cancer.* 1995;63(3):395–401.
 252. Coney LR, et al. Cloning of a tumor-associated antigen: MOv18 and MOv19 antibodies recognize a folate-binding protein. *Cancer Res.* 1991;51(22):6125–6132.
 253. Bagnoli M, et al. A step further in understanding the biology of the folate receptor in ovarian carcinoma. *Gynecol Oncol.* 2003;88(1 Pt 2):S140–S144.
 254. Bottero F, et al. Gene transfection and expression of the ovarian carcinoma marker folate binding protein on NIH/3T3 cells increases cell growth in vitro and in vivo. *Cancer Res.* 1993;53(23):5791–5796.

255. Neglia F, et al. DNA vaccination against the ovarian carcinoma-associated antigen folate receptor alpha (FRalpha) induces cytotoxic T lymphocyte and antibody responses in mice. *Cancer Gene Ther.* 1999;6(4):349–357.
256. Peoples GE, et al. Vaccine implications of folate binding protein, a novel cytotoxic T lymphocyte-recognized antigen system in epithelial cancers. *Clin Cancer Res.* 1999;5(12):4214–4223.
257. Toffoli G, et al. Overexpression of folate binding protein in ovarian cancers. *Int J Cancer.* 1997;74(2):193–198.
258. Konner JA, et al. Farletuzumab, a humanized monoclonal antibody against folate receptor alpha, in epithelial ovarian cancer: a phase I study. *Clin Cancer Res.* 2010;16(21):5288–5295.
259. Hernandez JJ, et al. Vaccination with dendritic cells transfected with mRNA-encoded folate-receptor-alpha for relapsed metastatic ovarian cancer. *Lancet Oncol.* 2007;8(5):451–454.
260. Loveland BE, et al. Mannan-MUC1-pulsed dendritic cell immunotherapy: a phase I trial in patients with adenocarcinoma. *Clin Cancer Res.* 2006;12(3 Pt 1):869–877.
261. Ioannides CG, Platsoucas CD, Freedman RS. Immunological effects of tumor vaccines: II. T cell responses directed against cellular antigens in the viral oncolysates. *In Vivo.* 1990;4(1):17–24.
262. Ioannides CG, et al. T-cell functions in ovarian cancer patients treated with viral oncolysates: I. Increased helper activity to immunoglobulins production. *Anticancer Res.* 1990;10(3):645–653.
263. Schirmacher V. Clinical trials of antitumor vaccination with an autologous tumor cell vaccine modified by virus infection: improvement of patient survival based on improved antitumor immune memory. *Cancer Immunol Immunother.* 2005;54(6):587–598.
264. Benencia F, et al. Direct vaccination with tumor cells killed with ICP4-deficient HSVd120 elicits effective antitumor immunity. *Cancer Biol Ther.* 2006;5(7):867–874.
265. Benencia F, et al. Herpes virus oncolytic therapy reverses tumor immune dysfunction and facilitates tumor antigen presentation. *Cancer Biol Ther.* 2008;7(8):1194–1205.
266. Hernandez JJ, et al. Vaccination with autologous tumour antigen-pulsed dendritic cells in advanced gynaecological malignancies: clinical and immunological evaluation of a phase I trial. *Cancer Immunol Immunother.* 2002;51(1):45–52.
267. Cannon MJ, O'Brien TJ. Cellular immunotherapy for ovarian cancer. *Expert Opin Biol Ther.* 2009;9(6):677–688.
268. Buckanovich RJ, et al. Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy. *Nat Med.* 2008;14(1):28–36.
269. Kandalaft LE, et al. Endothelin B receptor, a new target in cancer immune therapy. *Clin Cancer Res.* 2009;15(14):4521–4528.
270. Ghiringhelli F, et al. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. *Cancer Immunol Immunother.* 2007;56(5):641–648.
271. Rosenberg SA, Dudley ME. Adoptive cell therapy for the treatment of patients with metastatic melanoma. *Curr Opin Immunol.* 2009;21(2):233–240.
272. Yee C, et al. Adoptive T cell therapy using antigen-specific CD8+ T cell clones for the treatment of patients with metastatic melanoma: in vivo persistence, migration, and antitumor effect of transferred T cells. *Proc Natl Acad Sci USA.* 2002;99(25):16168–16173.
273. Freedman RS, et al. Intraperitoneal adoptive immunotherapy of ovarian carcinoma with tumor-infiltrating lymphocytes and low-dose recombinant interleukin-2: a pilot trial. *J Immunother Emphasis Tumor Immunol.* 1994;16(3):198–210.
274. Ioannides CG, Den Otter W. Concepts in immunotherapy of cancer: introduction. *In Vivo.* 1991;5(6):551–552.
275. Fujita K, et al. Prolonged disease-free period in patients with advanced epithelial ovarian cancer after adoptive transfer of tumor-infiltrating lymphocytes. *Clin Cancer Res.* 1995;1(5):501–507.
276. Aoki Y, et al. Use of adoptive transfer of tumor-infiltrating lymphocytes alone or in combination with cisplatin-containing chemotherapy in patients with epithelial ovarian cancer. *Cancer Res.* 1991;51(7):1934–1939.
277. Gattinoni L, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. *J Exp Med.* 2005;202(7):907–912.
278. Huang J, et al. Modulation by IL-2 of CD70 and CD27 expression on CD8+ T cells: importance for the therapeutic effectiveness of cell transfer immunotherapy. *J Immunol.* 2006;176(12):7726–7735.
279. Powell DJ Jr, et al. Transition of late-stage effector T cells to CD27+ CD28+ tumor-reactive effector memory T cells in humans after adoptive cell transfer therapy. *Blood.* 2005;105(1):241–250.
280. Shen X, et al. Persistence of tumor infiltrating lymphocytes in adoptive immunotherapy correlates with telomere length. *J Immunother.* 2007;30(1):123–129.
281. Zhou J, et al. Telomere length of transferred lymphocytes correlates with in vivo persistence and tumor regression in melanoma patients receiving cell transfer therapy. *J Immunol.* 2005;175(10):7046–7052.
282. Perret R, Ronchese R. Memory T cells in cancer immunotherapy: which CD8 T-cell population provides the best protection against tumours? *Tissue Antigens.* 2008;72(3):187–194.
283. Hinrichs CS, et al. Adoptively transferred effector cells derived from naive rather than central memory CD8+ T cells mediate superior antitumor immunity. *Proc Natl Acad Sci USA.* 2009;106(41):17469–17474.
284. Suhoski MM, et al. Engineering artificial antigen-presenting cells to express a diverse array of co-stimulatory molecules. *Mol Ther.* 2007;15(5):981–988.
285. Sadelain M, Riviere I, Brentjens R. Targeting tumours with genetically enhanced T lymphocytes. *Nat Rev Cancer.* 2003;3(1):35–45.
286. Morgan RA, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science.* 2006;314(5796):126–129.
287. Theoret MR, et al. Relationship of p53 overexpression on cancers and recognition by anti-p53 T cell receptor-transduced T cells. *Hum Gene Ther.* 2008;19(11):1219–1232.
288. Riley JL, June CH, Blazar BR. Human T regulatory cell therapy: take a billion or so and call me in the morning. *Immunity.* 2009;30(5):656–665.
289. Parkhurst MR, et al. Characterization of genetically modified T-cell receptors that recognize the CEA:691–699 peptide in the context of HLA-A2.1 on human colorectal cancer cells. *Clin Cancer Res.* 2009;15(1):169–180.
290. Robbins PF, et al. Single and dual amino acid substitutions in TCR CDRs can enhance antigen-specific T cell functions. *J Immunol.* 2008;180(9):6116–6131.
291. June CH, Blazar BR, Riley JL. Engineering lymphocyte subsets: tools, trials and tribulations. *Nat Rev Immunol.* 2009;9(10):704–716.
292. Walker RE, et al. Long-term in vivo survival of receptor-modified syngeneic T cells in patients with human immunodeficiency virus infection. *Blood.* 2000;96(2):467–474.
293. Brocker T, Karjalainen K. Adoptive tumor immunity mediated by lymphocytes bearing modified antigen-specific receptors. *Adv Immunol.* 1998;68:257–269.
294. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. *Proc Natl Acad Sci USA.* 1989;86(24):10024–10028.
295. Pinthus JH, et al. Immuno-gene therapy of established prostate tumors using chimeric receptor-redirection human lymphocytes. *Cancer Res.* 2003;63(10):2470–2476.
296. Sadelain M, Brentjens R, Riviere I. The promise and potential pitfalls of chimeric antigen receptors. *Curr Opin Immunol.* 2009;21(2):215–223.
297. Wang G, et al. A T cell-independent antitumor response in mice with bone marrow cells retrovirally transduced with an antibody/Fc-gamma chain chimeric receptor gene recognizing a human ovarian cancer antigen. *Nat Med.* 1998;4(2):168–172.
298. Parker LL, et al. Expansion and characterization of T cells transduced with a chimeric receptor against ovarian cancer. *Hum Gene Ther.* 2000;11(17):2377–2387.
299. Wilkie S, et al. Retargeting of human T cells to tumor-associated MUC1: the evolution of a chimeric antigen receptor. *J Immunol.* 2008;180(7):4901–4909.
300. Carpenito C, et al. Control of large, established tumor xenografts with genetically retargeted human T cells containing CD28 and CD137 domains. *Proc Natl Acad Sci USA.* 2009;106(9):3360–3365.
301. Kershaw MH, et al. A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer. *Clin Cancer Res.* 2006;12(20 Pt 1):6106–6115.
302. Coulie PG, et al. A new gene coding for a differentiation antigen recognized by autologous cytolytic T lymphocytes on HLA-A2 melanomas. *J Exp Med.* 1994;180(1):35–42.
303. Salgaller ML, et al. Recognition of multiple epitopes in the human melanoma antigen gp100 by peripheral blood lymphocytes stimulated in vitro with synthetic peptides. *Cancer Res.* 1995;55(21):4972–4979.
304. Robbins PF, et al. A mutated beta-catenin gene encodes a melanoma-specific antigen recognized by tumor infiltrating lymphocytes. *J Exp Med.* 1996;183(3):1185–1192.
305. Mandruzzato S, et al. A CASP-8 mutation recognized by cytolytic T lymphocytes on a human head and neck carcinoma. *J Exp Med.* 1997;186(5):785–793.
306. Gnjatich S, et al. Accumulation of the p53 protein allows recognition by human CTL of a wild-type p53 epitope presented by breast carcinomas and melanomas. *J Immunol.* 1998;160(1):328–333.
307. Jager E, Jager D, Knuth A. CTL-defined cancer vaccines: perspectives for active immunotherapeutic interventions in minimal residual disease. *Cancer Metastasis Rev.* 1999;18(1):143–150.
308. Chen YT, et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc Natl Acad Sci USA.* 1997;94(5):1914–1918.
309. Lethe B, et al. LAGE-1, a new gene with tumor specificity. *Int J Cancer.* 1998;76(6):903–908.
310. Kabawat SE, et al. Immunopathologic characterization of a monoclonal antibody that recognizes common surface antigens of human ovarian

- tumors of serous, endometrioid, and clear cell types. *Am J Clin Pathol.* 1983;79(1):98–104.
311. Mirandola L, et al. Cancer testis antigens: novel biomarkers and targetable proteins for ovarian cancer. *Int Rev Immunol.* 2011;30(2)–(3):127–137.
 312. Garg M, et al. Sperm-associated antigen 9, a novel cancer testis antigen, is a potential target for immunotherapy in epithelial ovarian cancer. *Clin Cancer Res.* 2007;13(5):1421–1428.
 313. Tammela J, et al. OY-TES-1 expression and serum immunoreactivity in epithelial ovarian cancer. *Int J Oncol.* 2006;29(4):903–910.
 314. Straughn JM Jr, et al. Expression of sperm protein 17 (Sp17) in ovarian cancer. *Int J Cancer.* 2004;108(6):805–811.
 315. Valmori D, et al. Expression of synovial sarcoma X (SSX) antigens in epithelial ovarian cancer and identification of SSX-4 epitopes recognized by CD4+ T cells. *Clin Cancer Res.* 2006;12(2):398–404.
 316. Sharma S, et al. A-kinase anchoring protein 3 messenger RNA expression correlates with poor prognosis in epithelial ovarian cancer. *Gynecol Oncol.* 2005;99(1):183–188.
 317. Tammela J, et al. SCP-1 cancer/testis antigen is a prognostic indicator and a candidate target for immunotherapy in epithelial ovarian cancer. *Cancer Immun.* 2004;4:10.

16 Hormones and Human Malignancies

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INTRODUCTION

Hormones have been linked to several of the most commonly occurring human malignancies, including breast, endometrium, ovary, and colon. The ability of hormones to stimulate cellular proliferation, leading to random genetic errors, is assumed to be the basis by which these peptides promote the development of human neoplasia. The pathways and mechanisms by which hormones affect their biologic responses is an exploding area of research, largely as a result of the tremendous potential for translational research and improved patient care. This chapter reviews the relationship between hormones and human malignancies, specifically as they relate to risk, prevention, and treatment.

HORMONE RECEPTOR PATHWAYS AND MECHANISMS

Steroid hormones perform critical functions in morphogenesis and normal physiology of female reproductive organs (1). These hormones are involved in many growth and developmental processes and exert their physiologic effects by binding to their particular receptors (2). Steroid hormone receptors are part of the ligand-activated nuclear transcription factor superfamily. The members of this superfamily also include glucocorticoid, mineralocorticoid, androgen, thyroid, retinoid, progesterone receptors (PR), and estrogen receptors (ER) (3). In the inactive state, these receptors are bound to repressor/chaperone complexes within the cytoplasm. Upon binding to their specific ligands, the receptor-ligand complex undergoes dimerization, which is followed by nuclear localization (leading to the name “nuclear receptor”). Inside the nucleus, the steroid hormone-receptor complex binds to specific DNA sequences called response elements. (4). Also participating in this interaction are nuclear receptor coactivators and corepressors, as well as the general transcription machinery (5). The net result of these interactions is the transcriptional activation or repression of hormone-responsive genes. More recently, nongenomic actions of ER and other nuclear receptors have been documented. These effects result from protein-protein interactions and membrane-associated nuclear receptor action (6).

Steroid Hormone Biosynthesis

While a comprehensive account of steroidogenesis is beyond the scope of this chapter, a succinct synopsis is presented (Fig. 16.1)

to underscore targets of therapeutic relevance. All steroid hormones are derived from cholesterol. In steroid biosynthesis, cytochrome P450-linked side-chain cleaving enzyme (P450 ssc) acutely regulates the rate-limiting step and converts cholesterol to pregnenolone (7). This naturally produced hormone in the body is sometimes referred to as the “mother hormone” and serves as a precursor for dehydroepiandrosterone (DHEA) and all steroid and sex hormones. Conversion of cholesterol to pregnenolone in the ovary is tightly regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) via cAMP and protein kinase A (PKA) signaling (8). This leads to increased production of androgen intermediates, androstenedione and testosterone, that are then converted by the P450-aromatase enzyme to estrone and estradiol (E2), respectively. P450-aromatase is not exclusively expressed in ovarian tissues. Interestingly, its expression in many other tissues results in biosynthesis of local E2 (9). The availability of locally produced E2 may be particularly important in both men and postmenopausal women, where ovarian hormone production is lacking. High levels of locally synthesized and readily available E2 have also been implicated in breast carcinogenesis (10).

Recently, Ghosh et al. have solved the crystal structure of CYP19A1 and revealed a small active cleft that is well suited to bind androstenedione snugly, prior to its conversion to estrone (11). Data also indicate that CYP19A1 has wide tissue distribution (including placenta, ovary, testes, and adipose tissue), and its expression has been demonstrated to be associated with about 75% of estrogen-dependent breast cancers (12). Aromatase inhibitors in this specific patient population have resulted in a substantial reduction in the risk of breast cancer recurrence (13). Although other risks emerge, including grade 3 and 4 cardiovascular events and bone fractures (14,15). Additionally, we now know that several tissue types have tissue-specific expression of the CYP19A1 gene promoter, and the presence of tissue-specific promoters has raised the possibility of developing more selective aromatase inhibitors. Such agents would be able to, for instance, block E2 in breast cancer, without affecting estrogenic pathways in bones (16,17).

Steroid Hormone Receptor Structure

Steroid receptors are comprised of six functional domains (Fig. 16.2) (18). The A/B domain is highly variable among the different members of this family and contains within it the hormone-independent activating 1, or AF-1, domain. The relatively conserved C region contains the DNA-binding domain (DBD). Within the central DBD, two zinc fingers target the receptors to their corresponding hormone response elements. The DBD binds as a dimer, with each monomer recognizing half of the palindromic DNA sequence of the response element. The D domain

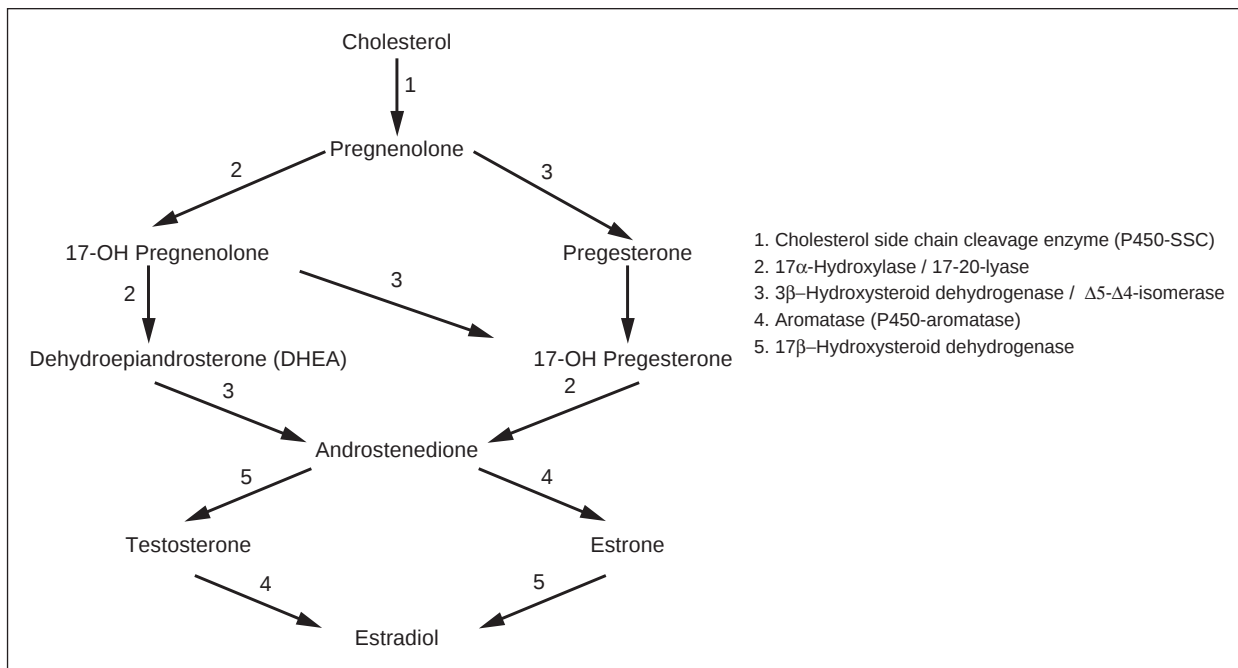


FIGURE 16.1. Molecular biology of steroid hormone synthesis. Notice the important role of aromatase in the conversion of androgens to estradiols.

is a peptide linker that connects the DBD to the ligand-binding domain (LBD). The E region is a multifunctional domain and contains amino acids involved in ligand binding, receptor dimerization, nuclear localization, coactivator/corepressor interaction, and ligand-dependent activating function (AF-2). The F region is a variable extension of the E region.

Estrogen Receptors

The ER mainly functions as a ligand-regulated, DNA-binding transcription factor, resulting in modulation of gene expression of proteins involved in key pathways related to cancer progression. However, additional ER functions, independent of DNA binding, have also been reported (19,20). ERs can be recruited to the DNA by indirect tethering through other DNA-bound transcription factors, including members of the activating protein-1 (AP-1) transcription family (4,21,22). Due to alternative RNA splicing, several isoforms of the ER are known to exist, but ER- α and ER- β are considered to be the main isoforms. We now know that ER- α is encoded by the *ESR1* gene

and ER- β is encoded by the *ESR2* gene. The *ESR1* and *ESR2* genes are located on the 6th and 14th chromosomes (6q25.1 and 14q23), respectively (23).

In humans, the ERs exhibit 96% and 58% homology in their DBD and LBD, respectively. These structural differences in ERs lead to discrete ligand affinities and physiological properties. For example, estrone and raloxifene bind preferentially to ER- α , while estriol and genistein have higher binding affinity for ER- β . Furthermore, tamoxifen and raloxifene exhibit partial agonist activities after binding to ER- α , while they act as pure antagonists when bound to ER- β (24). This is thought to result from distinct conformational changes induced by ligand binding in the two receptors (25).

Both ERs are widely expressed in many tissue types; however, there are important differences in the pattern of their expression. ER- α is the predominant ER isoform in many tissues, including breast cancer, endometrium, ovarian stroma, and the hypothalamus. ER- β has notably higher expression in ovarian granulosa cells, prostate gland, gastrointestinal tract, endothelial cells, heart, lung, kidney, brain, and bone (26–28). However, some expression of both receptors is observed in

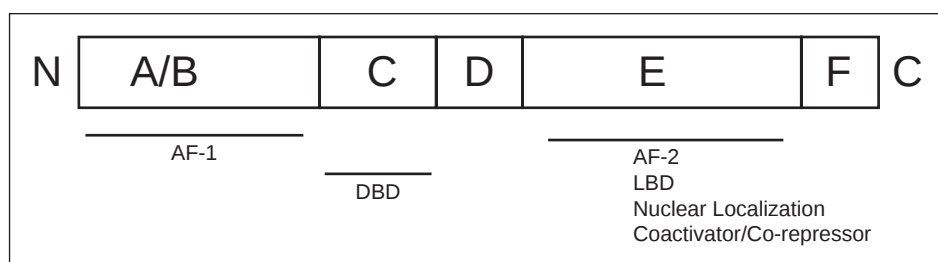


FIGURE 16.2. Functional domains of the human estrogen receptor: The A/B domain is highly variable among the different members of this family and contains the hormone-independent activating 1, or AF-1, domain. The C region consists of the DNA-binding domain (DBD). The D domain is a peptide linker that connects the DBD to the ligand-binding domain (LBD). The E region is a multifunctional domain and contains the LBD as well as amino acids involved in receptor dimerization, nuclear localization, coactivator/corepressor interaction, and ligand-dependent activating function (AF-2). The F region is a variable extension of the E region.

many tissues. Data now indicate a correlation between ER- β transcript levels and expression of oncogenes in cancer cells and also suggest a role of ER- β in endometrial carcinogenesis (29). As noted above, ER- α and ER- β have been shown to have unique physiologic properties. In addition, they are capable of forming ER- α (aa) or ER- β (bb) homodimers or (ER- α /ER- β) heterodimers, thus influencing each other's function (30). In this context, ER- β has been shown to function as a dominant inhibitor of ER- α (21). Therefore, it is likely that normal physiologic function in E2 responsive tissues relies on the relative expression ratio of ER- α and ER- β in those tissues. Recently, Iyer and colleagues have shown that estrogen promotes ER-negative breast tumor growth by recruitment of pro-angiogenic bone marrow-derived myeloid cells in murine xenograft models, and the researchers demonstrated that ER- α expression is present only in bone marrow-derived cells and this expression was required and sufficient to promote breast tumor growth when challenged with estrogen (31).

Accumulating evidence suggests that changes in normal ER- α -to-ER- β ratio may be associated with neoplastic states. Cancers of the ovary, colon, and endometrium are all characterized by a relative loss of the normally predominant ER subtype when compared with normal tissue (32–36). Whether these changes predispose to or are a result of carcinogenesis remains to be elucidated. The development of ER- α , ER- β , and double knockout mice (ERKO, β ERKO, and $\alpha\beta$ ERKO, respectively) has helped with the identification of each receptor's physiologic role in its target organs (37). These findings are summarized in Table 16.1. Recently, genotyping data from more than 12,000 BRCA1 and 7,000 BRCA2 mutation carriers compiled from 40 studies identified ER-related SNP (rs67397200) at chromosome 19p13.1 that portends an increased risk of ovarian cancer for BRCA1 (HR 1.16) and BRCA2 (HR 1.30) mutation carriers. Identification of this cancer susceptibility locus may also be useful for ovarian cancer risk prediction for BRCA1 and BRCA2 mutation carriers (38).

Several of the ER- α and ER- β “splice variants” have been demonstrated to possess altered hormone binding and/or transcriptional properties. Some can act in a dominant negative fashion by dimerizing with the wild-type receptors and interfering with their function *in vitro* (39). As mentioned above, ER has been shown to regulate transcription by interacting with other transcription factors and signal mediators (40–42). This mechanism involves protein-protein interaction and does not require DNA binding. An example of this type of interaction is the influence of ERs on the transcriptional activity mediated by the components of the AP-1 pathway such as jun and fos (34). In the presence of ER- α , E2 stimulates AP-1-dependent transcription, while tamoxifen and raloxifene inhibit it. In contrast, ER- β produces the opposite effect, with estradiol inhibiting and tamoxifen and raloxifene stimulating AP-1-mediated transcription. The activation of ER- α also results in induction

of fos-related antigen 1 (fra-1) and regulates uterine stromal differentiation and remodeling during early pregnancy (43). An additional mechanism of ER action involves “cross-talk” with growth factors including insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), and transforming growth factor β (TGF- β) (44,45). EGF can mimic the effects of E2 on the reproductive tract. This effect is dependent on ER- α because it can be blocked by ER antagonists and is absent in ERKO mice, despite an intact EGF signaling cascade (46). Mechanisms for this cross-talk involve signal transduction from growth factor receptors via the ras/raf/MAPK, as well as the AKT/PI3K cascade intermediaries culminating in the phosphorylation and activation of ER's AF-1 domain (47). AKT activation results in cell survival and inhibition of apoptosis. In normal tissue, this pathway is kept in check by a phosphatase called PTEN. PTEN is a tumor suppressor that negatively regulates the PI3K/AKT pathway by dephosphorylating PIP3. The activation of the PI3K/AKT pathway is particularly relevant in endometrial adenocarcinoma, where up to 80% of malignancies and 55% of premalignant lesions have been shown to harbor PTEN mutations (48,49). Most investigations of the growth factor–ER cross-talk have involved ER- α . However, positive regulation of AKT over ER- β was recently reported via phosphorylation of glucocorticoid receptor-interacting protein 1 (GRIP1) transcriptional coactivator (50).

For decades it has been observed that exposure to estrogens can lead to immediate physiologic sequelae independent of transcriptional effects. These observations supported the presence of ERs outside the nucleus as the mediators of these nongenomic steroid hormone effects (4,51). The nongenomic effects of estrogens appear to follow at least two major pathways. The interactions of ER- α and its splice variants with components of the growth factor signaling cascades including MAPK and PI3K pathways are important (52,53). Recently, *in vitro* and *in vivo* data indicate that estrogen promotes ovarian cancer growth both directly and indirectly, by making the tumor microenvironment more conducive to tumor growth (54). Here it is essential to recognize that cellular exposure to estrogen results in a multitude of functions that can be measured with distinct kinetics. Specifically, the rapid events that take place within minutes are termed pre-genomic and utilize the second messenger pathway. The pre-genomic events may also ultimately lead to changes in gene transcription, as do the delayed events (55). This mechanism involves a G-protein coupled receptor, GPR30, an intracellular transmembrane receptor that localizes mainly to the endoplasmic reticulum. In this pathway, estrogens diffuse through the plasma membrane and bind GPR30 at the endoplasmic reticulum. This results in intracellular calcium mobilization and synthesis of phosphatidylinositol 3,4,5-trisphosphate in the nucleus. Activation of this pathway has been demonstrated in cells that lack ER- α and ER- β expression (56).

Table 16.1 Summary of Findings from Estrogen Receptor Knockout Mice Experiments

Organ	Phenotype		
	ERKO	β ERKO	$\alpha\beta$ ERKO
Pituitary gland	High LH	None	High LH
Ovary	Hemorrhagic cysts, high estrogen and testosterone due to high LH, anovulatory	Reduced ovulation	Anovulatory, “sex-reversed” follicles with Sertoli-like cells
Endometrium	Estrogen insensitive, no growth or induction of estrogen-responsive genes	Normal growth and response to estrogen	Estrogen insensitive, no growth or induction of estrogen-responsive genes
Breast	No pubertal development	Normal development and lactation	No pubertal development

Abbreviation: LH, luteinizing hormone.

Progesterone Receptors

The progesterone receptor (PR) is an intracellular steroid receptor that belongs to the nuclear receptor subfamily of receptors (i.e., NR3C3) (57). These nuclear hormone receptors, in general, are involved in diverse physiological functions, including differentiation, embryonic development, and cellular homeostasis. However, dysregulation of nuclear receptor superfamily members has been implicated in many disease states, including cancer (58). Multiple mechanisms through which PR mediates gene expression are regulated by numerous cellular processes that originate either within the cell or in the extracellular environment (59). The effects of progesterone are mediated by two PR proteins, PRA and PRB. In humans, the two PR proteins are encoded by the gene, *PGR*, which is located on chromosome 11q22 (60). These 2 receptors differ due to the additional 164 amino acids present in the N-terminus of PRB. Both PRA and PRB contain transcription-activating functional (AF) domains: AF-1 and AF-2. The N-terminal region of PRB contains an additional AF domain (AF-3) (61). The two PRs exhibit differences in function that are cell context and promoter dependent. For example, PRB uniformly exhibits progestin-dependent transactivation in the various cell types examined. However, PRA's transcriptional activity is cell and response-element specific. When tested on simple progestin response elements (PRE), PRA and PRB display similar transactivational activity. However, PRA's activity is reduced or eliminated on more complex response elements (62). In addition, PRA has been shown to act in a dominant negative fashion, antagonizing the transcriptional activity of not only PRB, but also other nuclear receptors such as the glucocorticoid, mineralocorticoid, androgen, and estrogen receptors (63).

In general, most tissues express equal levels of the two PR isoforms. However, differential expression can be observed, as each promoter is regulated independently. For example, in the endometrium, stromal cells express predominantly PRA throughout the menstrual cycle, whereas the epithelial cells switch from PRA to PRB during the early secretory phase (64). PRA knockout mice (PRAKO) exhibit endometrial hyperplasia mediated by PRB following exposure to progestins (65). Similar studies using PRB knockout mice (PRBKO) have shown that PRA is sufficient for eliciting progesterone's reproductive responses in the ovary and the uterus. In contrast, PRB is required to elicit normal proliferative responses of the mammary gland to progesterone (66). Finally, changes in PR isoform relative or overall expression have been described in endometrial, ovarian, and breast cancers (30,46,67).

It is generally thought that the expression of PR in ovarian cancer may be protective (68,69). Recent data indicate that PRB activation by other second messengers (e.g., cAMP) results in cell cycle arrest, induction of cellular senescence, and suppression of oncogenicity of ovarian cancer (70). A decrease in *PGR* content due to loss of heterozygosity and/or polymorphisms of *PGR* are associated with increased risk of ovarian cancer, and signifies that activation of *PGR* may guard against the development of ovarian cancer (71–73). Preclinical data now indicate that certain microRNAs may also regulate the expression of *PGR*, and targeting of *PGR* by specific microRNAs is seen in transition from normal to endometrial cancer states (74). Additional evidence supports that progesterone may also signal through other receptors that may be localized to the membrane (75). For example, Peluso and colleagues, using orthotopic ovarian cancer mouse models, recently demonstrated that progesterone membrane component-1 regulates the development and sensitivity to cisplatin in ovarian cancer (76).

Nongenomic functions of *PGR* involve the extranuclear *PGR*s that associate through proline-rich domain to interact with SH3 domain of Src kinase. This complex cascade involves activation of the EGFR/c-Src/Ras/ERK pathway and the PI3K/AKT pathway, resulting in a pro-tumorigenic role in cancer cell

biology (77,78,79). More recently, progesterone was shown to mediate mammary gland stem cell self-renewal (80). Knowing that *PGR* function is altered by the action of protein kinases and that activation of *PGR* can lead to the activation of several kinases known to enhance tumor progression (81), it is essential to understand these critical molecular interactions in depth to significantly improve our approaches for prevention and treatment of human malignancy.

HORMONES AS RISK FACTORS FOR HUMAN MALIGNANCIES

Exogenous Hormones and Modulation of Cancer Risk

Breast

Hormone Replacement Therapy

Women without history of breast cancer. Multiple epidemiologic investigations have evaluated the relationship between hormone replacement therapy (HRT) and breast cancer. In a meta-analysis of 51 studies of 52,705 women with breast cancer and 108,411 women without breast cancer, the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) determined that the risk of developing breast cancer is increased in women using HRT. The risk increases especially among women with >5 years of use (relative risk [RR], 1.3; 95% confidence interval [CI], 1.21–1.49). The cumulative incidence of breast cancer was 45 per 1,000 women between the ages of 50 and 70 years, and use of HRT for >5 years was associated with an estimated cumulative excess of 2 breast cancers for every 1,000 users. The increased risk of breast cancer associated with prolonged HRT was greater for women with low weight or low Body Mass Index (BMI). Breast cancers diagnosed in women who had a history of HRT was inclined to be less advanced clinically compared with women with a negative history of HRT use (82). The Breast Cancer Detection Demonstration Project, a cohort study with 46,355 postmenopausal women, 2,082 of whom were diagnosed with incident cases of breast cancer, reported that women who had taken unopposed E2 had a 1.2-fold (95% CI, 1.0–1.4) increase in breast cancer risk, while women taking combination E2 and progestin regimens had a 1.4-fold (95% CI, 1.1–1.8) increased risk. Breast cancer risk was significantly elevated only in recent users with a BMI less than 24 (83). Finally, a recently reported case-control study involving 1,897 women with breast cancer revealed that women using combination HRT had a statistically higher risk of breast cancer (odds ratio [OR], 1.24; 95% CI, 1.07–1.45) than women taking unopposed E2 (OR, 1.06; 95% CI, 0.97–1.15) (84).

The Women's Health Initiative (WHI), a randomized, double-blind, placebo-controlled trial, recently reported the interim analysis of 8,506 women who received continuous combination HRT (0.625 mg of conjugated equine estrogen [CEE] plus 2.5 mg of medroxyprogesterone acetate [MPA]) versus 8,102 women prescribed placebo. The Data and Safety Monitoring Board for the trial recommended early cessation of this trial arm secondary to the observed adverse effects. Interim results from the WHI study revealed that the risk of coronary heart disease (hazard ratio [HR], 1.29; 95% CI, 1.02–1.63), stroke (HR, 1.41; 95% CI, 1.07–1.85), and pulmonary embolism (HR, 2.13; 95% CI, 1.39–3.25) were all significantly elevated in patients receiving continuous combination HRT. The observed increased risk of breast cancer (HR, 1.26; 95% CI, 1.0–1.59) was similar to results from the aforementioned observational studies (85). A more detailed evaluation of the WHI data used a weighted Cox proportion hazards analysis in an effort to account for the lag in time required to achieve the full effects of the hormone on breast

cancer incidence. In this analysis, the rate of invasive breast cancer was increased in patients receiving progestin plus estrogen (HR, 1.24, weighted $p < 0.003$) (86). Extended follow-up of the patients from the WHI intervention trial was continued among 8,052 surviving participants (95%) in a post-intervention study for a mean of 8 years. More breast cancers were diagnosed among women receiving CEE plus MPA versus placebo (HR, = 1.27; 95% CI, 1.06–1.51) (87). Estrogen plus MPA had a greater influence on breast cancer incidence than placebo if initiated closer to menopause (88). The breast cancer developing in patients receiving the hormonal regimen was also not restricted to hormone receptor–positive tumors (89).

Further analysis has revealed that breast cancer diagnosed in women receiving CEE plus MPA, when compared with placebo patients diagnosed with breast cancer, were more likely to have metastatic node involvement, even though between the two groups the tumors were similar in terms of grade and histology (88). The combination of CEE plus MPA compared with placebo has been shown to interfere with mammographic detection, potentially leading to breast cancers being diagnosed at a later stage of disease (90). Moreover, a 11-year follow-up analysis recently has shown that breast cancer mortality has increased among women who received CEE plus MPA compared with placebo (88). Since the original results from the WHI were released in 2002, there has been a decrease in the nationwide use of postmenopausal hormone therapy (91). In addition, patients on HRT were diagnosed with larger tumors at a more advanced stage, compared with patients who received placebo (88).

In the WHI trial, 10,739 postmenopausal women with prior hysterectomy received 0.625 mg of CEE ($n = 5,310$) versus placebo ($n = 5,429$). In the initial manuscript, the WHI investigators reported that there was a possible reduction in breast cancer incidence, but the results were not statistically significant (HR, 0.77; 95% CI, 0.59–1.01) (92). Further analysis of the data revealed that treatment with CEE for 7 years does not appear to increase the incidence of breast cancer (77). Extended follow-up of the patients from the WHI intervention trial was continued among 7,645 surviving participants (78%) in a post-intervention study for a mean of 10 years. Analysis of intervention and post-intervention data revealed a lower incidence of breast cancer among patients receiving CEE (HR, 0.77; 95% CI, 0.62–0.95) (93).

Women with a history of breast cancer. Physicians are apprehensive about prescribing HRT to women with a positive personal history of breast cancer. The theoretical concern has been that exogenous hormones may stimulate the growth of dormant microscopic disease and ultimately lead to a decreased disease-free interval and survival.

Several case-control studies have reported that the rates of breast cancer recurrence among survivors taking HRT vary from 3% to 7% (94,80) and do not appear to significantly diverge from stage-specific population rates of recurrence. In a case control study by DiSaia et al. (81), 41 sporadic breast cancer patients taking HRT were matched to controls according to age, stage, and socioeconomic status. A majority of the patients had early-stage disease. Recurrences were detected in 12 patients with stage I disease, 1 with stage II, and 2 with stage III. No evidence of increased disease recurrence was noted among the patients receiving HRT. In a subsequent analysis by the same authors, 125 sporadic breast cancer survivors receiving HRT were compared with 363 control subjects matched according to age at diagnosis, stage of breast cancer, and year of diagnosis. The analysis revealed that the risk of death was lower among the breast cancer patients receiving HRT (OR, 0.28; 95% CI, 0.11–0.71). According to the American College of Obstetricians and Gynecologists, the projected absolute lifetime risk for non-HRT users is approximately 10 cases of breast cancer per 100 women. This risk would increase to 12 cases per 100 women using unopposed E2 and 14 cases per 100 women using

combined E2 and progestin (95). Data from a prospective, randomized trial is not available to answer this question.

Oral Contraceptives

Since their introduction in the 1960s, oral contraceptives (OCs) have been taken by over 200 million women throughout the world. The CGHFBC performed a meta-analysis of 54 epidemiologic studies on 53,297 women with breast cancer and 100,239 women without breast cancer. Women who were current users or had used OCs in the previous 10 years were at an increased risk of breast cancer (RR, 1.24; 95% CI, 1.15–1.33). Among women taking OCs, the breast cancers that developed were less advanced than those diagnosed in women with no history of OCP use (96). Because the results from this meta-analysis reflected data from studies completed over the prior 25 years, the Women's Contraceptive and Reproductive Experiences (Women's CARE) study was initiated in an effort to provide a more contemporary analysis of the relationship between OCs and breast cancer risk (97). In this case-control study, a total of 4,574 women with breast cancer and 4,682 controls were compared. The RR was 1.0 (95% CI, 0.8–1.3) for current OCP use and 0.9 (95% CI, 0.8–1.0) for previous use, suggesting that among women aged 35 to 64 years, current or former OCP use is not associated with a significantly increased risk of breast cancer.

Women with BRCA mutations. In the meta-analysis by the CGHFBC, the increased risk of breast cancer associated with OCP use was not influenced by a family history of breast cancer (96). However, a threefold increased risk of breast cancer was observed among women taking OCs who had a positive family history of breast cancer. This increased risk was observed only in women using high potency estrogen formulations before 1975 (98). A subsequent matched case-control study by Narod et al. revealed that among *BRCA1* carriers, an increased risk of early-onset breast cancer was evident in women who used OCs prior to 1975 (OR, 1.42; 95% CI, 1.17–1.75), used OCs prior to age 30 (OR, 1.29; 95% CI, 1.09–1.52), or who used OCs for 5 or more years. Despite the increased risk associated with OCP usage among *BRCA1* carriers, an increased risk of breast cancer was not observed among women with a *BRCA2* carrier status (99). In *BRCA1* carriers, the protective effects of OCs against ovarian cancer must be weighed against the possible increased risk of OCP use and breast cancer.

Ovary

Hormone Replacement Therapy

Women without a history of ovarian cancer. Recently, several well-designed case-control and cohort studies have evaluated the relationship between HRT and ovarian carcinoma. The American Cancer Society's Cancer Prevention Study II found that after accounting for OCP use and parity, postmenopausal women using HRT had higher rates of ovarian cancer-related deaths compared with nonusers (RR, 1.51; 95% CI, 1.16–1.96). The increased mortality risk was most notable for women using HRT for 10 or more years and persisted for up to 29 years after HRT cessation (100). This study is limited by the lack of information regarding estrogen and progestin potency. Another cohort study of 44,241 former participants in the Breast Cancer Detection Demonstration Project identified 329 women who developed ovarian cancer during follow-up. Multivariate analysis revealed an increased association of estrogen-only HRT with ovarian cancer (RR, 1.6; 95% CI, 1.2–2.0) after accounting for age, menopause type, and OCP use (101). In contrast, an increased risk of ovarian cancer was not noted among women who used estrogen and progestin. A Swedish case-controlled trial evaluated 655 case subjects with ovarian cancer and 3,819 control subjects. An

increased risk of ovarian cancer was noted among women with a history of either estrogen (OR, 1.43; 95% CI, 1.02–2.00) or estrogen with sequentially added progestins (OR 1.54; 95% CI, 1.15–2.05), particularly with hormone use exceeding 10 years. However, use of estrogen with continuously added progestin was not associated with an increased risk of ovarian cancer when compared with nonuse (102). The latter 2 studies suggest that HRT regimens containing both E2 and progestin may not have the increased risk of ovarian cancer observed with E2 therapy alone. However, the WHI recently identified, in women taking continuous combined HRT, an HR of 1.58 (95% CI, 0.77–3.24) for developing invasive ovarian carcinoma (103). The importance of the presence or absence of progesterone in HRT, as well as the type and potency, remains to be elucidated.

Women with a history of ovarian cancer. Only one randomized, controlled clinical trial exists evaluating the risk of ovarian cancer recurrence in patients receiving HRT. This study was designed to detect a 20% difference in survival between the two treatment groups. In this study, 130 patients less than 59 years of age with invasive ovarian cancer were randomized to continuous E2 HRT or no supplementation. The median disease-free interval for women receiving HRT versus those not receiving HRT was 34 months and 27 months, respectively, not reaching statistical significance (104). Multiple epidemiologic studies have revealed that OCPs are not a risk factor for ovarian cancer, but rather a means of prevention. See below.

Endometrium

Hormone Replacement Therapy

Women without a history of endometrial cancer. Multiple case-control and cohort studies also have suggested that the risk of endometrial cancer is elevated among patients receiving unopposed estrogen. A meta-analysis of 30 studies indicated that the summary RR of endometrial cancer was 2.7 for patients receiving unopposed estrogen (105). The use of unopposed estrogen has also been shown to be associated with the development of endometrial hyperplasia. In the Postmenopausal E2/Progestin Intervention (PEPI) trial, 875 patients were randomized to receive one of five regimens: (a) placebo; (b) CEE, 0.625 mg/day; (c) CEE, 0.625 mg/day plus continuous MPA, 2.5 mg/day; (d) CEE, 0.625 mg/day plus MPA, 10 mg for 12 days each month; or (e) CEE, 0.625 mg/day plus micronized progesterone (MP), 200 mg/day for 12 days per month. Patients receiving unopposed estrogen had a significantly increased risk of atypical adenomatous endometrial hyperplasia (34% vs. 1%) (106).

The addition of progestin to HRT has been shown to eliminate the increased risk of hyperplasia associated with unopposed E2. Although progestins have been associated with the effective treatment of endometrial hyperplasia, the data supporting the protective effects of progestins in HRT are limited. Many of the initial HRT regimens combining progestin and estrogens utilized the progestin for 7 days a month (107). Subsequent studies have recommended prolongation of the progestin component to at least 10 days each month. A case-control study of 832 endometrial cancer patients and 1,114 controls in Washington State revealed that patients using a regimen of estrogen combined with progestin (0.625 mg/day CEE, 2.5 mg/day MPA) had a significantly lower RR (RR, 1.4; 95% CI, 1.0–1.9) of endometrial cancer compared with patients who had taken unopposed estrogen (RR, 4.0; 95% CI, 3.2–5.1). However, patients receiving less than 10 days of cyclic progestin had an RR that was much higher (RR, 3.1; 95% CI, 1.7–5.7) than patients receiving 10 to 21 days of cyclic progestin (RR, 1.3; 95% CI, 0.8–2.2). Patients using either regimen of cyclic combination HRT had an increased risk of endometrial cancer when these regimens were taken for a duration exceeding 5 years (cyclic progestin <10 days per month: RR 3.7; 95% CI, 1.7–8.2; cyclic progestin

10 to 21 days each month: RR, 2.5; 95% CI, 1.1–5.5) (108). Subsequent data from the same investigators suggested that use of a continuous progestin HRT regimen may actually be protective against endometrial cancer (109). The largest case-control study of continuous HRT involved 79 case subjects and 88 control subjects, and it revealed that the RR of patients receiving continuous HRT was 1.07 (95% CI, 0.80–1.43) (92). Data from the WHI indicated that the HR for endometrioid endometrial cancer (EEC) was 0.81 (95% CI, 0.48–1.36) in patients receiving continuous HRT with average follow-up of 5.6 years (103). Extended follow-up of the patients from the WHI intervention and post-intervention trials over 8 years revealed that the incidence of endometrial cancer was still decreased among patients receiving CEE plus MPA compared with placebo, but this observation was not statistically significant (HR, 0.78, 0.52–1.16) (87).

There has recently been some suggestion that the degree of endometrial cancer risk reduction may be dependent on the type of progestin used in the continuous HRT regimen. A Swedish case-control study found that patients with a continuous HRT involving testosterone-derived progestins (i.e., norethisterone, norethisterone acetate, levonorgestrel, lynestrenol) were associated with a lower RR of endometrial cancer than those patients whose regimens involved progesterone-derived progestins (i.e., medroxyprogesterone) (110). Data from the Continuous Hormones as Replacement Therapy (CHART) study found no evidence of endometrial hyperplasia in participants who received norethindrone acetate (a testosterone-derived progestin). In this clinical trial, 1,265 patients were randomized to placebo versus one of eight treatment groups involving either various doses of unopposed ethinyl estradiol or various combinations of ethinyl estradiol plus norethindrone. A total of 1,134 endometrial biopsies were performed over a 2-year follow-up period among women who received the combination HRT regimen; 1,232 biopsies were performed in the women given unopposed E2. As the dose of unopposed ethinyl estradiol was increased, there were increased percentages of subjects with endometrial hyperplasia. There were no cases of hyperplasia noted among the subjects who received different doses of the testosterone-derived progestin norethindrone. The protective effect was noted even among patients randomized to receive doses of norethindrone as low as 0.2 mg (106). In contrast, the PEPI trial identified hyperplasia by a surveillance endometrial biopsy in 3 of 339 patients who received E2 with a progesterone-derived progestin. Further studies are needed to determine the degree of endometrial cancer risk influenced by the progestational activity of the progestin.

Women with a history of endometrial cancer. The use of E2 among patients with endometrial cancer is controversial. *In vitro* treatment of Ishikawa endometrial cancer cells with estrogen upregulates ER expression and augments growth in endometrial cancer cells (111,112). However, *in vivo* growth of residual microscopic endometrial cancer in patients has not been proven to date. Four retrospective cohort studies have evaluated patients with early-stage endometrial cancer receiving E2 postoperatively. Creasman et al. evaluated 221 patients with stage I disease, of whom 47 received postoperative HRT and 174 did not (113). Patients receiving HRT were followed for a median of 26 months. Regression analysis revealed that there was no increased risk of recurrent disease associated with HRT use, even when adjusting for age, tumor grade, myometrial lymph node status, and peritoneal cytology. A subsequent study by Lee et al. (114) compared the outcomes of 44 low-risk endometrial cancer patients (stage IA/IB G1/G2 disease) who received HRT following treatment, with 62 patients who received no HRT. There were no recurrences observed among the endometrial cancer patients receiving HRT for a median duration of 64 months. Investigators from the University of California, Irvine, have also failed to demonstrate an increased risk of recurrent disease associated with postoperative HRT (115).

In the first study, investigators evaluated 123 women with surgical stage I and II endometrial cancer. Sixty-one women received postoperative estrogen, and the mean duration of follow-up was 40 months. The disease-free interval was not significantly shortened among the patients receiving E2 (116). The second study was a retrospective cohort study that involved 75 patients with stage I–III disease who received HRT (51% E2 only, 49% E2 with added progestin) postoperatively. This group of patients was then matched according to decade of age at diagnosis and stage of disease to a group of endometrial cancer patients in the study cohort not receiving HRT. Both groups were comparable in terms of parity, tumor grade, depth of myometrial invasion, histology, lymph node status, surgical treatment, concurrent morbidities, and postoperative radiation. The patients receiving HRT were followed for a mean interval of 83 months, and the patients not receiving HRT were followed for a comparable interval of 69 months. Patients using HRT had a longer disease-free interval compared with nonusers of hormones. Among the 150 patients, only 8 patients had stage III disease (115).

In a Committee Opinion by the American College of Obstetricians and Gynecologists Committee of Gynecologic Practice, the members announced that “the decision to use HRT in these women (endometrial cancer patients) should be individualized on the basis of potential benefit and risk to the patient” (117). The Gynecologic Oncology Group (GOG) initiated a multicenter randomized, controlled trial aimed at an enrollment of 2,100 patients with stage I and II endometrial cancer. The study was closed after enrollment of 1,200 patients, because the majority of the patients were low-risk with stage IA and G1 disease. In the absence of adequate enrollment of more intermediate-to-high risk early-stage endometrial cancer patients, the number of recurrences used in the ad hoc sample-size determination would be underestimated, leading to suboptimal power for the clinical trial. With the closure of this GOG protocol, the safety of exogenous estrogen use in women who have undergone surgical management of endometrial cancer may never be fully ascertained.

Oral Contraceptives

Multiple epidemiologic studies have revealed that OCPs are not a risk factor for endometrial cancer, but rather a means of prevention (see below).

Selective Estrogen Receptor Modulators

The antiestrogen tamoxifen has been used in the adjuvant therapy of advanced breast cancer for years, and it has recently been evaluated as a chemopreventive agent in patients at a high risk for developing this malignancy. Tamoxifen increases the risk of second primary malignancies at other sites. A randomized, controlled trial involving 2,729 women performed by the Stockholm Breast Cancer Study Group revealed that patients given tamoxifen (40 mg/day) had a nearly sixfold increased risk of endometrial cancer, and a threefold increased risk of gastrointestinal cancer (118,119). These findings were confirmed in the National Surgical Adjuvant Breast and Bowel Project (NSABP). In this study, 2,843 patients with node-negative invasive breast cancer were randomized to receive tamoxifen (40 mg/day) or placebo. The RR of endometrial cancer in patients receiving tamoxifen was 7.5 (95% CI, 1.7–32.7) (120), compared with placebo (118). When the population-based rates of endometrial cancer from another NSABP trial (B-06), and data from the Surveillance, Epidemiology, and End Results (SEER) program were used in the calculation of risk, the RRs of endometrial cancer associated with tamoxifen use were 2.3 and 2.2, respectively. In addition, the average annual HR during follow-up was only 1.6 out of 1,000 in the group receiving tamoxifen (118,120), suggesting that routine screening would not be cost-effective.

Other selective estrogen receptor modulators (SERMs) are being evaluated as adjuvant treatment for breast cancer in an

attempt to avoid the increased risk of secondary malignancies, while maintaining the same or greater effectiveness. Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study indicate that patients receiving raloxifene had a lower incidence of breast cancer without any increase in endometrial cancer risk (118,121). However, the primary endpoint in this investigation was risk reduction of fracture in postmenopausal women with osteoporosis. In the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 trial, investigators found that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer. Although the overall risk of developing endometrial cancer was similar in patients on raloxifene versus tamoxifen (RR, 0.62; 95% CI, 0.35–1.08), the incidence of hyperplasia was lower in the raloxifene group (RR, 0.16; 95% CI, 0.09–0.29) (122). Several other SERMs are under investigation. The results of ongoing clinical trials will confirm these preliminary findings and establish the applicability of this contemporary generation of SERMs.

Colon

Hormone Replacement Therapy

Multiple epidemiologic studies have revealed that HRT is not a risk factor for *colon* cancer, but rather protects against this malignancy (see below). The WHI randomized controlled trial revealed that colorectal cancer was reduced among patients who received CEE plus MPA (123). But the interpretation was obscured by a later stage at diagnosis. In the trial involving patients with a history of hysterectomy, patients receiving CEE compared with placebo had similar incidences of colorectal cancer (92). Extended follow-up of the patients from the WHI intervention and post-intervention trials over 8 years revealed that the incidence of colon cancer was still decreased among patients receiving CEE plus MPA compared with placebo (87).

Oral Contraceptives

Multiple epidemiologic studies have revealed that OCPs are not a risk factor for colon cancer, but rather protect against this malignancy (See below).

SERMs

In vitro evidence has revealed that both tamoxifen and raloxifene are effective in reducing cell proliferation and viability of colon cancer cell lines, suggesting a possible application in the prevention of colon cancer (124). Unfortunately, the available epidemiologic evidence is limited and controversial regarding the issue of tamoxifen's effects on colorectal cancer risk. A meta-analysis by the Stockholm Breast Cancer Study Group analyzed 4,914 postmenopausal women participating in one of three Scandinavian clinical trials evaluating adjuvant tamoxifen: the Stockholm Trial, the Danish Breast Cancer Group Trial, and the South-Swedish Trial (119). The joint analysis of these three trials revealed that adjuvant tamoxifen therapy in breast cancer patients increased the risk of colorectal cancer (RR, 1.9; 95% CI, 1.1–1.3). In contrast, findings from the NSABP B-14 and the SEER program (125) have failed to confirm an increased risk of colorectal cancer among patients receiving adjuvant tamoxifen therapy. Additional epidemiologic trials are needed to resolve the issue of adjuvant tamoxifen therapy and the risk of secondary sporadic colorectal cancers.

Although some epidemiologic evidence suggests that tamoxifen may be associated with an increased risk of sporadic colorectal cancer, SERMs have been used in the treatment of desmoid tumors associated with hereditary colorectal cancer. Colorectal cancer includes 2 main mechanisms of inheritance: familial adenomatous polyposis (FAP) and hereditary nonpolyposis

colorectal cancer (HNPCC). Desmoid tumors are fibroaponeurotic tumors that occur rarely in the general population but can be found in 12% to 17% of patients with FAP (126). Tamoxifen has been shown to have growth inhibition in desmoid tumor cell lines in an E2-independent mechanism (127). According to the practice guidelines of the Standard Task Force of Colon and Rectal Surgeons, high-dose tamoxifen (120 mg/day) and other SERMs may be used in the treatment of aggressive desmoid tumors. This recommendation is weak (level III) and based on limited descriptive European case series (128,129). The use of tamoxifen in the prevention or treatment of primary colorectal cancer is not advocated.

Phytoestrogens

Increased rates of breast, colon, ovarian, and endometrial cancer are found in Western societies. Phyto-E2s are possible dietary mediators of increased cancer risk that are subdivided into two groups: isoflavonoids and lignans. Isoflavonoids are compounds with inherent estrogenic activity that can lead to low IGF expression and inhibition of aromatase and growth factors, resulting in a possible chemoprotective effect in the breast. Lignans are compounds formed from plant lignan precursors by intestinal microflora. Both isoflavonoids and lignans are found in foods such as whole grain rye bread, soybeans, and red clover. Studies suggest that the development period during which the isoflavonoid is ingested is important in modulation of future cancer risk. Ingestion of soy before or during adolescence may decrease the risk of future breast cancer. However, there is no convincing evidence indicating that soy or other isoflavonoids are protective against breast cancer or colon cancer if ingested during adulthood (118,130). There is a paucity of data regarding the association between isoflavonoids and other cancers affecting women. A case-control study using a Hawaiian group revealed that the high consumption of soy products in adults significantly decreased the risk of endometrial cancer, even after accounting for confounding influences (118,131). Large, population-based studies are needed to determine the effects of isoflavonoids on specific cancer risk, particularly since they are becoming a more common component of the American diet.

Lignans can be indirectly measured via urinary enterolactone. Although women with breast cancer have significantly lower levels of urinary enterolactone, it is unknown whether higher levels of enterolactone are protective against breast cancer or whether they are a marker for an unknown chemoprotective compound associated with a healthier diet. High enterolactone production has been associated with inhibition of colon cancer in animal models, but elevated levels have not been confirmed to be protective against colon cancer in humans (118,130). In contrast, obesity as well as increased dietary fat intake is associated with decreased levels of urinary lignans, suggesting that the increased risk of cancer associated with obesity may be in part related to lignan production.

HORMONES AND THE PREVENTION OF HUMAN CANCERS

Chemoprevention can be defined as the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent the progression toward malignancies. Human carcinogenesis proceeds through multiple discernible stages of molecular and cellular alterations, thus providing the scientific rationale for clinical cancer chemoprevention. The necessary requirements for evaluation of chemoprevention include (a) identification of high-risk individuals based on family history and/or genetic mutations; (b) identification of putative surrogate endpoints or biomarkers for cancer; and (c) the possibility that relatively nontoxic agents

may decrease the risk of a given malignancy. Prospective clinical trials are mandatory for evaluating potential strategies for preventing human malignancies.

Breast Cancer Chemoprevention

SERMs

Reducing the incidence of breast cancer has the potential to provide a major impact on the morbidity of the disease and its treatment, cost to the individual and to society, and overall cancer mortality. Epidemiologic studies indicate that E2-mediated events play a role in the development of breast cancer. Tamoxifen, a SERM, has been utilized as a chemopreventive agent for breast cancer in four randomized, prospective, placebo-controlled clinical trials. Raloxifene, a second-generation SERM, was investigated in the MORE trial, in which the primary endpoint was risk reduction of fracture in postmenopausal women with osteoporosis; the incidence of breast cancer was a secondary endpoint. These 5 studies are reviewed and summarized below.

National surgical adjuvant breast and bowel project breast cancer prevention trial (P-1). In 1992, the National Cancer Institute, in collaboration with the NSABP, initiated the Breast Cancer Prevention Trial (BCPT, P-1) (132). The primary goal was to determine whether tamoxifen administered for 5 years prevented breast cancer in women at high risk, including women 60 years or older, women 35 to 59 with a 5-year predicted risk of breast cancer of at least 1.66%, or women who had a history of lobular carcinoma *in situ* (LCIS). Risk was estimated using the Gail model (133). Each of the 13,388 women enrolled was randomly assigned to receive tamoxifen 20 mg/day or placebo. The median follow-up time was 54.6 months, with 175 cases of invasive breast cancer in the placebo group compared with 89 in the tamoxifen group (RR, 0.51; 95% CI, 0.39–0.66; $p < 0.00001$). Tamoxifen reduced the incidence of ER+ tumors by 69%, but there was no difference in the incidence of ER- tumors. Major toxicities included endometrial cancer (RR = 2.53) and thromboembolic disease (RR = 3.01). The P-1 data has been updated recently, and they have confirmed that the magnitudes of desirable and undesirable effects of tamoxifen are similar to what was observed in the original report (134).

Italian tamoxifen prevention study. Recruitment for this double-blind, placebo-controlled, randomized trial began in October 1992 and ended in July 1997, and included healthy women aged 35 to 70 years (135). The trialist and data-monitoring committee ended recruitment because 26% of women dropped out of this study; 5,408 women were randomized to receive tamoxifen 20 mg/day or placebo for 5 years. Women were allowed to take HRT. The primary endpoints were reduction in the frequency and mortality of breast cancer. At a median follow-up of 46 months, 19 cancers were diagnosed in the tamoxifen arm and 22 among women in the placebo arm ($p = 0.6$). A 2007 update reported (after 11 years of follow-up) that although there was no overall difference in breast cancer between patients receiving placebo versus tamoxifen, high-risk breast cancers were much less often found among women receiving tamoxifen (RR, 0.24; 95% CI, 0.10–0.59) (136).

Royal Marsden Hospital chemoprevention trial. This trial was initiated in 1986 as a preliminary pilot study for the International Breast Cancer Intervention Study (IBIS-I) (137). The aim of this study was to assess whether tamoxifen would prevent breast cancer in healthy women at increased risk for the disease based on family history only. Each participant had at least one first-degree relative under the age of 50 with breast cancer, one first-degree relative with bilateral breast cancer, or one affected first-degree relative of any age and another affected first-degree or second-degree relative. The women were allowed to take HRT during this study. The participants, 2,494 women between the

ages of 30 and 70, were randomized to tamoxifen 20 mg/day or placebo. The median follow-up was 70 months, and 2,471 of the women were analyzed. The frequency of breast cancer was the same for women receiving tamoxifen and placebo (tamoxifen = 34, placebo = 36; RR, 1.06; 95% CI, 0.7–1.7), and there appeared to be no interaction between the use of HRT and the effect of tamoxifen on breast cancer occurrence. An update of this trial reported that contrary to the initial published findings based on 5-year follow-up, there was a clear reduction of invasive estrogen-positive cancers at 10 years (6.2% vs. 5.2%), and the effect was even larger at 15 years (9.6% vs. 7.5%) (138).

International breast cancer intervention study (IBIS). Randomization occurred to tamoxifen 20 mg/day or placebo for 7,152 women, aged 35 to 70 years and at high risk for breast cancer (139). Eligible women had risk factors for breast cancer indicating at least a twofold relative risk among those aged 45 to 70 years, a fourfold relative risk among those aged 40 to 44 years, and a tenfold relative risk among those aged 35 to 39 years. The women enrolled in this study were at moderately increased risk of developing breast cancer, with 60% of the study cohort having a 10-year risk ranging from 5% to 10%. The IBIS-I investigators used a model to predict the absolute 10-year risk of developing breast cancer, but the details of their model have not been published. Use of HRT was permitted, and approximately 40% of women used such therapy at some point during the trial. The primary endpoint was the incidence of breast cancer, including ductal carcinoma *in situ* (DCIS). At a median follow-up of 50 months (7,139 women analyzed), 69 women in the tamoxifen group compared with 101 women in the placebo group developed breast cancer (overall, 32% reduction in breast cancer rate; 95% CI, 8–50; $p = 0.01$). Further long-term follow-up has revealed that for ER-positive invasive tumors, the cumulative incidence in the IBIS-I was reduced after 5 years from 2.0% in the placebo arm to 1.5% in the tamoxifen arm, but after 10 years the values were 4.3% versus 2.9%, respectively (140).

Multiple outcome of raloxifene evaluation. The MORE study was a multicenter, randomized, double-blind trial, raloxifene 60 or 120 mg/day or placebo for 3 years, with the primary endpoint of rate of fracture in postmenopausal women with osteoporosis (141). Breast cancer incidence was a secondary endpoint. A total of 7,705 women were enrolled, all of whom were at least 2 years postmenopausal and no older than 80 years of age. Women who were taking E2 during the previous 6 months were excluded, and 12.3% of women reported a family history of breast cancer. There were 27 cases of invasive breast cancer in the placebo group compared with 13 in the raloxifene group (RR 0.24; 95% CI, 0.13–0.44; $p < 0.001$). There was no difference in breast cancer incidence between the 2 doses of raloxifene. Raloxifene reduced the risk of invasive ER+ breast cancer by 90% (RR 0.10; 95% CI, 0.04–0.24) but did not reduce the risk of ER- breast cancer. The 4-year results from this study, with extension to 4 years after initiation of the trial, were consistent with the results based on the 3-year follow-up (142). The Continuing Outcomes Relevant to Evista (CORE) trial examined the effect of an additional 4 years of raloxifene therapy on the incidence of breast cancer in women in MORE. Over the 8 years of both trials, the incidence of invasive breast cancer and ER-positive breast cancer were significantly reduced, but the incidence of ER-negative tumors was not (143).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol P-2 or the Study of Tamoxifen and Raloxifene (STAR) Trial. This study, opened to accrual on July 1, 1999, was powered to demonstrate superior efficacy or equivalence of either tamoxifen (20 mg/day) or raloxifene (60 mg/day) in reducing the incidence of primary breast cancer. The trial enrolled 19,747 women, and data are available for 19,471 of them—9,726 women in the tamoxifen arm and 9,745 women in the raloxifene arm. All women had a projected 5-year risk of developing breast

cancer of 1.66% or higher as determined by the Gail model. Eligible women included postmenopausal women 35 years or older with no prior history of invasive breast cancer or DCIS. Postmenopausal women aged 35 or older with a history of LCIS were also eligible. Preliminary results of the STAR trial revealed that tamoxifen and raloxifene were as effective as tamoxifen in reducing the risk of invasive breast cancer (RR, 0.70; 95% CI) (122). Recent updates of the STAR trial have shown after 8 years of follow-up that raloxifene is less effective than tamoxifen in reducing invasive cancer, but it is less often associated with endometrial cancer or endometrial hyperplasia (144). In addition, patients treated with raloxifene are diagnosed with endometrial polyps and have fewer hysterectomies while in treatment, compared with women who receive tamoxifen (145).

Aromatase Inhibitors

Aromatase inhibitors (AIs) are being considered for use in breast cancer chemoprevention. In contrast to SERMs, which are competitive inhibitors of E2 at its receptor, AIs suppress plasma E2 levels by inhibiting or inactivating aromatase, the enzyme responsible for the synthesis of E2s from androgenic substrates. This class of compounds has effectively challenged tamoxifen for use as adjuvant therapy in postmenopausal women with ER+ breast cancers, who constitute the majority of patients with breast cancer. Evaluating women with early-stage breast cancer, the ATAC (Arimidex, Tamoxifen, Alone or in Combination) Trialists' Group found that the incidence of contralateral invasive breast cancer was lower in those receiving the third-generation AI (anastrozole [Arimidex]), when compared with tamoxifen, after a median of 100 months of follow-up. For estrogen-positive tumors, disease-free survival and time to survival were both improved significantly among patients receiving anastrozole compared with those given tamoxifen (HR, 0.85, 95% CI, 0.76–0.94; and HR, 0.76, 95% CI, 0.67–0.87). Fracture rates were higher among patients receiving anastrozole than those receiving tamoxifen during active treatment, but there was no difference after the treatment was completed (146).

Prophylactic Oophorectomy

The potential role for oophorectomy as *chemoprevention* (decreased E2 levels) for breast cancer in premenopausal women is an area of active investigation. In genetically uncharacterized premenopausal women, oophorectomy is associated with a 50% reduction in breast cancer incidence, but it also incurs the associated negative effects of a surgically induced early menopause (147,148). In this patient population, where the overall incidence of breast cancer is 1 in 8, it is not standard practice to offer oophorectomy for breast cancer prevention. However, in premenopausal women with germ-line *BRCA1* and *BRCA2* mutations, the cumulative lifetime risk (to 70 years of age) of invasive breast cancer is 60% to 85%, allowing for more serious consideration of prophylactic oophorectomy as a chemoprevention. The prevalence of germ-line *BRCA1* or *BRCA2* in the general population is 0.1% to 0.2%, contributing to a small fraction of all cases of breast cancer, but as many as 10% of cases diagnosed in women younger than 40 years of age and approximately 75% of familial cases. Two publications support the practice of recommending prophylactic oophorectomy after the completion of childbearing in premenopausal women (149,150). Kauff et al. in a prospective study, reported on 170 carriers of *BRCA* mutations with a mean follow-up of 24.2 months, 98 of whom underwent prophylactic salpingo-oophorectomy (149). A 70% risk reduction in breast cancer incidence was identified. Rebbeck et al. in a multicenter retrospective analysis, reported on 551 carriers of *BRCA* mutations with 11 years of follow-up, 259 of whom underwent a prophylactic salpingo-oophorectomy. A 53% risk reduction in breast cancer incidence was identified (150). The reduced risk of a breast cancer diagnosis after salpingo-oophorectomy

in women with *BRCA* mutations confirms an earlier report of a 47% reduction in this patient population (151). The age at risk-reducing depends on the type of mutation and the family history (152). The American College of Obstetricians and Gynecologists has recommended that women who are either at average risk of ovarian cancer or undergoing a hysterectomy for benign conditions, and must make a decision about prophylactic oophorectomy, should be provided an overview of recent studies that suggest a negative health impact (particularly on cardiovascular disease risk) when performed before the age of menopause, particularly in the absence of estrogen replacement (153).

Phytochemicals

Phytochemicals with potential anticancer properties span a wide range of chemical types and activities. Their presence, concentration, and bioavailability in any of thousands of plant species used by humans are variably and incompletely documented. Several studies have specifically examined the effects of vegetable and fruit intake on breast cancer risk. These studies suggest a protective effect of vegetable intake, particularly those rich in carotenoids. Beta-carotene intake has been associated with lower breast cancer risk in several studies (154,155,156). High dietary fiber intake has also been associated with a lower risk of breast cancer (157). The multiplicity of phytochemical actions at different sites in the process of tumorigenesis complicates the investigative effort needed for the development of chemopreventive agents from this class of compounds.

Endometrial Cancer Chemoprevention

Chemoprevention strategies for endometrioid endometrial cancer (EEC) have been based on the observation that exposure to E2 with insufficient progestational stimulation predisposes women to EEC and its precursor lesion, atypical endometrial hyperplasia. While marked obesity, use of exogenous E2, early menarche, and diabetes have been identified as risk factors for the development of EEC, only early menarche has been associated with serous carcinoma, as well as its precursor lesion, endometrial intraepithelial carcinoma (EIC) (158). This observation, as well as other investigational work, supports the existence of a dualistic model for endometrial carcinogenesis, where atypical endometrial hyperplasia and EEC are E2-related, and EIC and serous carcinoma are E2-unrelated. Further delineation of E2-independent pathways of endometrial carcinogenesis will be necessary to develop chemoprevention strategies for serous carcinoma, which accounts for a minority of endometrial carcinomas but a disproportionate number of endometrial cancer deaths. Chemoprevention strategies for EEC, because of its clear association with E2, have been more easily identified, and are described below.

Continuous Combined HRT

Premature termination of one comparison (continuous combined HRT: daily conjugated equine E2 0.625 mg and medroxyprogesterone acetate 2.5 mg) in the WHI primary prevention trial occurred because cardiovascular disease and breast cancer were increased, recognizing that colorectal cancer, endometrial cancer, and osteoporotic fractures were reduced (85). The reduction seen in the incidence of EEC with continuous HRT is in agreement with case-control studies that have documented a reduction in the incidence of this malignancy in women taking continuous combined HRT (108,109,110).

Oral Contraceptives

There is substantial evidence that *ever-use* of OCPs reduces the risk of EEC by approximately 50%. Numerous epidemiologic

studies demonstrate that the reduced risk depends on the duration of OCP use. The risk is reduced by 20% with 1 year of use, 40% with 2 years of use, and 60% with 4 or more years of use (159).

A preliminary analysis of the Centers for Disease Control and Prevention (CDC) Cancer and Steroid Hormone (CASH) study attempted to characterize the protective effect of specific OCP formulations on EEC risk by comparing 187 endometrial cancer cases with 1,320 controls (160). The CASH study determined that continuous OCP formulations provided protective effects (RR, 0.4; 95% CI, 0.2–0.9) while sequential OCPs did not (RR, 2.1; 95% CI, 0.8–5.8). Similarly, in the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 132 cases of EEC and 835 matched controls were evaluated to determine the protective effects of OCPs on endometrial cancer. Investigators found that the risk of EEC was decreased among women who had a history of combination OCP use (OR, 0.53; 95% CI, 0.29–0.97) (161). In both the CASH and the initial WHO study, combination OCP formulations were not categorized according to the potency of estrogen and progestin, thereby preventing an assessment of the effects on EEC risk according to the potency of the hormonal components.

To better understand the protective effects of combination OCPs, 2 case-control studies have attempted to evaluate progestin and estrogen potency of OCP formulations in relation to EEC risk. Following further enrollment of patients in the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, investigators reported an analysis of 220 cases of EEC and 1,537 controls (162). In this study, a lower risk of EEC was observed with high progestin potency OCP formulations compared with low progestin potency. Although the number of patients using high-potency progestin was very small in this study, the results suggested that high progestin potency OCP formulations could be more protective against EEC. A second case-control study evaluated 316 cases and 501 controls from women in the King or Pierce counties of Washington. The relative risk for women who had used a high progestin potency OCP (RR 0.3; 95% CI, 0.1–0.9) was as low as the relative risk for women using a low-potency progestin (RR, 0.2; 95% CI, 0.1–0.8) (118). These results did not find a potency-dependent protective effect, and suggested that the progestin potency was adequate to achieve a protective effect against endometrial cancer in most combination OCP formulations. The methods of classifying progestin potency were the same in both the WHO study and the Washington State study, thereby eliminating differences in classification as a reason for the different findings from these two studies. Details regarding the specific OCPs taken by case and control subjects were not reported in the Washington State study. The OCP formulations used in the second WHO study contained progestins that are no longer used in OCPs marketed in the United States. A third case-control study using data from the CASH study included 434 endometrial cancer cases and 2,557 control subjects. Overall, high-potency OCPs did not confer more protection than low-potency OCPs. However, among women with a BMI >22.1 kg/m², those who used high progestin potency OCPs had a lower risk of endometrial cancer than those who used low potency OCPs (OR, 0.31; 95% CI, 0.11–0.92); those with a BMI <22.1 kg/m² did not (OR, 1.36; 95% CI, 0.39–4.70) (163). The small number of cases that were overweight (BMI >25 kg/m²) or obese (BMI >30 kg/m²) prevented an analysis with sufficient power to detect a statistically significant modifying effect of overweight status or obesity on the relationship between progestin potency and endometrial cancer risk. However, these findings suggest that high-potency OCPs may be associated with a greater protective effect than low-potency OCPs among women with a higher BMI who are at the greatest risk of endometrial cancer. Obese women often develop Type I endometrioid endometrial cancer. Population-based data have suggested that endometrial cancer-related mortality may be increased among obese women, compared with nonobese women, suggesting

that prevention in this group of high-risk patients may not only affect morbidity but also mortality. Although the biologic mechanism(s) that underlie the protective effect of progestins have not been well characterized, a growing body of evidence has implicated apoptotic and transforming growth factor-beta (TGF- β) signaling events as important mediators of the chemopreventive effect of progestins in the endometrium. Progestins have been shown to induce apoptosis in endometrial glands and stroma, an effect that is modulated by a number of well-known apoptosis-related proteins (164–166).

Intrauterine Devices

Seven studies have reported the relationship between previous copper or nonmedicated intrauterine device (IUD) use and endometrial cancer (167–173). In all but one study, previous IUD use was associated with a decreased risk of EEC. The one study where this relationship was not validated was based on research in China, where the steel ring IUD was utilized, suggesting that this type of IUD is not protective against this malignancy (172). One of the studies to report significant protection against EEC was the landmark CASH study by the Centers for Disease Control (CDC) (167). The majority of the articles reported subgroup analyses regarding factors such as type of IUD and duration/timing of use. In general, no consistent pattern emerged from the articles to suggest that length or timing of use, or type of IUD was associated with an increase or decrease in the risk of EEC (174).

The levonorgestrel-releasing IUD was investigated by Gardner et al. in women taking tamoxifen as adjuvant therapy for breast cancer (175). This preliminary investigation, which included 122 women, randomized 64 patients to the IUD group and 58 patients to the non-IUD group. The authors did an outpatient hysteroscopic assessment with endometrial sampling at entry into the study and after 12 months. A uniform decidual response was seen in all women with the IUD in place. Similar histologic patterns were identified in both groups at baseline and after 12 months. Further follow-up of the patient cohort for an additional year revealed a persistent beneficial effect on prevention of polyps, and no endometrial cancers were diagnosed in the study (175). A second randomized controlled trial of prophylactic IUD in women treated with tamoxifen has been performed by Chan et al. In this study, 113 women who received adjuvant tamoxifen for breast cancer after the completion of postoperative radiation and chemotherapy were randomized to receive an IUD or observational surveillance. Women in the treatment group had a much lower incidence of endometrial polyp at 12 months, compared with the control group (1.8% vs. 15.5%; $p = 0.017$) (176). A statement on the effect of this device on the incidence of EEC in women taking tamoxifen cannot be made, but this warrants further prospective evaluation.

Phytochemicals

The effect of dietary phytochemical consumption on endometrial cancer risk is not clearly delineated. Levi et al. found a strong negative association between beta-carotene and vitamin C intake and endometrial carcinoma among Swiss women, but no clear effect was seen in similar studies in China and the United States (177–179). Barbone et al. demonstrated a protective effect of carotene intake on endometrial cancer (180). Zheng et al. found a weak negative correlation between endometrial cancer and plant food intake in the Iowa Women's Health Study (181). In an analysis of phytoestrogen (i.e., isoflavones, coumestans, and lignans) consumption and endometrial cancer risk, investigators found that a lower risk was associated with increased intake. Obese postmenopausal women consuming relatively low amounts of phytoestrogens had the highest risk of endometrial cancer (OR 6.9; 95% CI, 3.3–14.5), compared with nonobese postmenopausal women consuming high amounts of isoflavones

(182). As is the case with breast cancer, further investigative efforts are necessary to establish the role of phytochemicals in the prevention of endometrial cancer.

Ovarian Cancer Chemoprevention

Although efforts to improve the survival of ovarian cancer patients continue to focus on the development of more effective systemic therapies, the prevention of ovarian cancer is an area of increasing interest. As is the case with breast cancer, assessment of prevention efforts must be analyzed by genetic predisposition. In genetically uncharacterized U.S. women, the lifetime risk of developing ovarian cancer is approximately 1.5%. *BRCA1* mutations increase the risk to 30% to 60%, while women who harbor a mutant *BRCA2* gene have an estimated risk of 10% to 30% (183). Precancerous lesions have not been well-defined for ovarian cancer, although phenotypic changes have recently been described (184). Future chemoprevention trials in ovarian cancer have the potential to utilize biochemical markers of transformation, including cell cycle progression and apoptosis, as surrogate endpoint markers (185,186). Although hysterectomy alone, as well as tubal ligation, has been associated with a decreased risk of developing ovarian cancer, this review will focus on chemoprevention.

Oral Contraceptives

The ability of OCPs to reduce the risk of ovarian cancer has been extensively studied, and it is estimated that there is an overall reduction in risk approximating 40% (187). The adjusted odds ratio for ever-use of OCPs has consistently been shown to be between 0.6 and 0.7 (188–190). The degree of protection and the length of protection appear to be associated with the duration of OCP usage. Prolonged risk reduction has been reported when OCPs are used longer than 4 to 6 years, and minimal benefit has been observed if utilization is restricted to a period of 6 months to 2 years (191–194). One of the largest case-control studies to date is the CDC CASH study. In this study, 546 women with ovarian cancer and 4,228 control subjects from eight population-based cancer registries were compared. Women with a history of OCP use had a 40% reduced risk of epithelial ovarian cancer (RR, 0.6; 95% CI, 0.5–0.7) when compared with women with no history of OCP use. This protective effect was evident with as little as 3 months of OCP use and continued for up to 15 years following discontinuation of OCP use. OCP-mediated risk reduction was independent of the histologic type of ovarian cancer (195).

It has been estimated that more than half of all ovarian cancers in the United States could be prevented by OCP usage for at least 4 to 5 years (189,190,196). The protective effect of OCPs appears to be consistent across races, as John. et al. demonstrated a reduction in risk of 0.6 in African-American women with OCP use of 6 years or more (197). The estrogen/progestin content of any particular OCP and how it relates to protection against ovarian carcinoma needs further investigation. Ness et al. demonstrated identical risk reduction for OCPs with high-estrogen/high-progesterone content, when compared with low-estrogen/low-progesterone content pills (198). Schildkraut et al., in an observational study, recently reported that low-progesterone OCP formulations were associated with a significantly higher risk of ovarian cancer when compared with high-progesterone potency OCP formulations (199).

The lifetime risk of ovarian cancer is approximately 45% in *BRCA1* carriers and 25% among *BRCA2* carriers (200). In women carrying *BRCA1*- or -2 mutations, Modan et al. concluded that OCPs did not protect against ovarian cancer in Israeli Jewish women. However, Narod et al. showed that the use of OCPs in Jewish and non-Jewish women with *BRCA* mutations was strongly protective against this malignancy, with

an odds ratio of 0.44 (95% CI, 0.28–0.68) (201,202). Important differences exist between the two studies, most notably that the controls in the Narod et al. study were all mutation carriers, while in the Modan et al. study only 1.7% of the controls carried the mutation. The use of OCP as a chemopreventive agent against ovarian cancer should be considered in *BRCA* carriers.

Little is known about the mechanism of the protective effect of OCPs against ovarian cancer, although it has been postulated that a major mechanism of OCP protection relates to a decrease in ovulatory cycles. There are data to suggest that an increased rate of apoptosis in aberrant epithelial cells, secondary to the progestational component, may also play an important role. Rodriguez et al. examined the effect on ovarian epithelium of levonorgestrel in 130 ovulatory macaque monkeys (203). These authors demonstrated significantly increased apoptotic cell counts in the ovarian epithelium of animals exposed to progesterone, leading to the hypothesis that progestin-induced apoptosis of the ovarian epithelium is responsible for the chemopreventive effect of OCPs.

Colon Cancer Chemoprevention

Colorectal cancer is the second most common cause of cancer death in the U.S. (behind only lung cancer, as breast and prostate cancer are sex-linked), and the third most common cause of cancer death for U.S. women. In 2012, there were an estimated 70,040 new cases of colorectal cancer diagnosed in U.S. women, and an estimated 25,220 deaths (204).

Hormone Replacement Therapy

Two recent meta-analyses have calculated an approximate one-third reduction in risk of colon cancer among current or recent users of HRT, compared with about a 10% to 20% reduction among ever-users versus never-users of HRT (204,205). Although Nanda et al. determined that *rectal* cancer was not related to HRT usage, Grodstein et al. determined a reduction in risk for ever-users versus never-users (RR, 0.81; 95% CI, 0.72–0.92). Both meta-analyses are limited by lack of consistent and accurate reporting on type of HRT, as well as lack of control for potential confounders, such as diet, site of cancer, family history, or screening. Adenomatous polyps precede colorectal cancers by a decade or more, thus any association between their presence and HRT is of obvious interest. Two case-control studies have found a protective effect of HRT on the development of adenomatous polyps (206,207). The prospective Nurses' Health Study reported a decreased risk of large adenomatous polyps for current users (RR, 0.74; 95% CI, 0.55–0.99), whereas there was no association between small adenomatous polyps and HRT (208).

The Women's Health Initiative confirmed what other observational studies have suggested. This randomized, controlled primary prevention trial, in which 16,608 postmenopausal women aged 50 to 79 years with an intact uterus at baseline were recruited by 40 U.S. clinical centers in 1993 to 1998, showed a reduction in the incidence of colorectal cancer in those women taking combined estrogen and progesterone therapy. In 8,506 women prescribed estrogen and progesterone and in a placebo control group of 8,102 women, a hazard ratio of 0.63 with a nominal 95% CI of 0.43 to 0.92 was observed. Colorectal cancer rates were reduced by 37% (10 vs. 16 per 10,000 person-years) (85,208).

There are several hypotheses regarding a protective effect of HRT on the risk of colorectal cancer, including alteration of the predominant ER isoform, as well as E2's ability to decrease production of secondary bile acids.

Oral Contraceptives

The relationship between OCPs and colorectal cancer has not been clearly delineated. Recently, a large case-control study

was conducted in northern Italy between the years 1985 and 1992, with 709 cases of colorectal cancer and 992 control subjects (209). Ever-use of OCPs versus never-use through use of a multiple logistic regression was associated with a reduced risk of colorectal cancer (RR, 0.58; 95% CI, 0.36–0.92). Further, there was a suggestion that duration of use (i.e., more than 2 years) was associated with increased protection. More recently, the Nurses' Health Study cohort identified 502 cases of colorectal cancer among participants between 1980 and 1992 (210). Among women using OCPs, use for 6 or more years was associated with a 40% reduction in risk of colorectal cancer (RR, 0.60; 95% CI, 0.40–0.89). The trend for the duration effect was statistically significant ($p = 0.02$). Several smaller studies, all with serious limitations in study design and/or execution, have reported varying results regarding the relationship between OCPs and colorectal cancer.

HORMONES AND THE TREATMENT OF HUMAN CANCERS

The role of hormones in the treatment of human malignancies has been most extensively examined in the management of breast carcinoma. Now, the potential to exploit hormone-signaling pathways in the management of other malignancies, affecting both men and women, is rapidly becoming a reality. As our understanding of both the molecular biology of cancer and the human genome expands, targeted therapeutics, including hormonal manipulation, will undoubtedly assume a more critical role in the management of human malignancies.

Breast

Overview

When considering hormonal treatment (HT) of breast cancer, it is important to distinguish between premenopausal women, in whom the primary source of estrogen is the ovaries, and postmenopausal women, in whom aromatization of androgens in the peripheral tissue is the major source of estrogen production. In premenopausal women, removal of the ovaries via surgical or radiologic ablation, or inhibition of ovarian estrogen production with a gonadotropin-releasing hormone (GnRH) analog, results in marked decrease in estrogen levels. SERMs, most notably tamoxifen, are a treatment option for both premenopausal and postmenopausal women with ER-positive disease; they reduce tumor cell proliferation by binding to and blocking the activation of ERs. In premenopausal women, treatment with tamoxifen plus ovarian ablation may provide added benefit by decreasing estrogen effect by two complementary mechanisms.

AIs interfere with estrogen production by targeting the peripheral aromatization of androgens. In postmenopausal women, in whom peripheral tissue production of estrogen is responsible for the majority of circulating estrogen, AIs are a logical choice in the selection of HT. The role of AIs in premenopausal women is less clear, owing to the high level of ovarian estrogen in this patient population.

Adjuvant Hormonal Therapy for Early-Stage Breast Cancer

Postmenopausal Women

Tamoxifen prescribed for approximately 5 years after surgery to patients with early ER-positive breast cancer remains the current standard of adjuvant therapy worldwide. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted

Table 16.2 Hormone Receptor Status: Effect on Response Rate in Early-Stage Disease

Receptor Status	N	Reduction in Recurrence % (95% CI)	Reduction in Mortality % (95% CI)
ER ⁺ , PgR ⁺	7,000	37 (±6)	16 (±8)
ER ⁺ , PgR ⁻	2,000	32 (±12)	18 (±14)
ER ⁻ , PgR ⁺	602	23 (±24)	9 (±28)
ER ⁻ , PgR ⁻	2,000	1 (±14)	1 (±14)

Note: All patients were treated with tamoxifen.

Source: Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351:1451-1467.

a meta-analysis to assess recurrence and mortality rates among randomized trials of women with primary breast cancer who received adjuvant tamoxifen therapy or placebo. Table 16.2 details the reduction in recurrence and mortality, stratified by ER and PR status, revealing that women with hormone receptor-positive tumors experience a more significant improvement in both endpoints. Conversely, women with hormone receptor-negative tumors received little, if any, benefit from HT. Furthermore, the EBCTCG established that hormone receptor-positive women receiving tamoxifen demonstrated a 21%, 28%, and 50% reduction in recurrence. Additionally, this group of women experienced a 14%, 18%, and 28% reduction in mortality in the treatment groups of 1 year, 2 years, and approximately 5 years, respectively, with consistent benefits across various tamoxifen dosing regimens (20 to 40 mg/day) (211). Although the efficacy of tamoxifen in the adjuvant setting has been established, the toxicity profile of this agent, including an increased risk of EEC and thromboembolic events, has prompted investigative efforts into alternative, adjuvant anti-estrogenic therapies, specifically AIs.

In 2002, anastrozole alone was approved as adjuvant treatment for early breast cancer. The ATAC trial included 9,366 postmenopausal women with operable, early, invasive breast cancer who had completed primary treatment and were candidates for adjuvant HT. The data demonstrated superior efficacy of anastrozole, when compared with tamoxifen, in improving disease-free survival in postmenopausal women with hormone receptor-positive or unknown early-stage breast cancer. Disease-free survival was significantly longer for patients on anastrozole alone than for those who received tamoxifen alone (HR, 0.83; 95% CI, 0.71–0.96; $p = 0.013$) or the combination of both (HR 0.81; 95% CI, 0.70–0.94; $p = 0.006$). The combination was not significantly different from tamoxifen alone (HR, 1.02; 95% CI, 0.89–1.18; $p = 0.8$). The disease-free survival estimates at 3 years were 89.4%, 87.4%, and 87.2% on anastrozole, tamoxifen, and the combination, respectively. Incidence of contralateral breast cancer was significantly lower with anastrozole than with tamoxifen (OR, 0.42 [0.22 – 0.79]; $p = 0.007$) (212). The ATAC data were recently updated with 68 months of follow-up, and the benefit of the anastrozole over tamoxifen was maintained (213). After publication of the ATAC data, the American Society of Clinical Oncology (ASCO) Health Services Research Committee suggested that a 5-year course of tamoxifen remain the standard adjuvant HT, pending updated data from the ATAC trial and other trials of third-generation AIs in the adjuvant setting (214). Goss et al. conducted a double-blind, placebo-controlled trial evaluating the effectiveness of 5 years of letrozole in 5,187 postmenopausal women with early-stage breast cancer who had completed 5 years of tamoxifen therapy (215). The estimated 4-year disease-free survival rates were 93% for the letrozole group and 87% for the control group ($p < 0.001$), suggesting

that in this subset of breast cancer patients, AI therapy after tamoxifen provides a survival advantage. An analysis of the post-unblinding data revealed that among the 2,594 women initially randomized to placebo, 1,655 women chose to receive open-label letrozole. At 54 months, a statistically significant benefit in disease-free survival favored the crossover patients (HR, 0.31; $p < 0.0001$) (216).

The Breast International Group (BIG) 1-98 study, a randomized, phase 3, double-blind trial, compared 5 years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone receptor-positive breast cancer: letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole. A total of 8,010 women with data that could be assessed were enrolled: 4,003 in the letrozole group and 4,007 in the tamoxifen group. After a median follow-up of 25.8 months, 351 events had occurred in the letrozole group and 428 events in the tamoxifen group, with 5-year disease-free survival estimates of 84.0% and 81.4%, respectively. As compared with tamoxifen, letrozole significantly reduced the risk of an event ending a period of disease-free survival (HR, 0.81; 95% CI, 0.70–0.93; $p = 0.003$), especially the risk of distant recurrence (HR, 0.73; 95% CI, 0.60–0.88; $p = 0.001$). In postmenopausal women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease, especially at distant sites (217). These large randomized trials, as well as others, have assessed the benefit of third-generation aromatase inhibitors anastrozole, letrozole, and exemestane, compared with 5 years of tamoxifen (13,146,218–220). These trials have established that AIs are associated with reduced recurrence rates and improved disease-free survival, but the trials have *not* demonstrated a statistically significant improvement in overall survival. A recent meta-analysis with greater statistical power that reviewed the randomized trials confirmed that the use of aromatase inhibitors was associated with improved disease-free survival. This meta-analysis also showed a statistically significant—albeit modest—improvement in overall survival for patients who took aromatase inhibitors for 2 to 3 years after treatment with tamoxifen for 2 to 3 years (13). However, no overall survival benefit was seen in those who received AIs as initial therapy. In another meta-analysis, Amir et al. found that the cumulative toxicity of AIs when used as up-front treatment may explain the lack of overall survival benefit, despite improvements in disease-free survival (221). In this study, up-front treatment with AIs was associated with nonstatistically significant higher odds of death without recurrence, compared with the use of tamoxifen alone or switching from tamoxifen to aromatase inhibitors (OR, 1.11; 95% CI, 0.98–1.26; $p = 0.09$). Conversely, switching from tamoxifen to AIs was associated with decreased odds of death without recurrence, compared with up-front tamoxifen for 5 years (OR, 0.75; 95% CI, 0.58–0.98; $p = 0.04$) (309). In summary, beginning with tamoxifen and switching to aromatase inhibitors is likely the best balance between efficacy and toxicity.

Many issues regarding the adjuvant use of AIs remain unsettled, including the optimal duration of treatment, the optimal sequencing with tamoxifen, and the optimal AI. ASCO guidelines published in 2010 recommend that postmenopausal women with hormone receptor-positive breast cancer consider incorporating an AI therapy at some point during adjuvant treatment, either as up-front therapy or as sequential treatment after tamoxifen. The optimal timing and duration of endocrine treatment remain unresolved. The ASCO Update Committee supports careful consideration of adverse effect profiles and patient preferences in deciding whether and when to incorporate AI therapy (222).

Premenopausal Women

The optimal adjuvant therapy for premenopausal women with hormone-responsive breast cancer remains uncertain,

despite numerous clinical trials over the past 60 years that have attempted to address this issue. Various strategies of ovarian suppression/ablation, tamoxifen, and/or chemotherapy alone or in combination have been evaluated. The EBCTCG overview analysis has confirmed that adjuvant tamoxifen confers a survival benefit for ER-positive patients, regardless of menopausal status. Accumulated clinical trial data as well as the EBCTCG overview analysis have confirmed that ablation of functioning ovaries significantly improves survival in breast cancer patients younger than 50 years of age, at least in the absence of chemotherapy (223). In the last several years, several investigations have supported the utilization of tamoxifen and ovarian suppression/ablation as adjuvant therapy in premenopausal women with early-stage, receptor-positive breast cancer (224–228).

Two basic strategies exist to abrogate ovarian function. Ovarian suppression (OS) refers to the use of temporary means to suppress ovarian function, generally with luteinizing hormone releasing hormone (LHRH) analogs. Ovarian ablation (OA) refers to permanent strategies using either oophorectomy or ovarian radiation. Despite the clear benefits seen with OA/OS as compared with no adjuvant therapy, the additional benefits of OA/OS in women who have also received chemotherapy is less clear. With the known advantages of both chemotherapy and OA/OS alone as monotherapies, additional studies were designed to evaluate the benefit of adding OA/OS to standard chemotherapeutic regimens, as well as the reverse scenario of assessing the benefit of chemotherapy when added to OS/OA. In aggregate, these studies do not show a clear overall survival benefit with the addition of OS/OA to chemotherapy, although a small benefit appears to emerge, particularly in younger women with hormone-responsive disease.

There is a persistent need to define optimal endocrine therapy in premenopausal women with hormone receptor-positive breast cancer. Several ongoing trials are expected to definitively address the various roles of combining chemotherapy, OS/OA, tamoxifen, and AIs in premenopausal patients with early-stage hormone receptor-positive breast cancer. Contemporaneous trials, such as the Suppression of Ovarian Function Trial (SOFT), Tamoxifen and Exemestane Trial (TEXT), Premenopausal Endocrine Responsive Chemotherapy (PERCHE), and Austrian Breast and Colorectal Cancer Study Group (ABCSG), hopefully will provide direction. Additionally, biomarker and pharmacogenomic data will help further supplement individualized patient decision-making.

Consideration of maintaining fertility is an issue for a subset of premenopausal women with early-stage breast cancer. The prevention of premature ovarian failure after cytotoxic chemotherapy utilizing GnRH analogs for temporary ovarian suppression has been investigated by several studies. Several Phase II studies have reported a high rate of preserved menstruation in treated patients. Other studies have suggested no benefit, with tamoxifen use in either case not being routinely considered. Recently, in a prospective study, Munster et al. randomized premenopausal women to receive either triptorelin or no triptorelin during adjuvant chemotherapy. The women were further stratified by age (<35, 35 to 39, and >39 years); estrogen receptor status; and chemotherapy regimen. Objectives included the resumption of menses and serial monitoring of FSH and inhibin A and B levels. The authors concluded that when women were stratified for age, estrogen receptor status, and treatment regimen, amenorrhea rates on triptorelin were comparable with those seen in the control group (229).

Hormonal Therapy for Metastatic Breast Cancer

Metastatic breast cancer (MBC) remains a major therapeutic challenge, whether it is the first presentation of breast cancer or a recurrence after prior treatment of early-stage disease.

Median survival of patients with metastatic breast cancer is between 2 and 3 years. In premenopausal women, regression of advanced breast cancer as a result of prophylactic oophorectomy was first described in 1896 (230). In multiple series of premenopausal women with metastatic breast cancer, where hormone receptor status was unknown, oophorectomy resulted in cancer regression in 30% to 40% of cases. In premenopausal women with known ER-positive tumors, a 50% to 60% regression after oophorectomy has been noted.

Endocrine therapy for postmenopausal women with advanced, hormonally responsive ER+ breast cancer is based on the observation that greater than three-fourths of these patients respond to HT. In contrast, only 11% of patients with hormone receptor-negative tumors show a response. Tamoxifen was the gold standard of first-line HT for metastatic breast cancer for more than 40 years. However, third-generation AIs have eclipsed tamoxifen in the treatment of postmenopausal women with metastatic estrogen-dependent breast cancer (231). Several large, multinational randomized trials have been undertaken to assess the efficacy and toxicity of AIs in breast cancer in the advanced setting. Results from these trials have demonstrated the superiority of third-generation AIs over tamoxifen in advanced disease (232–235).

Importantly, AIs were demonstrated to exhibit a much less adverse toxicity profile compared with tamoxifen, particularly concerning development of deep vein thrombosis and pulmonary emboli (236). Such evidence has led to the approval of third-generation AIs as first-line therapeutics for advanced breast cancer.

Fulvestrant, an anti-estrogen receptor (anti-ER) drug, is a Selective ER Down Regulator (SERD) that destroys ERs and decreases the number of PRs in breast cancer cells. Fulvestrant is now approved for tamoxifen-resistant tumors. Furthermore, it has been established that fulvestrant and exemestane are equally active and well-tolerated in a meaningful proportion of postmenopausal women with advanced breast cancer who have experienced progression or recurrence during treatment with a nonsteroidal AI (237).

Endometrium

Hormonal Treatment of Endometrioid Endometrial Cancer

The median survival of women with advanced or recurrent EEC is less than 1 year. When the best chemotherapeutic regimen available is used, the complete response rate in those patients with advanced-stage EEC is only 22%. Histologic grade is known to be a predictor of stage and survival, with grade 3, poorly differentiated cancers portending a higher risk of extrauterine disease and thus poorer survival. Furthermore, Carcangiu et al. evaluated 183 patients with EEC, establishing a correlation between the International Federation of Gynecology and Obstetrics (FIGO) grade and hormone receptor expression (238). The recognized association of higher grade with lower ER/PR expression carries implications for the use of HT in advanced EEC. A majority of advanced cases of EEC are grade 3 lesions, limiting the use of HT in this patient population.

Advanced or Recurrent Endometrioid Endometrial Cancer

Progestational agents. The use of progestational agents in women with advanced or recurrent EEC has been under investigation for several decades. Several different types of progestational agents have been investigated, including hydroxyprogesterone caproate (Delalutin), medroxyprogesterone acetate (MPA, Provera), and megestrol acetate (Megace). A majority of

studies evaluating this treatment modality have included small numbers of patients with no stratification for well-recognized predictors of response. In the last decade, several studies with larger patient sample size, clearer eligibility criteria, and clearer definition of response and toxicity have evaluated the effectiveness of progestational agents in the treatment of advanced or recurrent EEC. Thigpen et al. evaluated women with advanced or recurrent EEC who were randomized to receive either oral MPA 200 mg/day or oral MPA 1,000 mg/day until unacceptable toxicity or disease progression (239).

The overall response rates (complete plus partial) favored the low-dose regimen (25% and 16% for low- and high-dose regimens, respectively). The median progression-free survival (PFS) time was 3.2 months for the low-dose regimen and 2.5 months for the high-dose regimen. There was an association, including patients receiving both dosing regimens of MPA, between response and histologic grade, with well-differentiated tumors responding more frequently than poorly differentiated lesions. The response rates were 37% (22 of 59 patients), 23% (26 of 113 patients), and 9% (12 of 127 patients) for those with grade 1, 2, or 3, respectively. There also was a noteworthy correlation between response and receptor content. The response rate was 8% (7 of 86 patients) for patients who were PR negative and 37% (17 of 46) for patients who were PR positive ($p < 0.001$). The response rate was 7% (4 of 55) for patients who were ER negative and 26% (20 of 77) for patients who were ER positive ($p = 0.005$). An association between receptor status and tumor grade was established as well. After adjusting for tumor grade, PR concentration remained an important predictor of survival. In summary, the overall response rate for the progestational agents in women with advanced or recurrent EEC is relatively low. However, progestational agents remain a therapeutic alternative for this patient population, where significant comorbid conditions frequently exist, particularly in those women who can predictably expect a higher response based on grade and receptor content.

Combination chemotherapy and progestational agents. Combining chemotherapy with hormonal therapy is an area of active research. Pinelli et al. prospectively treated 13 advanced EEC patients with carboplatinum 300 mg/mm² every 4 weeks for 6 cycles. Subsequent to the chemotherapy, Megace 80 mg/day for 3 weeks alternating with tamoxifen 40 mg/day for 3 weeks was prescribed. A complete response was obtained in 30% of patients, a partial response in 46%, stable disease in one patient, and disease progression in 2 patients (240). There are ongoing investigations to study the role of combination cytotoxic chemotherapy and HT in the treatment of advanced or recurrent EEC.

Selective estrogen receptor modulators. SERMs have been and continue to be investigated for HT of EEC. Tamoxifen was studied by the GOG in a phase 2 study of patients with advanced or recurrent EEC. At a dose of 20 mg twice daily, only 10% of 68 patients demonstrated objective response, but response occurred more commonly in grades 1 and 2 tumors (23% and 14%, respectively) compared with grade 3 tumors (3%) (241). From pooled reports of eight other studies including 257 patients, 22% of patients with advanced EEC responded to tamoxifen, but with a wide range of responses (0 to 53%) (242).

Tamoxifen can increase PgR content in endometrial cancer tissues. Theoretically, this increase would enhance the activity of progestins, which frequently downregulate PgR within the target tissue, shortening the duration of response. Clinical studies on alternating treatment with tamoxifen and progestin have provided conflicting results (239,241,243–246). Other SERMs are also under investigation, including raloxifene and its metabolite, LY353381.HCl (arzoxifene). First-generation SERMs, such as tamoxifen, have mixed estrogenic agonist and antagonist activity, whereas second-generation SERMs, such as raloxifene, have more selective E2 antagonism. Arzoxifene (LY353381),

a third-generation SERM, is a potent E2 antagonist in mammary and uterine tissues, with enhanced bioavailability and antiestrogenic activity compared with raloxifene. This SERM elicited a complete response in 1 and a partial response in 8 of 29 patients with advanced EEC, with an overall response rate of 31%. The median duration of response was 13.9 months, with minimal toxicity. All responses occurred in progestin-sensitive patients. The relatively high response rate and the favorable toxicity profile make this agent worthy of further investigation (247,248).

Aromatase inhibitors. Anastrozole and letrozole are active, highly selective, nonsteroidal, competitive inhibitors of the enzyme aromatase. It has been shown that significant amounts of aromatase are found in endometrial cancer, with low amounts being present in the surrounding normal endometrial tissue. Rose et al. recently found that in 23 patients anastrozole at 1 mg a day for 28 days has minimal activity, with only a 9% partial response rate and a progression-free interval of 1 to 6 months in women with advanced EEC (249).

The National Cancer Institute of Canada completed a multicenter phase 2 trial evaluating letrozole in postmenopausal women with recurrent or advanced endometrial carcinoma. Thirty-two eligible patients were treated with letrozole at 2.5 mg daily continuously. Of the 28 patients evaluated for response, one complete and two partial responses were noted; overall response was 9.4% (95% CI, 2–25). Eleven patients had stable disease for a median duration of 6.7 months (range, 3.7–19.3 months). In conclusion, letrozole is well-tolerated, but it has little overall activity in this cohort of women with endometrial cancer (250).

Antigonadotropins. Antigonadotropins, such as danazol, antagonize pituitary gonadotropin release and limit adrenal and estrogen production. Danazol has yet to be clinically tested in patients with endometrial cancer. However, *in vitro* studies have shown it to inhibit endometrial tumor cell migration (similar to MPA) and inhibit invasive activity (not demonstrated by MPA) (251,252). The clinical effects of danazol on endometrial hyperplasia have been evaluated (253). Of 15 patients with pathologically proven hyperplasia, all were successfully converted to atrophic endometrium by day 90 of danazol 400 mg/day. Given the perceived low toxicity of danazol compared with conventional chemotherapy, the lack of effective agents in this disease, and a theoretical rationale for its activity in endometrial cancer, a phase 2 trial was undertaken by the GOG (GOG-0180). The results of this trial showed that danazol has minimal activity in advanced, recurrent, or persistent endometrial carcinoma (254). Fulvestrant, a pure antiestrogen hormonal agent without any estrogen agonist activity, has also been tested in a phase II GOG trial (protocol 188), but showed limited activity in ER positive or ER negative tumors (255).

In a recent Cochrane Analysis, the authors found insufficient evidence that hormonal treatment in any form or dose, or as part of combination therapy improves the survival of patients with advanced or recurrent endometrial cancer (Table 16.3). In the absence of a proven survival advantage, the decision to use any type of hormonal therapy should be individualized with the intent to palliate the disease. It is debatable whether outcomes such as quality of life, treatment response, or palliative measures such as relieving symptoms should take preference over overall and PFS as the major objectives of future trials (256).

Adjuvant Therapy for Endometrioid Endometrial Cancer

The use of progestational agents as adjuvant therapy for stages I and II EEC has been investigated by von Minckwitz et al. (257). They conducted a randomized trial of 388 patients with early-stage EEC who received either MPA ($n = 133$), or tamoxifen ($n = 121$)

Table 16.3 Selected Trials of Hormonal Therapy in Metastatic Endometrial Cancer

Treatment	No. of Patients	RR (%)	PFS (mo)	OS (mo)	Reference
MPA 200 mg/d	331	17	4	10.4	(289)
MPA 200 mg/d	145	25	3.2	11.1	(239)
MPA 1000 mg/d	154	15	25	7.0	(239)
Tamoxifen 20 mg b.i.d	68	10	1.9	8.8	(241)
Tamoxifen 20 mg b.i.d	45	53.4	NR	NR	(290)
MA + tamoxifen	42	18	NR	12.0	(244)
MA 160 mg for 3 wk, then tamoxifen 40 mg for 3 wk, alternating	61	26.8	2.7	14.0	(245)
Arzoxifene	34	31	13.9	NR	(248)
Goserelin acetate 3.6 mg monthly, subcutaneously	17	35	20	NR	(291)
Goserelin acetate 3.6 mg monthly, subcutaneously [41]	40	12	1.9	7.3	(292)
Anastrozole 1 mg/day [42]	23	9	1.0	6.0	(249)
Letrozole 2.5 mg/day [43]	28	9.4	NR	NR	(250)

Abbreviations: RR, response rate; PFS, progression-free survival; OS, overall survival; MPA, medroxyprogesterone acetate; NR, not reported; MA, megestrol acetate.

orally for 2 years, or were observed only ($n = 134$) after surgical therapy. After 56 months of follow-up, no benefit was observed from adjuvant progestin or tamoxifen therapy after surgical treatment in early-stage EEC. However, given the low frequency of recurrence in this patient population, larger randomized studies are needed to fully evaluate the role of progestational agents as adjuvant therapy in early EEC.

Progestational Agents as Primary Therapy for Endometrioid Endometrial Cancer

Several small series have retrospectively reported on the use of progestational agents alone, not preceded by hysterectomy, in the treatment of patients with EEC, either because of the desire to maintain fertility or because of comorbid conditions. No randomized, controlled studies evaluating progestational agents in either clinical scenario are available. Montz et al., in a prospective pilot study, reported on the use of the progesterone IUD in women with presumed stage IA, grade 1 EEC, who were at significant risk for perioperative morbidity (258). Follow-up endometrial biopsies were negative in 7 of 11 patients at 6 months, and in 6 of 8 patients at 12 months. Recently, Ramirez et al. searched MEDLINE and other databases for English language articles describing patients with grade 1 EEC treated with hormonal therapy. Ultimately, 81 patients in 27 articles were included in the study. Sixty-two patients (76%) responded to treatment. The median time to response was 12 weeks (range, 4–60 weeks). Fifteen patients (24%) who initially responded to treatment recurred. The median time to recurrence was 19 months (range, 6–44 months). Ten (67%) of the patients with recurrence ultimately underwent total abdominal hysterectomy. Residual endometrial carcinoma was found in 6 of the 10 patients (60%). Twenty patients were able to become pregnant at least once after completing treatment. No patients died of their disease. Further investigation is needed into this approach to the primary management of EEC (259). More recently, Westin et al. from M. D. Anderson Cancer Center prospectively evaluated, in a single-arm phase 2 study, the levonorgestrel intrauterine system (LIUS) in the treatment of complex adenomatous hyperplasia (CAH) and EEC grade 1. After confirmation of no extrauterine disease, dilation and curettage was performed and the LIUS was placed. Endometrial biopsies were performed every 3 months. The primary efficacy end-point was pathological response rate (RR) at 12 months, defined as

complete response (CR) and partial response (PR). CR is defined as no abnormality or as hyperplasia without atypia in CAH or EEC patients. PR is defined as CAH in EEC patients. Twenty-six evaluable patients have been enrolled thus far: 18 had CAH, and 8 had EEC. The overall 12-month response rate was 58%. At 12 months, 11 patients had CR (1 with EEC, 10 with CAH); 1 patient had PR (EEC); 2 patients had stable disease (CAH); and 5 patients had progressive disease (4 with EEC, 1 with CAH). Seven of the 26 patients did not reach the 12-month mark in the study. After stratification for histology, response rate was 85% for CAH (13 evaluable) and 33% for EEC (6 evaluable). The LIUS has encouraging activity in CAH and EEC. Response may be predicted by presence of exogenous progesterone effect (260).

Ovary

Hormones and their receptors have been associated with ovarian cancer and may be related to its causation. Some data suggest that hormonal therapies may have an effect on ovarian cancer in palliative settings (261). Several investigators have established that hormone receptors are expressed in epithelial ovarian cancer, and that significant alterations occur with malignant transformation. Rao and Slotman reviewed 45 series, including 2,508 ovarian cancer patients, and reported that 67% of tumors expressed ER and 47% expressed PR (262). The expression of the ERs and PRs has been found to correlate with long-term survival in invasive ovarian cancer. The ER-PR⁺ phenotype predicted a more favorable tumor biology and long-term survival (263). A large number of hormonal agents have been evaluated in the treatment of ovarian cancer, including SERMs, E2, progestins, androgens, AIs, and GnRH agonists. Progestin therapy in patients with advanced ovarian cancer has a global response rate of 8% to 15% (264). Tamoxifen, in preclinical studies, inhibits ovarian cell growth *in vitro*, providing rationale for the use of this agent in the treatment of ovarian cancer. Several studies have evaluated the activity of single-agent tamoxifen in the treatment of advanced ovarian cancer (Table 16.4) (265–282).

Perez-Garcia and Carrasco reviewed the literature evaluating single-agent tamoxifen in the treatment of patients with advanced ovarian cancer, most of whom were heavily pretreated and refractory to chemotherapy (283). A total of 648 patients were included with an overall response rate (ORR) of 13% (95% CI, 10.4–15.6; range, 56), including a 4% complete response

Table 16.4 Tamoxifen Therapy for Advanced Ovarian Cancer

Study (Reference)	No. of Evaluable Patients	Median no. of Lines Prior CT (%)	Dose (mg/h)	No. of Patients Responding (%)			
				OR	CR	SD	PR
Hatch et al. (268)	105	1 (100)	20/12	18 (17)	10 (10)	8 (8)	40 (38)
Trope et al. (293)	65 ^a	1 (24) ≥2 (74)	30–40/24	4 (6)	2 (3)	2 (3)	50 (77)
Landoni et al. (294)	55	NS	40/24	0	0	0	19 (35)
Osborne et al. (272)	51	0 (2) 1 (41) 2 (57)	20/12 ^b	1 (2)	0 (0)	1 (2)	5 (9)
Gennatas et al. (295)	50	0 (50) 1–2 (50)	20/12	28 (56)	2 (4)	26 (52)	NS
Rolski et al. (296)	47	1–4	40/24	3 (6)	1 (2)	2 (4)	22 (47)
Quinn (297)	40	1	20/12	9 (23)	5 (13)	4 (10)	12 (30)
Jager et al. (269)	33	NS (≥1)	30/24	0 (0)	0 (0)	0 (0)	2 (6)
Weiner et al. (282)	31	3	10/12 ^b	3 (10)	1 (3)	2 (6)	6 (19)
Van der Velden et al. (280)	16	1	20/12	2 (13)	2 (13)	0 (0)	6 (38)
	14	2 or 3	20/12	0 (0)	0 (0)	0 (0)	4 (29)
Ahlgren et al. (265)	29	1 (50) ≥2 (50)	20/12 ^b	5 (17)	2 (7)	3 (10)	18 (62)
Shirey et al. (278)	23	NS (≥1)	20–40/24	0 (0)	0 (0)	0 (0)	19 (83)
Slevin et al. (279)	22	2	20/12	0 (0)	0 (0)	0 (0)	1 (5)
Pagel et al. (298)	21	NS	NS	8 (38)	1 (5)	7 (3)	12 (57)
Hamerlynck et al. (299)	18	NS	20/12	1 (6)	0 (0)	1 (6)	2 (11)
Schwartz et al. (277)	13	≥2	10/12	1 (8)	0 (0)	1 (8)	4 (31)
Rowland et al. (300)	9	1–3	20/24	0 (0)	0 (0)	0 (0)	NS
Van der Vange et al. (281)	6	2	20/12	1 (17)	0 (0)	1 (17)	1 (17)
Total	648			84 (13.0)	26 (4.0)	58 (9.0)	223 (37.9) ^c

Note: CR, complete response; CT, chemotherapy; NS, not stated; OR, overall response; PR, partial response; SD, stable disease.

^aOnly evaluable patients are included (but prior CT lines refer to the whole population).

^bWith a loading dose of 100 mg/24 h during 1 d (Osborne et al. [272]), 40 mg/24 h during 7 d (Weiner et al. [282]), and 40 mg/24 h during 30 d (Ahlgren et al. [265]).

^cCalculated over the number of patients included in trials that report these data.

rate and a 9% partial response rate. In 38% of patients, stable disease was noted. These results are not entirely dissimilar from those seen with progestins.

Gershenson et al. recently studied the role of tamoxifen in women with low-grade serous ovarian tumors. They identified 64 patients with recurrent low-grade serous carcinoma of the ovary or peritoneum. Patients' median time to progression (TTP) and median overall survival (OS) were 7.4 and 78.2 months, respectively. Patients received 89 separate hormonal patient regimens, which produced an overall response rate of 9% (6 complete responses and 2 partial responses). Sixty-one percent of the patient-regimens resulted in a PFS of at least 6 months. Patient regimens involving ER+/PR+ disease produced a longer median TTP (8.9 months) than patient regimens involving ER+/PR– disease (6.2 months; $p < 0.053$). This difference approached, but did not reach statistical significance. The authors concluded that hormonal therapies have moderate antitumor activity in patients with recurrent low-grade serous carcinoma of the ovary

or peritoneum. Further study is warranted to determine whether ER/PR expression status is a predictive biomarker for this rare cancer subtype (284).

The role of GnRH agonists in the management of refractory ovarian cancer has been evaluated in multiple studies and has been summarized by Paskeviciute et al. (285). GnRH agonists induced an overall objective response in 8.5% of refractory ovarian cancer patients, with disease stabilization in 23% of these women.

Several investigators have compared chemotherapy and hormonal therapy with chemotherapy alone, primarily in patients with advanced ovarian cancer. However, these studies had small patient sample size and were not randomized, controlled studies.

Emons et al. randomized 135 patients with advanced ovarian cancer to receive the GnRH triptorelin or placebo, following surgery and chemotherapy, until the patient's death or termination of the trial. There were no significant differences in OS or PFS between the groups, with documented gonadotropin suppression (286).

At least four randomized studies comparing chemotherapy and MPA or a GnRH versus chemotherapy alone in ovarian cancer patients have been reported. These studies contain many of the same flaws as noted throughout this discussion, namely, small sample size and no stratification for optimal versus suboptimal surgical status, menopausal status, and histologic status.

Argenta et al. evaluated fulvestrant in women with recurrent ovarian or primary peritoneal cancer. Thirty-one women were enrolled, and 26 women (median age, 61 years) met inclusion criteria and received at least one dose. Patients had received a median of five prior chemotherapeutic regimens (range, 2–13). One CR (4%), one PR (4%), and 9 patients with SD (35%) were observed, using response evaluation criteria in solid tumors (RECIST) (CA-125 level). Using modified-RECIST criteria, 13 patients (50%) achieved SD. The median time to disease progression was 62 days (mean, 86 days). Grade I toxicity included headache (1 patient) and bromhidrosis (2 patients). Fulvestrant was well-tolerated and efficacious. Objective response rates were low, but disease stabilization was common (287).

Smyth et al. in a phase II study of letrozole evaluated the efficacy of this aromatase inhibitor in preselected ER positive relapsed epithelial ovarian cancer patients (288). The primary end-point was response according to CA-125 and RECIST. Marker expression was measured by semiquantitative immunohistochemistry in sections from the primary tumor. Of 42 patients evaluable for CA-125 response, 7 (17%) had a response (decrease of >50%), and 11 (26%) patients had not progressed (doubling of CA-125) following 6 months of treatment. The median time taken to achieve the CA-125 nadir was

13 weeks (range, 10–36). Of 33 patients evaluable for radiological response, 3 (9%) had a partial remission, and 14 (42%) had stable disease at 12 weeks. Eleven patients (26%) had a PFS of > 6 months. This is the first study of a hormonal agent in a pre-selected group of ER-positive ovarian cancer patients. Further studies must be undertaken.

As previously stated, in patients with ovarian cancer, receptor status does not reproducibly correlate with prognostic factors, including survival or disease-free interval. However, receptor status may be useful in predicting response to hormonal agents. Although several investigators have approached this question, results are inconclusive. The ascertainment of receptor status as a predictor of hormonal activity in ovarian cancer will require a randomized clinical trial comparing hormonal activity in patients expressing hormone receptors versus those with no receptor expression, controlling for the many variables recognized as important prognosticators in ovarian cancer.

Colon

The clinical data available evaluating the relationship between hormones and colon cancer relate primarily to hormones as risk factors for the development of this common human malignancy. There is a plethora of data in colon cancer cell lines regarding the effect of hormonal agents on cell growth, as well as cell death. To date, there are no clinical studies evaluating the treatment of colon cancer, either in the adjuvant setting or otherwise, with hormonal agents.

REFERENCES

- Lee JH, Lee MJ. Emerging roles of the ubiquitin-proteasome system in the steroid receptor signaling. *Arch Pharm Res*. 2012;35(3):397–407.
- Heldring N, Pike A, Andersson S, et al. Estrogen receptors: how do they signal and what are their targets. *Physiol Rev*. 2007;87(3):905–931.
- Evans RM. The steroid and thyroid hormone receptor superfamily. *Science*. 1988;240(4854):889–895.
- O'Malley BW, Tsai SY, Bagchi M, et al. Molecular mechanism of action of a steroid hormone receptor. *Recent Prog Horm Res*. 1991;47:1–24; discussion 24–26.
- Molenda HA, Kilts CP, Allen RL, et al. Nuclear receptor coactivator function in reproductive physiology and behavior. *Biol Reprod*. 2003;69(5):1449–1457.
- Bjornstrom L, Sjoberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. *Mol Endocrinol*. 2005;19(4):833–842.
- Miller WL. Molecular biology of steroid hormone synthesis. *Endocr Rev*. 1988;9(3):295–318.
- Channing CP, Tsafirri A. Mechanism of action of luteinizing hormone and follicle-stimulating hormone on the ovary in vitro. *Metabolism*. 1977;26(4):413–468.
- Simpson ER. Aromatase: biologic relevance of tissue-specific expression. *Semin Reprod Med*. 2004;22(1):11–23.
- Pasqualini JR, Chetrite GS. Recent insight on the control of enzymes involved in estrogen formation and transformation in human breast cancer. *J Steroid Biochem Mol Biol*. 2005;93(2–5):221–236.
- Ghosh D, Griswold J, Erman M, et al. Structural basis for androgen specificity and oestrogen synthesis in human aromatase. *Nature*. 2009;457(7226):219–223.
- Johnston SR, Dowsett M. Aromatase inhibitors for breast cancer: lessons from the laboratory. *Nat Rev Cancer*. 2003;3(11):821–831.
- Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28(3):509–518.
- Cuppone F, Bria E, Verma S, et al. Do adjuvant aromatase inhibitors increase the cardiovascular risk in postmenopausal women with early breast cancer? Meta-analysis of randomized trials. *Cancer*. 2008;112(2):260–267.
- Obiorah I, Jordan VC. Progress in endocrine approaches to the treatment and prevention of breast cancer. *Maturitas*. 2011;70(4):315–321.
- Miller WR. Aromatase and the breast: regulation and clinical aspects. *Maturitas*. 2006;54(4):335–341.
- Kumar V, Green S, Stack G, et al. Functional domains of the human estrogen receptor. *Cell*. 1987;51(6):941–951.
- Levin ER. Integration of the extranuclear and nuclear actions of estrogen. *Mol Endocrinol*. 2005;19(8):1951–1959.
- Cheung E, Kraus WL. Genomic analyses of hormone signaling and gene regulation. *Annu Rev Physiol*. 2010;72:191–218.
- Heldring N, Isaacs GD, Diehl AG, et al. Multiple sequence-specific DNA-binding proteins mediate estrogen receptor signaling through a tethering pathway. *Mol Endocrinol*. 2011;25(4):564–574.
- Kushner PJ, Agard DA, Greene GL, et al. Estrogen receptor pathways to AP-1. *J Steroid Biochem Mol Biol*. 2000;74(5):311–317.
- Mosselman S, Polman J, Dijkema R. ER beta: identification and characterization of a novel human estrogen receptor. *FEBS Lett*. 1996;392(1):49–53.
- Barkhem T, Carlsson B, Nilsson Y, et al. Differential response of estrogen receptor alpha and estrogen receptor beta to partial estrogen agonists/antagonists. *Mol Pharmacol*. 1998;54(1):105–112.
- Paige LA, Christensen DJ, Gron H, et al. Estrogen receptor (ER) modulators each induce distinct conformational changes in ER alpha and ER beta. *Proc Natl Acad Sci USA*. 1999;96(7):3999–4004.
- Kuiper GG, Carlsson B, Grandien K, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology*. 1997;138(3):863–870.
- Taylor AH, Al-Azzawi F. Immunolocalisation of oestrogen receptor beta in human tissues. *J Mol Endocrinol*. 2000;24(1):145–155.
- Babiker FA, De Windt LJ, van Eickels M, et al. Estrogenic hormone action in the heart: regulatory network and function. *Cardiovasc Res*. 2002;53(3):709–719.
- Haring J, Skrzypczak M, Stegerer A, et al. Estrogen receptor β transcript variants associate with oncogene expression in endometrial cancer. *Int J Mol Med*. 2012;29(6):1127–1136.
- Matthews J, Gustafsson JA. Estrogen signaling: a subtle balance between ER alpha and ER beta. *Mol Interv*. 2003;3(5):281–292.
- Hall JM, McDonnell DP. The estrogen receptor beta-isoform (ERbeta) of the human estrogen receptor modulates ERalpha transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. *Endocrinology*. 1999;140(12):5566–5578.
- Iyer V, Klebba I, McCready J, et al. Estrogen promotes ER-negative tumor growth and angiogenesis through mobilization of bone marrow-derived monocytes. *Cancer Res*. 2012;72(11):2705–2713.

32. Pujol P, Rey JM, Nirde P, et al. Differential expression of estrogen receptor- α and - β messenger RNAs as a potential marker of ovarian carcinogenesis. *Cancer Res.* 1998;58(23):5367–5373.
33. Li AJ, Baldwin RL, Karlan BY. Estrogen and progesterone receptor subtype expression in normal and malignant ovarian epithelial cell cultures. *Am J Obstet Gynecol.* 2003;189(1):22–27.
34. Jazaeri AA, Nunes KJ, Dalton MS, et al. Well-differentiated endometrial adenocarcinomas and poorly differentiated mixed müllerian tumors have altered ER and PR isoform expression. *Oncogene.* 2001;20(47):6965–6969.
35. Foley EF, Jazaeri AA, Shupnik MA, et al. Selective loss of estrogen receptor β in malignant human colon. *Cancer Res.* 2000;60(2):245–248.
36. Hewitt SC, Korach KS. Oestrogen receptor knockout mice: roles for oestrogen receptors α and β in reproductive tissues. *Reproduction.* 2003;125(2):143–149.
37. Couch FJ, Gaudet MM, Antoniou AC, et al. Common variants at the 19p13.1 and ZNF365 loci are associated with ER subtypes of breast cancer and ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. *Cancer Epidemiol Biomarkers Prev.* 2012;21(4):645–657.
38. Palmieri C, Lam EW, Mansi J, et al. The expression of ER β in human breast cancer and the relationship to endocrine therapy and survival. *Clin Cancer Res.* 2004;10(7):2421–2428.
39. Drummond AE, Fuller PJ. Activin and inhibin, estrogens and NF κ B, play roles in ovarian tumorigenesis: is there crosstalk? *Mol Cell Endocrinol.* 2012;359(1–2):85–91.
40. Paech K, Webb P, Kuiper GG, et al. Differential ligand activation of estrogen receptors ER α and ER β at AP1 sites. *Science.* 1997;277(5331):1508–1510.
41. Kumar P, Wu Q, Chambliss KL, et al. Direct interactions with G α i and G $\beta \gamma$ mediate nongenomic signaling by estrogen receptor α . *Mol Endocrinol.* 2007;21(6):1370–1380.
42. Das A, Li Q, Laws MJ, et al. Estrogen-induced expression of Fos-related antigen 1 (FRA-1) regulates uterine stromal differentiation and remodeling. *J Biol Chem.* 2012;287(23):19622–19630.
43. Lee AV, Weng CN, Jackson JG, et al. Activation of estrogen receptor-mediated gene transcription by IGF-I in human breast cancer cells. *J Endocrinol.* 1997;152(1):39–47.
44. Ignar-Trowbridge DM, Nelson KG, Bidwell MC, et al. Coupling of dual signaling pathways: epidermal growth factor action involves the estrogen receptor. *Proc Natl Acad Sci USA.* 1992;89(10):4658–4662.
45. Manavathi B, Kumar R. Steering estrogen signals from the plasma membrane to the nucleus: two sides of the coin. *J Cell Physiol.* 2006;207(3):594–604.
46. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. *J Clin Oncol.* 2006;24(29):4783–4791.
47. Maxwell GL, Risinger JI, Gumbs C, et al. Mutation of the PTEN tumor suppressor gene in endometrial hyperplasias. *Cancer Res.* 1998;58(12):2500–2503.
48. Duong BN, Elliott S, Frigo DE, et al. AKT regulation of estrogen receptor β transcriptional activity in breast cancer. *Cancer Res.* 2006;66(17):8373–8381.
49. Losel RM, Falkenstein E, Feuring M, et al. Nongenomic steroid action: controversies, questions, and answers. *Physiol Rev.* 2003;83(3):965–1016.
50. Song RX, Santen RJ. Membrane initiated estrogen signaling in breast cancer. *Biol Reprod.* 2006;75(1):9–16.
51. Simoncini T, Hafezi-Moghadam A, Brazil DP, et al. Interaction of oestrogen receptor with the regulatory subunit of phosphatidylinositol-3-OH kinase. *Nature.* 2000;407(6803):538–541.
52. Armaiz-Pena GN, Mangala LS, Spanuth WA, et al. Estrous cycle modulates ovarian carcinoma growth. *Clin Cancer Res.* 2009;15(9):2971–2978.
53. Filardo EJ, Thomas P. Minireview: G protein-coupled estrogen receptor-1, GPER-1: its mechanism of action and role in female reproductive cancer, renal and vascular physiology. *Endocrinology.* 2012;153(7):2953–2962.
54. Revankar CM, Cimino DF, Sklar LA, et al. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. *Science.* 2005;307(5715):1625–1630.
55. Misrahi M, Atger M, d'Auriol L, et al. Complete amino acid sequence of the human progesterone receptor deduced from cloned cDNA. *Biochem Biophys Res Commun.* 1987;143(2):740–748.
56. De Vos P, Schmitt J, Verhoeven G, et al. Human androgen receptor expressed in HeLa cells activates transcription in vitro. *Nucleic Acids Res.* 1994;22(7):1161–1166.
57. Daniel AR, Knutson TP, Lange CA. Signaling inputs to progesterone receptor gene regulation and promoter selectivity. *Mol Cell Endocrinol.* 2009;308(1–2):47–52.
58. Law ML, Kao FT, Wei Q, et al. The progesterone receptor gene maps to human chromosome band 11q13, the site of the mammary oncogene int-2. *Proc Natl Acad Sci USA.* 1987;84(9):2877–2881.
59. Sartorius CA, Melville MY, Hovland AR, et al. A third transactivation function (AF3) of human progesterone receptors located in the unique N-terminal segment of the B-isoform. *Mol Endocrinol.* 1994;8(10):1347–1360.
60. Graham JD, Clarke CL. Expression and transcriptional activity of progesterone receptor A and progesterone receptor B in mammalian cells. *Breast Cancer Res.* 2002;4(5):187–190.
61. Huse B, Verca SB, Matthey P, et al. Definition of a negative modulation domain in the human progesterone receptor. *Mol Endocrinol.* 1998;12(9):1334–1342.
62. Mote PA, Balleine RL, McGowan EM, et al. Heterogeneity of progesterone receptors A and B expression in human endometrial glands and stroma. *Hum Reprod.* 2000;15(suppl. 3):S48–S56.
63. Conneely OM, Mulac-Jericevic B, DeMayo F, et al. Reproductive functions of progesterone receptors. *Recent Prog Horm Res.* 2002;57:339–355.
64. Arnett-Mansfield RL, deFazio A, Wain GV, et al. Relative expression of progesterone receptors A and B in endometrial cancers of the endometrium. *Cancer Res.* 2001;61(11):4576–4582.
65. Peluso JJ. Progesterone signaling mediated through progesterone receptor membrane component-1 in ovarian cells with special emphasis on ovarian cancer. *Steroids.* 2011;76(9):903–909.
66. Peluso JJ, Romak J, Liu X. Progesterone receptor membrane component-1 (PGRMC1) is the mediator of progesterone's antiapoptotic action in spontaneously immortalized granulosa cells as revealed by PGRMC1 small interfering ribonucleic acid treatment and functional analysis of PGRMC1 mutations. *Endocrinology.* 2008;149(2):534–543.
67. Takahashi A, Kato K, Kuboyama A, et al. Induction of senescence by progesterone receptor-B activation in response to cAMP in ovarian cancer cells. *Gynecol Oncol.* 2009;113(2):270–276.
68. Davis M, Hitchcock A, Foulkes WD, et al. Refinement of two chromosome 11q regions of loss of heterozygosity in ovarian cancer. *Cancer Res.* 1996;56(4):741–744.
69. Gabra H, Langdon SP, Watson JE, et al. Loss of heterozygosity at 11q22 correlates with low progesterone receptor content in epithelial ovarian cancer. *Clin Cancer Res.* 1995;1(9):945–953.
70. Panda H, Chuang TD, Luo X, et al. Endometrial miR-181a and miR-98 expression is altered during transition from normal into cancerous state and target PGR, PGRMC1, CYP19A1, DDX3X, and TIMP3. *J Clin Endocrinol Metab.* 2012;97(7):E1316–E1326.
71. Thomas P. Characteristics of membrane progesterone receptor α (mPR α) and progesterone membrane receptor component 1 (PGRMC1) and their roles in mediating rapid progestin actions. *Front Neuroendocrinol.* 2008;29(2):292–312.
72. Boonyaratankornkit V, Scott MP, Ribon V, et al. Progesterone receptor contains a proline-rich motif that directly interacts with SH3 domains and activates c-Src family tyrosine kinases. *Mol Cell.* 2001;8(2):269–280.
73. Levin ER. Minireview: extranuclear steroid receptors: roles in modulation of cell functions. *Mol Endocrinol.* 2011;25(3):377–384.
74. Carnevale RP, Proietti CJ, Salatino M, et al. Progestin effects on breast cancer cell proliferation, protease activation, and in vivo development of metastatic phenotype all depend on progesterone receptor capacity to activate cytoplasmic signaling pathways. *Mol Endocrinol.* 2007;21(6):1335–1358.
75. Joshi PA, Jackson HW, Beristain AG, et al. Progesterone induces adult mammary stem cell expansion. *Nature.* 2010;465(7299):803–807.
76. Hagan CR, Daniel AR, Dressing GE, et al. Role of phosphorylation in progesterone receptor signaling and specificity. *Mol Cell Endocrinol.* 2012;357(1–2):43–49.
77. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* 2006;295(14):1647–1657.
78. Eden JA. A case-control study of combined continuous estrogen-progestin replacement therapy among women with a personal history of breast cancer. *Menopause.* 1995;2:67–72.
79. Bluming AZ, Waisman JR, Dosik GA, et al. Hormone replacement therapy in women with previously treated primary breast cancer: update III (abstract 131a). *Proc Am Soc Clin Oncol.* 1997;16A:463.
80. Vassilopoulou-Sellin R, Asmar L, Hortobagyi GN, et al. Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. *J Clin Oncol.* 1999;17(5):1482–1487.
81. DiSaia PJ, Brewster WR, Ziogas A, et al. Breast cancer survival and hormone replacement therapy: a cohort analysis. *Am J Clin Oncol.* 2000;23(6):541–545.
82. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet.* 1997;350(9084):1047–1059.
83. Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA.* 2000;283(4):485–491.
84. Ross RK, Paganini-Hill A, Wan PC, et al. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst.* 2000;92(4):328–332.
85. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA.* 2002;288(3):321–333.
86. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA.* 2003;289(24):3243–3253.

87. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008;299(9):1036–1045.
88. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010;304(15):1684–1692.
89. Chlebowski RT, Anderson GL. Changing concepts: menopausal hormone therapy and breast cancer. *J Natl Cancer Inst*. 2012;104(7):517–527.
90. McTiernan A, Martin CF, Peck JD, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. *J Natl Cancer Inst*. 2005;97(18):1366–1376.
91. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291(1):47–53.
92. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–1712.
93. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA*. 2011;305(13):1305–1314.
94. Boonyaratankornkit V, Scott MP, Ribon V, et al. Progesterone receptor contains a proline-rich motif that directly interacts with SH3 domains and activates c-Src family tyrosine kinases. *Mol Cell*. 2001;8(2):269–280.
95. Estrogen replacement therapy in women with previously treated breast cancer. ACOG Committee Opinion: Committee on Gynecologic Practice Number 135-April 1994. *Int J Gynaecol Obstet*. 1994;45(2):184–188.
96. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1996;347(9017):1713–1727.
97. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med*. 2002;346(26):2025–2032.
98. Grabrick DM, Hartmann LC, Cerhan JR, et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *JAMA*. 2000;284(14):1791–1798.
99. Narod SA, Dube MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst*. 2002;94(23):1773–1779.
100. Rodriguez C, Patel AV, Calle EE, et al. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA*. 2001;285(11):1460–1465.
101. Lacey JV Jr, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA*. 2002;288(3):334–341.
102. Riman T, Dickman PW, Nilsson S, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst*. 2002;94(7):497–504.
103. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1739–1748.
104. Guiozzzi F, Daponte A. Estrogen replacement therapy for ovarian carcinoma survivors: a randomized controlled trial. *Cancer*. 1999; 86(6):1013–1018.
105. Grady D, Gebretsadik T, Kerlikowske K, et al. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol*. 1995;85(2):304–313.
106. Speroff L, Rowan J, Symons J, et al. The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART study): a randomized controlled trial. *JAMA*. 1996;276(17):1397–1403.
107. Flowers CE Jr, Wilborn WH, Hyde BM. Mechanisms of uterine bleeding in postmenopausal patients receiving estrogen alone or with a progestin. *Obstet Gynecol*. 1983;61(2):135–143.
108. Beresford SA, Weiss NS, Voigt LF, et al. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet*. 1997;349(9050):458–461.
109. Hill DA, Weiss NS, Beresford SA, et al. Continuous combined hormone replacement therapy and risk of endometrial cancer. *Am J Obstet Gynecol*. 2000;183(6):1456–1461.
110. Weiderpass E, Adami HO, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst*. 1999;91(13):1131–1137.
111. Holinka CF, Hata H, Kuramoto H, et al. Responses to estradiol in a human endometrial adenocarcinoma cell line (Ishikawa). *J Steroid Biochem*. 1986;24(1):85–89.
112. Farnell YZ, Ing NH. The effects of estradiol and selective estrogen receptor modulators on gene expression and messenger RNA stability in immortalized sheep endometrial stromal cells and human endometrial adenocarcinoma cells. *J Steroid Biochem Mol Biol*. 2003;84(4):453–461.
113. Creasman WT, Henderson D, Hinshaw W, et al. Estrogen replacement therapy in the patient treated for endometrial cancer. *Obstet Gynecol*. 1986;67(3):326–330.
114. Lee RB, Burke TW, Park RC. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. *Gynecol Oncol*. 1990; 36(2):189–191.
115. Chapman JA, DiSaia PJ, Osann K, et al. Estrogen replacement in surgical stage I and II endometrial cancer survivors. *Am J Obstet Gynecol*. 1996;175(5):1195–1200.
116. Suriano KA, McHale M, McLaren CE, et al. Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstet Gynecol*. 2001;97(4):555–560.
117. Committee on Gynecologic Practice. ACOG committee opinion. Hormone replacement therapy in women treated for endometrial cancer. Number 234, May 2000 (replaces number 126, August 1993). *Int J Gynaecol Obstet*. 2001; 73(3):283–284.
118. Voigt LF, Deng Q, Weiss NS. Recency, duration, and progestin content of oral contraceptives in relation to the incidence of endometrial cancer (Washington, USA). *Cancer Causes Control*. 1994;5(3):227–233.
119. Rutqvist LE, Johansson H, Signomklao T, et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. *J Natl Cancer Inst*. 1995;87(9):645–651.
120. Fisher B, Costantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst*. 1994;86(7): 527–537.
121. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282(7):637–645.
122. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295(23):2727–2741.
123. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*. 2004;350(10):991–1004.
124. Picariello L, Fiorelli G, Martinetti V, et al. Growth response of colon cancer cell lines to selective estrogen receptor modulators. *Anticancer Res*. 2003;23(3B):2419–2424.
125. Newcomb PA, Solomon C, White E. Tamoxifen and risk of large bowel cancer in women with breast cancer. *Breast Cancer Res Treat*. 1999; 53(3):271–277.
126. Church J, Simmang C. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer). *Dis Colon Rectum*. 2003;46(8):1001–1012.
127. Serpell JW, Paddle-Ledinek JE, Johnson WR. Modification of growth of desmoid tumours in tissue culture by anti-oestrogenic substances: a preliminary report. *Aust N Z J Surg*. 1996;66(7):457–463.
128. Bus PJ, Verspaget HW, van Krieken JH, et al. Treatment of mesenteric desmoid tumours with the anti-oestrogenic agent toremifene: case histories and an overview of the literature. *Eur J Gastroenterol Hepatol*. 1999;11(10):1179–1183.
129. Kadmon M, Moslein G, Buhr HJ, et al. [Desmoid tumors in patients with familial adenomatous polyposis (FAP). Clinical and therapeutic observations from the Heidelberg polyposis register]. *Chirurg*. 1995;66(10):997–1005.
130. Adlercreutz H. Phyto-oestrogens and cancer. *Lancet Oncol*. 2002;3(6):364–373.
131. Goodman MT, Wilkens LR, Hankin JH, et al. Association of soy and fiber consumption with the risk of endometrial cancer. *Am J Epidemiol*. 1997;146(4):294–306.
132. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90(18):1371–1388.
133. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989; 81(24):1879–1886.
134. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 2005;97(22):1652–1662.
135. Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. *Lancet*. 1998; 352(9122):93–97.
136. Veronesi U, Maisonneuve P, Rotmensz N, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. *J Natl Cancer Inst*. 2007;99(9):727–737.

137. Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet*. 1998;352(9122):98–101.
138. Powles TJ, Ashley S, Tidy A, et al. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst*. 2007;99(4):283–290.
139. Cuzick J, Forbes J, Edwards R, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet*. 2002;360(9336):817–824.
140. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst*. 2007;99(4):272–282.
141. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. *JAMA*. 1999;281(23):2189–2197.
142. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat*. 2001;65(2):125–234.
143. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst*. 2004;96(23):1751–1761.
144. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. *Cancer Prev Res (Phila)*. 2010;3(6):696–706.
145. Runowicz CD, Costantino JP, Wickerham DL, et al. Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). *Am J Obstet Gynecol*. 2011;205(6):535 e1–e5.
146. Forbes JF, Cuzick J, Buzdar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol*. 2008;9(1):45–53.
147. Parazzini F, Braga C, La Vecchia C, et al. Hysterectomy, oophorectomy in premenopause, and risk of breast cancer. *Obstet Gynecol*. 1997;90(3):453–456.
148. Satagopan JM, Offit K, Foulkes W, et al. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev*. 2001;10(5):467–473.
149. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2002;346(21):1609–1615.
150. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002;346(21):1616–1622.
151. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. *J Natl Cancer Inst*. 1999;91(17):1475–1479.
152. Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. 2007;107(2):159–162.
153. Berek JS, Chalas E, Edelson M, et al. Prophylactic and risk-reducing bilateral salpingo-oophorectomy: recommendations based on risk of ovarian cancer. *Obstet Gynecol*. 2010;116(3):733–743.
154. Buring JE, Hennekens CH. Beta-carotene and cancer chemoprevention. *J Cell Biochem Suppl*. 1995;22:226–230.
155. Howe GR, Hirohata T, Hislop TG, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst*. 1990;82(7):561–569.
156. Van 't Veer P, Kolb CM, Verhoef P, et al. Dietary fiber, beta-carotene and breast cancer: results from a case-control study. *Int J Cancer*. 1990;45(5):825–828.
157. Shankar S, Lanza E. Dietary fiber and cancer prevention. *Hematol Oncol Clin North Am*. 1991;5(1):25–41.
158. Sherman M, Sturgeon S, Brinton L, et al. Endometrial cancer risk factors differ by histopathologic type. (Abstract). *Mod Pathol*. 1995;8:97A.
159. Schlesselman JJ. Oral contraceptives and neoplasia of the uterine corpus. *Contraception*. 1991;43(6):557–559.
160. Oral contraceptive use and the risk of endometrial cancer. The Centers for Disease Control Cancer and Steroid Hormone Study. *JAMA*. 1983;249(12):1600–1604.
161. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer*. 1991;49(2):186–190.
162. Rosenblatt KA, Thomas DB. Hormonal content of combined oral contraceptives in relation to the reduced risk of endometrial carcinoma. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer*. 1991;49(6):870–874.
163. Maxwell GL, Schildkraut JM, Calingaert B, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. *Gynecol Oncol*. 2006;103(2):535–540.
164. Vereide AB, Kaino T, Sager G, et al. Bcl-2, BAX, and apoptosis in endometrial hyperplasia after high dose gestagen therapy: a comparison of responses in patients treated with intrauterine levonorgestrel and systemic medroxyprogesterone. *Gynecol Oncol*. 2005;97(3):740–750.
165. Wang S, Pudney J, Song J, et al. Mechanisms involved in the evolution of progestin resistance in human endometrial hyperplasia—precursor of endometrial cancer. *Gynecol Oncol*. 2003;88(2):108–117.
166. Rodriguez GC, Rimel BJ, Watkin W, et al. Progestin treatment induces apoptosis and modulates transforming growth factor-beta in the uterine endometrium. *Cancer Epidemiol Biomarkers Prev*. 2008;17(3):578–584.
167. Castellsague X, Thompson WD, Dubrow R. Intra-uterine contraception and the risk of endometrial cancer. *Int J Cancer*. 1993;54(6):911–916.
168. Hill DA, Weiss NS, Voigt LF, et al. Endometrial cancer in relation to intra-uterine device use. *Int J Cancer*. 1997;70(3):278–281.
169. Parazzini F, La Vecchia C, Moroni S. Intrauterine device use and risk of endometrial cancer. *Br J Cancer*. 1994;70(4):672–673.
170. Rosenblatt KA, Thomas DB. Intrauterine devices and endometrial cancer. The WHO collaborative study of neoplasia and steroid contraceptives. *Contraception*. 1996;54(6):329–332.
171. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, et al. Reproductive factors of ovarian and endometrial cancer risk in a high fertility population in Mexico. *Cancer Res*. 1999;59(15):3658–3662.
172. Shu XO, Brinton LA, Zheng W, et al. A population-based case-control study of endometrial cancer in Shanghai, China. *Int J Cancer*. 1991;49(1):38–43.
173. Sturgeon SR, Brinton LA, Berman ML, et al. Intrauterine device use and endometrial cancer risk. *Int J Epidemiol*. 1997;26(3):496–500.
174. Hubacher D, Grimes DA. Noncontraceptive health benefits of intrauterine devices: a systematic review. *Obstet Gynecol Surv*. 2002;57(2):120–128.
175. Gardner FJ, Konje JC, Abrams KR, et al. Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: a randomised controlled trial. *Lancet*. 2000;356(9243):1711–1717.
176. Chin J, Konje JC, Hickey M. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev*. 2009. (4):CD007245.
177. Levi F, La Vecchia C, Gulie C, et al. Dietary factors and breast cancer risk in Vaud, Switzerland. *Nutr Cancer*. 1993;19(3):327–335.
178. Potischman N, Swanson CA, Brinton LA, et al. Dietary associations in a case-control study of endometrial cancer. *Cancer Causes Control*. 1993;4(3):239–250.
179. Shu XO, Zheng W, Potischman N, et al. A population-based case-control study of dietary factors and endometrial cancer in Shanghai, People's Republic of China. *Am J Epidemiol*. 1993;137(2):155–165.
180. Barbone F, Austin H, Partridge EE. Diet and endometrial cancer: a case-control study. *Am J Epidemiol*. 1993;137(4):393–403.
181. Zheng W, Kushi LH, Potter JD, et al. Dietary intake of energy and animal foods and endometrial cancer incidence. The Iowa Women's Health Study. *Am J Epidemiol*. 1995;142(4):388–394.
182. Horn-Ross PL, John EM, Canchola AJ, et al. Phytoestrogen intake and endometrial cancer risk. *J Natl Cancer Inst*. 2003;95(15):1158–1164.
183. Shaw PA, Deavers MT, Mills GB. Clinical characteristics of genetically determined ovarian cancer. In: Vogel IVG, ed. *Management of Patients at High Risk for Breast Cancer*. Oxford, UK: Blackwell Science; 2001:94–107.
184. Salazar H, Godwin AK, Daly MB, et al. Microscopic benign and invasive malignant neoplasms and a cancer-prone phenotype in prophylactic oophorectomies. *J Natl Cancer Inst*. 1996;88(24):1810–1820.
185. van Hooen KH, Ramondetta L, Kovatich AJ, et al. Quantitative image analysis of MIB-1 reactivity in inflammatory, hyperplastic, and neoplastic endocervical lesions. *Int J Gynecol Pathol*. 1997;16(1):15–21.
186. Williams GT, Smith CA. Molecular regulation of apoptosis: genetic controls on cell death. *Cell*. 1993;74(5):777–779.
187. Prentice RL, Thomas DB. On the epidemiology of oral contraceptives and disease. *Adv Cancer Res*. 1987;49:285–401.
188. Ness RB, Grisso JA, Vergona R, et al. Oral contraceptives, other methods of contraception, and risk reduction for ovarian cancer. *Epidemiology*. 2001;12(3):307–312.
189. Stanford JL. Oral contraceptives and neoplasia of the ovary. *Contraception*. 1991;43(6):543–556.
190. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol*. 1992;136(10):1184–1203.
191. Gross TP, Schlesselman JJ, Stadel BV, et al. The risk of epithelial ovarian cancer in short-term users of oral contraceptives. *Am J Epidemiol*. 1992;136(1):46–53.

192. Parazzini F, La Vecchia C, Negri E, et al. Oral contraceptive use and the risk of ovarian cancer: an Italian case-control study. *Eur J Cancer*. 1991;27(5):594–598.
193. Rosenberg L, Palmer JR, Zauber AG, et al. A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am J Epidemiol*. 1994;139(7):654–661.
194. Hartge P, Whittemore AS, Itnyre J, et al. Rates and risks of ovarian cancer in subgroups of white women in the United States. The Collaborative Ovarian Cancer Group. *Obstet Gynecol*. 1994;84(5):760–764.
195. The reduction in risk of ovarian cancer associated with oral-contraceptive use. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *N Engl J Med*. 1987;316(11):650–655.
196. Hankinson SE, Colditz GA, Hunter DJ, et al. A quantitative assessment of oral contraceptive use and risk of ovarian cancer. *Obstet Gynecol*. 1992;80(4):708–714.
197. John EM, Whittemore AS, Harris R, et al. Characteristics relating to ovarian cancer risk: collaborative analysis of seven U.S. case-control studies. Epithelial ovarian cancer in black women. Collaborative Ovarian Cancer Group. *J Natl Cancer Inst*. 1993;85(2):142–147.
198. Ness RB, Grisso JA, Klapper J, et al. Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. SHARE Study Group. *Steroid Hormones and Reproductions*. *Am J Epidemiol*. 2000;152(3):233–241.
199. Schildkraut JM, Calingaert B, Marchbanks PA, et al. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst*. 2002;94(1):32–38.
200. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1998;62(3):676–689.
201. Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2001;345(4):235–240.
202. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med*. 1998;339(7):424–428.
203. Rodriguez GC, Walmer DK, Cline M, et al. Effect of progestin on the ovarian epithelium of macaques: cancer prevention through apoptosis? *J Soc Gynecol Investig*. 1998;5(5):271–276.
204. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med*. 1999;106(5):574–582.
205. Nanda K, Bastian LA, Hasselblad V, et al. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol*. 1999;93(5 Pt 2):880–888.
206. Peipins LA, Newman B, Sandler RS. Reproductive history, use of exogenous hormones, and risk of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev*. 1997;6(9):671–675.
207. Potter JD, Bostick RM, Grandits GA, et al. Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study. *Cancer Epidemiol Biomarkers Prev*. 1996;5(10):779–784.
208. Grodstein F, Martinez ME, Platz EA, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Intern Med*. 1998;128(9):705–712.
209. Fernandez E, La Vecchia C, D'Avanzo B, et al. Oral contraceptives, hormone replacement therapy and the risk of colorectal cancer. *Br J Cancer*. 1996;73(11):1431–1435.
210. Martinez ME, Grodstein F, Giovannucci E, et al. A prospective study of reproductive factors, oral contraceptive use, and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 1997;6(1):1–5.
211. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351(9114):1451–1467.
212. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*. 2002;359(9324):2131–2139.
213. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365(9453):60–62.
214. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol*. 2005;23(3):619–629.
215. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. 2003;349(19):1793–1802.
216. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst*. 2005;97(17):1262–1271.
217. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353(26):2747–2757.
218. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. *Ann Oncol*. 2006;17(suppl. 7):vii10–14.
219. Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. *J Clin Oncol*. 2007;25(5):486–492.
220. Jakesz R, Jonat W, Gnani M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet*. 2005;366(9484):455–462.
221. Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011;103(17):1299–1309.
222. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol*. 2010;28(23):3784–3796.
223. Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1996;348(9036):1189–1196.
224. Love RR, Van Dinh N, Quay TT, et al. Survival after adjuvant oophorectomy and tamoxifen in operable breast cancer in premenopausal women. *J Clin Oncol*. 2008;26(2):253–257.
225. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol*. 2001;19(2):343–353.
226. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol*. 2005;23(25):5973–5982.
227. Ingle JN, Krook JE, Green SJ, et al. Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. *J Clin Oncol*. 1986;4(2):178–185.
228. Cuzick J, Ambroisine L, Davidson N, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet*. 2007;369(9574):1711–1723.
229. Munster PN, Moore AP, Ismail-Khan R, et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 2012;30(5):533–538.
230. Beatson CT. Inoperable cases of carcinoma of the mamma. *Lancet*. 1896;162–165.
231. Brueggemeier RW. Update on the use of aromatase inhibitors in breast cancer. *Expert Opin Pharmacother*. 2006;7(14):1919–1930.
232. Thurlimann B, Hess D, Koberle D, et al. Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95—a sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial. *Breast Cancer Res Treat*. 2004;85(3):247–254.
233. Nabholz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women; results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol*. 2000;22(22):3758–3767.
234. Bonnetterre J, Thurlimann B, Robertson JE, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol*. 2000;22(22):3748–3757.
235. Chin YS, Beresford MJ, Ravichandran D, et al. Exemestane after non-steroidal aromatase inhibitors for post-menopausal women with advanced breast cancer. *Breast*. 2007;16(4):436–439.
236. Nabholz JM, Bonnetterre J, Buzdar A, et al. Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. *Eur J Cancer*. 2003;39(12):1684–1689.
237. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in

- postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFFECT. *J Clin Oncol.* 2008;26(10):1664–1670.
238. Carcangiu ML, Chambers JT, Voynick IM, et al. Immunohistochemical evaluation of estrogen and progesterone receptor content in 183 patients with endometrial carcinoma. Part I: Clinical and histologic correlations. *Am J Clin Pathol.* 1990;94(3):247–254.
 239. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Oncol.* 1999;17(6):1736–1744.
 240. Pinelli DM, Fiorica JV, Roberts WS, et al. Chemotherapy plus sequential hormonal therapy for advanced and recurrent endometrial carcinoma: a phase II study. *Gynecol Oncol.* 1996;60(3):462–467.
 241. Thigpen T, Brady MF, Homesley HD, et al. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2001;19(2):364–367.
 242. Moore TD, Phillips PH, Nerenstone SR, et al. Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. *J Clin Oncol.* 1991;9(6):1071–1088.
 243. Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004;92(1):10–14.
 244. Pandya KJ, Yeap BY, Weiner LM, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). *Am J Clin Oncol.* 2001;24(1):43–46.
 245. Whitney CW, Brunetto VL, Zaino RJ, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004;92(1):4–9.
 246. Gadducci A, Cosio S, Genazzani AR. Old and new perspectives in the pharmacological treatment of advanced or recurrent endometrial cancer: hormonal therapy, chemotherapy and molecularly targeted therapies. *Crit Rev Oncol Hematol.* 2006;58(3):242–256.
 247. Burke TW, Walker CL. Arzoxifene as therapy for endometrial cancer. *Gynecol Oncol.* 2003;90(2 Pt 2):S40–S46.
 248. McMeekin DS, Gordon A, Fowler J, et al. A phase II trial of arzoxifene, a selective estrogen response modulator, in patients with recurrent or advanced endometrial cancer. *Gynecol Oncol.* 2003;90(1):64–69.
 249. Rose PG, Brunetto VL, VanLe L, et al. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2000;78(2):212–216.
 250. Ma BB, Oza A, Eisenhauer E, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers—a study of the National Cancer Institute of Canada Clinical Trials Group. *Int J Gynecol Cancer.* 2004;14(4):650–658.
 251. Fujimoto J, Ichigo S, Hori M, et al. Progestins and danazol effect on cell-to-cell adhesion, and E-cadherin and alpha- and beta-catenin mRNA expressions. *J Steroid Biochem Mol Biol.* 1996;57(5–6):275–282.
 252. Ueda M, Fujii H, Yoshizawa K, et al. Effects of sex steroids and growth factors on migration and invasion of endometrial adenocarcinoma SNG-M cells in vitro. *Jpn J Cancer Res.* 1996;87(5):524–533.
 253. Soh E, Sato K. Clinical effects of danazol on endometrial hyperplasia in menopausal and postmenopausal women. *Cancer.* 1990;66(5):983–988.
 254. Covens A, Brunetto VL, Markman M, et al. Phase II trial of danazol in advanced, recurrent, or persistent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2003;89(3):470–474.
 255. Covens AL, Filiaci V, Gersell D, et al. Phase II study of fulvestrant in recurrent/metastatic endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011;120(2):185–188.
 256. Kokka F, Brockbank E, Oram D, et al. Hormonal therapy in advanced or recurrent endometrial cancer. *Cochrane Database Syst Rev.* 2010;(12):CD007926.
 257. von Minckwitz G, Loibl S, Brunnert K, et al. Adjuvant endocrine treatment with medroxyprogesterone acetate or tamoxifen in stage I and II endometrial cancer—a multicentre, open, controlled, prospectively randomised trial. *Eur J Cancer.* 2002;38(17):2265–2271.
 258. Montz FJ, Bristow RE, Bovicelli A, et al. Intrauterine progesterone treatment of early endometrial cancer. *Am J Obstet Gynecol.* 2002;186(4):651–657.
 259. Ramirez PT, Frumovitz M, Bodurka DC, et al. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. *Gynecol Oncol.* 2004;95(1):133–138.
 260. *Abstracts/Gynecol Oncol.* 2012;125(suppl. 1):S3–S9.
 261. Rao GG, Miller DS. Hormonal therapy in epithelial ovarian cancer. *Expert Rev Anticancer Ther.* 2006;6(1):43–47.
 262. Rao BR, Sloman B. Endocrine role in ovarian cancer. *Cancer.* 1996;3:309–326.
 263. Munstedt K, Steen J, Knauf AG, et al. Steroid hormone receptors and long term survival in invasive ovarian cancer. *Cancer.* 2000;89(8):1783–1791.
 264. Schwartz PE, GDMW. The role of hormonal therapy in the management of ovarian cancer. In: Gershenson DM, McGuire WP, eds. *Ovarian Cancer: Controversies in Management.* Edinburgh, UK: Churchill Livingstone; 1998:325–341.
 265. Ahlgren JD, Ellison NM, Gottlieb RJ, et al. Hormonal palliation of chemoresistant ovarian cancer: three consecutive phase II trials of the Mid-Atlantic Oncology Program. *J Clin Oncol.* 1993;11(10):1957–1968.
 266. Gennatas C, Dardoufas C, Karvouni H, et al. Phase II trial of tamoxifen in patients with advanced epithelial ovarian cancer. *Proc Am Soc Clin Oncol.* 1996;15:782.
 267. Hamerlynck JV, Vermorken JB, Van der Burgh ME. Tamoxifen therapy in advanced ovarian cancer (abstract). *Proc Am Soc Clin Oncol.* 1985;4:115.
 268. Hatch KD, Beecham JB, Blessing JA, et al. Responsiveness of patients with advanced ovarian carcinoma to tamoxifen. A gynecologic oncology group study of second-line therapy in 105 patients. *Cancer.* 1991;68(2):269–271.
 269. Jager W, Sauerbrei W, Beck E, et al. A randomized comparison of triptorelin and tamoxifen as treatment of progressive ovarian cancer. *Anticancer Res.* 1995;15(6B):2639–2642.
 270. Landoni F, Bonazzi C, Regallo M, et al. Antiestrogen as last-line treatment in epithelial ovarian cancer. *Chemioterapia.* 1985;4(suppl. 2):S1059–S1060.
 271. Trope C, Marth C, Kaern J. Tamoxifen in the treatment of recurrent ovarian carcinoma. *Eur J Cancer.* 2000;36(suppl. 4):S59–S61.
 272. Osborne RJ, Malik ST, Slevin ML, et al. Tamoxifen in refractory ovarian cancer: the use of a loading dose schedule. *Br J Cancer.* 1988;57(1):115–116.
 273. Pagel J, RCTSHI. Treatment of advanced ovarian carcinoma with tamoxifen: a phase II trial (abstract). *Proc 2nd Eur Conf Clin Oncol.* 1983;42.
 274. Quinn MA. *Hormonal Therapy of Ovarian Cancer.* London: Royal College of Obstetricians and Gynaecologists; 1987:383–393.
 275. Rolski J, Pawlicki M. Evaluation of efficacy and toxicity of tamoxifen in patients with advanced chemotherapy resistant ovarian cancer. *Ginekol Pol.* 1998;69:586–589.
 276. Rowland K, Bonomi P, WGYEGJDC. Hormone receptors in ovarian cancer (abstract C-456). *Proc Am Soc Clin Oncol.* 1985;4:117.
 277. Schwartz PE, Chambers JT, Kohorn EI, et al. Tamoxifen in combination with cytotoxic chemotherapy in advanced epithelial ovarian cancer. A prospective randomized trial. *Cancer.* 1989;63:1074–1078.
 278. Shirey DR, Kavanagh JJ Jr, Gershenson DM, et al. Tamoxifen therapy of epithelial ovarian cancer. *Obstet Gynecol.* 1985;66(4):575–578.
 279. Slevin ML, Harvey VJ, Osborne RJ, et al. A phase II study of tamoxifen in ovarian cancer. *Eur J Cancer Clin Oncol.* 1986;22(3):309–312.
 280. Van Der Velden J, Gitsch G, Wain GV, et al. Tamoxifen in patients with advanced epithelial ovarian cancer. *Int J Gynecol Cancer.* 1995;5(4):301–305.
 281. van der Vange N, Gregg S, Burger CW, et al. Experience with hormonal therapy in advanced epithelial ovarian cancer. *Acta Oncol.* 1995;34(6):813–820.
 282. Weiner SA, Alberts DS, Surwit EA, et al. Tamoxifen therapy in recurrent epithelial ovarian carcinoma. *Gynecol Oncol.* 1987;27(2):208–213.
 283. Perez-Gracia JL, Carrasco EM. Tamoxifen therapy for ovarian cancer in the adjuvant and advanced settings: systematic review of the literature and implications for future research. *Gynecol Oncol.* 2002;84(2):201–209.
 284. Gershenson DM, Sun CC, Iyer RB, et al. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. *Gynecol Oncol.* 2012;125(3):661–666.
 285. Paskeviciute L, Roed H, Engelholm A. No rules without exception: a long-term complete remission observed in a study using a LH-RH agonist in platinum-refractory ovarian cancer. *Eur J Cancer.* 2002;38(suppl. 6):S73.
 286. Emons G, Ortmann O, Teichert HM, et al. Luteinizing hormone-releasing hormone agonist triptorelin in combination with cytotoxic chemotherapy in patients with advanced ovarian carcinoma. A prospective double blind randomized trial. *Deceptepl Ovarian Cancer Study Group.* *Cancer.* 1996;78(7):1452–1460.
 287. Argenta PA, Thomas SG, Judson PL, et al. A phase II study of fulvestrant in the treatment of multiply-recurrent epithelial ovarian cancer. *Gynecol Oncol.* 2009;113(2):205–209.
 288. Smyth JF, Gourley C, Walker G, et al. Anti-estrogen therapy is active in selected ovarian cancer cases: the use of letrozole in estrogen receptor-positive patients. *Clin Cancer Res.* 2007;13(12):3617–3622.
 289. Thigpen T, Blessing J, DiSaia P, et al. Oral medroxyprogesterone acetate in advanced or recurrent endometrial carcinoma: results of therapy and correlation with estrogen and

- progesterone receptor levels—the gynecologic oncology group experience. In: Baulier E, Iacobelli S, McGuire W, eds. *Endocrinology and Malignancy*. Pearl River, NY: Parthenon Publishers; 1986. p. 446–454.
290. Rendina GM, Donadio C, Fabri M, et al. Tamoxifen and medroxyprogesterone therapy for advanced endometrial carcinoma. *Eur J Obstet Gynecol Reprod Biol*. 1984;17(4):285–291.
 291. Gallagher CJ, Oliver RT, Oram DH, et al. A new treatment for endometrial cancer with gonadotrophin releasing-hormone analogue. *Br J Obstet Gynaecol*. 1991;98(10):1037–1041.
 292. Asbury RF, Brunetto VL, Lee RB, et al. Goserelin acetate as treatment for recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Am J Clin Oncol*. 2002;25(6):557–560.
 293. Trope C, Marth C, Kaern J. Tamoxifen in the treatment of recurrent ovarian carcinoma. *Eur J Cancer*. 2000;36(suppl. 4):S59–S61.
 294. Landoni F, Bonazzi C, Regallo M, et al. Antiestrogen as last-line treatment in epithelial ovarian cancer. *Chemioterapia*. 1985;4(suppl. 2):1059–1060.
 295. Gennatas C, Dardoufas C, Karvouni H, et al. Phase II trial of tamoxifen in patients with advanced epithelial ovarian cancer. *Proc Am Soc Clin Oncol*. 1996;15:782.
 296. Rolski J, Pawlicki M. Evaluation of efficacy and toxicity of tamoxifen in patients with advanced chemotherapy resistant ovarian cancer. *Ginekol Pol*. 1998;69(7):586–589.
 297. Quinn MA. *Hormonal Therapy of Ovarian Cancer*. London: Royal College of Obstetricians and Gynaecologists. 1987;383–393.
 298. Pagel J, RCTSHI. Treatment of advanced ovarian carcinoma with tamoxifen: a phase II trial (abstract). *Proc 2nd Eur Conf Clin Oncol*. 1983;42.
 299. Hamerlynck JM, Vermorken JB, Van der Burgh ME. Tamoxifen therapy in advanced ovarian cancer (abstract). *Proc Am Soc Clin Oncol*. 1985;4:115.
 300. Rowland K, Bonomi P, WGYEGJDC. Hormone receptors in ovarian cancer (abstract C-456). *Proc Am Soc Clin Oncol*. 1985;4:117.

Clinical Trials Methodology and Biostatistics

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Issues involved in the design, conduct, and analyses of clinical trials are presented in this chapter. Phase 1, 2, and 3 trials are presented, as well as screening trials. Statistical jargon and mathematical notation are avoided wherever possible. Studies from the field of gynecologic oncology are used as examples in order to illustrate specific points. This chapter is an overview of these very expansive topics. Details concerning the design, conduct, and analysis of clinical trials can be found in books dedicated to this subject, such as Piantadosi (2005) (1), Green et al. (2003) (2).

This chapter begins with some historical snippets in order to provide a sense of how the concepts of clinical trials evolved and matured from an intuition-based practice of medicine to the more sophisticated evidence-based medicine used today. The procedures for designing, conducting, and analyzing clinical trials continue to mature as the demand for evidence-based medicine increases. Next, a general system of classifying study designs is presented. The subsequent sections in this chapter describe the components of a clinical trial and essential considerations for developing new trials. Since translational research objectives are incorporated into many modern cancer trials, some issues related to design and analyses of these components are also considered.

HISTORICAL PERSPECTIVE

Clinicians make treatment recommendations daily. These recommendations arise from culling information from standardized clinical guidelines, published reports, expert opinion, or personal experiences. The synthesis of information from these sources into a particular recommendation for an individual patient is based on a clinician's personal judgment. But what constitutes reliable and valid information worthy of consideration? Clinicians have long recognized that properly planned and conducted clinical trials are important sources of empirical evidence for shaping clinical judgment.

The Greek physician Hippocrates in the 5th century BCE had a profound influence in freeing medicine from superstition. He rejected the notion that the cause of an individual's disease had a divine origin. Rather, he postulated that diseases originated from natural causes that could be determined from observing environmental factors like diet, drinking water, or local weather. He also proposed the revolutionary concept that a physician could anticipate the course of a disease after carefully observing

a sufficient number of cases. Despite these insights, medicine all too frequently continued to consist of a mixture of herbal concoctions, purging, bloodletting, and astrology.

In the Middle Ages, Avicenna (980–1037 CE) wrote *Canon of Medicine*, a work considered to be the pre-eminent source of medical and pharmaceutical knowledge of its time. In his writings Avicenna proposed some rules for testing clinical interventions. First, he pointed to the need to experiment in humans, since “testing a drug on a lion or horse might not prove anything about its effect on man.” Also, he described the basic experiment as observing pairs of individuals with uncomplicated but similar forms of the disease. Finally, he emphasized the need for careful observation of the times of an intervention and then reporting the reproducibility of its effects (3). Despite these insights, his *Canon of Medicine* does not include any specific reports of clinical experimentation.

Early trials frequently lacked concurrent comparison groups. For example, Lady Mary Wortley-Montague in 1721 urged King George I to commute the sentences of 6 inmates from the Newgate prison if they agreed to participate in a smallpox inoculation trial (3). The prisoners were inoculated with smallpox matter from a patient with a naturally occurring form of the disease. Since these individuals remained free of smallpox, this finding was considered to be evidence supporting treatment by inoculation. Later, however, the results of this trial were considered less compelling, when it was discovered that some of the inmates might have been exposed to smallpox prior to the trial (4). Without a proper control group, it can be difficult to interpret the efficacy of an intervention. There are frequently many factors, both known and unknown, that influence an individual's outcome.

Subjective assessments from either the subject or the practitioner may also influence the interpretability of a trial. In the late 18th century, the King of France selected Benjamin Franklin to head a royal commission to investigate the physician Franz Mesmer's claims that he could promote good health by manipulating a force he called “animal magnetism” (5). Franklin devised several ingenious experiments in which the subjects were blindfolded and not told whether or not they were receiving Mesmer's treatment. These trials led Franklin to conclude that the therapeutic effects of mesmerism were due to imagination and illusion. Several years later, John Haygarth demonstrated the importance of controlling for assessment biases. At that time, magnetic healing rods were commonly used to relieve pain due to chronic rheumatism (4). Haygarth treated 5 patients on 2 consecutive days, once with sham wooden rods and once with genuine magnetic rods. He noted that 4 individuals reported pain relief and 1 experienced no relief, regardless of which rods were used. Franklin's and Haygarth's trials established the importance of implementing experimental procedures aimed at removing subjectivity from the assessment of treatment effects.

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It had long been appreciated that there is a potential for misguided inference about the effectiveness of a treatment when the comparison involves a group with a dissimilar prognosis. The apparent benefits attributed to a new treatment might in fact be biases due to prognostic differences in patients between treatment groups. One of the earliest clinical trials to attempt to address this bias was reported in 1898 by Johannes Fibiger (6). Four hundred and eighty-four patients admitted to his clinic with diphtheria were given either standard care or diphtheria serum twice daily. In order to disassociate the mode of treatment from the individual's prognosis, the patient's treatment was to be determined by the day of clinic admission, and it alternated from day to day (7). Using this type of procedure to disassociate prognosis from treatment is only partially effective, since the practitioner or the subject knew which treatment would be applied, and this knowledge may have influenced the individual's decision to participate in the study. Therefore, masking the treatment assignment so that it cannot be part of the decision to participate in the trial is important for controlling this source of selection bias.

Treatment randomization in agricultural trials was performed as early as 1926 (8). However, it was not until the 1940s when Corwin Hinshaw (9), using a coin toss, and later Bradford Hill (10), using random numbers in sealed envelopes, established the methodologic importance of randomizing treatments in clinical trials. Balancing the unpredictable and spontaneous remissions exhibited by some patients with pulmonary tuberculosis motivated Amberson (8) and later Hinshaw (9). While methodologic principles motivated Hill, the short supply of streptomycin after World War II provided the opportunity to use randomization as an equitable way to distribute the drug (11).

One of the first randomized clinical trials in the study of gynecologic malignancies was initiated in 1948 (12). This trial compared ovarian irradiation to standard treatment for breast cancer. Initially, shuffled sealed envelopes were used to designate treatment. However, this procedure was later changed due to administrative difficulties so that treatment depended on the woman's date of birth. This later procedure is susceptible to the same selection bias mentioned in Fibiger's trials, since the treatments were not masked.

Despite these methodological advances, the inadequate justification for selecting one medical procedure over another led one contemporary physician to express his frustration:

Early in my medical career I was appalled at the 'willy-nilly' fashion by which treatment regimens slipped in and out of popularity. How many operations that I was trained to do or medicines that I was instructed to give because of somebody's conviction they were beneficial passed into oblivion for no apparent reason, only to be replaced by others of equally dubious worth? (13)

The first randomized clinical trial at the National Cancer Institute (NCI) was begun in 1955 (14). This trial involved 65 evaluable patients with acute leukemia from 4 different institutions. The trial incorporated many elements that should be part of any modern clinical trial: uniform criteria for response assessment, a randomized comparison of at least 2 treatment regimens, and a complete accounting of all patients entered. The published report included considerations for such issues as patient selection bias and the study's impact on the patient's welfare (15). The first NCI randomized clinical trial in solid tumors followed shortly thereafter and was organized by the Eastern Group for Solid Tumor Chemotherapy (16). By 2010, there were 12 NCI-sponsored cooperative groups conducting clinical trials and the annual funding for these groups was \$163 million dollars (17).

In the late 1950s, most patients with gynecologic cancers were included incidentally in small trials to screen new agents for broad-range activity. The first NCI-sponsored group to organize

trials specifically for gynecologic malignancies was the Surgical Ovarian Adjuvant Group. This group was formed in the late 1950s, initiated a few trials, and then disbanded in 1964. Starting in 1963, the Surgical Endometrial Adjuvant Group was one of the earliest efforts toward a multidisciplinary group. This multidisciplinary cooperative group included gynecologic surgeons, medical oncologists, pathologists, radiation oncologists, and biostatisticians. It was from this group that the Gynecologic Oncology Group (GOG) was eventually formed in 1970 to deal with a broader range of gynecologic malignancies (18). Over the following 10 years, the field of gynecologic oncology matured. Board certification procedures for gynecologic oncologists were developed, fellowship programs were initiated in the comprehensive cancer centers, and a professional Society of Gynecologic Oncologists was organized in 1969.

Classification of Study Designs

In general, a clinical trial is any experiment involving human subjects that evaluates an intervention that attempts to reduce the impact of a specific disease in a particular population. When an intervention is applied in order to prevent the onset of a particular disease, the trial is classified as a primary prevention trial. For example, a primary prevention trial may evaluate healthy lifestyles or a vitamin supplement in a population of individuals who are considered to be at risk for a particular disease. Secondary prevention trials evaluate interventions that are applied to individuals with early stages of a disease in order to reduce their risk of progressing to more advanced stages of the disease. Tertiary intervention trials are aimed at evaluating interventions that reduce the risk of morbidity or mortality due to a particular disease.

Clinical trials that evaluate methods for detecting a disease in a preclinical state are called screening trials. Early detection may mean diagnosing a malignancy in an early stage (e.g., the use of mammography in the detection of breast cancer) or in a premalignant state (e.g., the use of Papanicolaou smear in the detection of cervical intraepithelial neoplasia). There are typically 2 interventions in a screening trial. The first intervention is the screening program (e.g., annual mammograms), which involves individuals who appear to be free of the disease. However, once the disease is detected in an individual, a secondary intervention (e.g., surgery) is performed in hopes of stopping the disease from progressing to more advanced stages. Consequently, screening trials require *both* interventions to be effective. An effective screening procedure is useless if the secondary intervention does not alter the course of the disease. On the other hand, an ineffective screening procedure would cause the secondary intervention to be applied indiscriminately.

Nonexperimental studies (or observational studies) can be classified into 3 broad design categories: cohort (or prospective), case-control (or retrospective), and cross-sectional. In a cohort study, individuals are initially identified according to their exposure status, which can include environmental, genetic, lifestyle, or therapeutic treatment factors. These individuals are then followed in order to determine who develops the disease. The aim of these studies is to assess whether the exposure is associated with the incidence of the disease under study. This design is in contrast to the case-control study, which identifies individuals on the basis of whether they have the disease and then measures and compares their exposure histories. Measuring exposure may be as simple as questioning the individuals about their personal or employment history, or it may involve a more sophisticated assessment such as analyzing the individual's biologic specimens for markers of exposure. Though the case-control study is susceptible to several methodological flaws, it has the advantage of often being less expensive, easier, and quicker to perform than a cohort study, especially when the disease is rare. The power of the case-control design is apparent

from a review of the case-control studies published between 1975 and 1985(19), which demonstrated the deleterious effects of exogenous estrogens in perimenopausal women. Finally, the goal of the cross-sectional study is to describe the prevalence of a disease and an exposure in a population during a specific period of time. These studies can often be conducted more quickly than either the cohort or case-control study, but they are often not used when the time between exposures and the disease onset is long, as it is for cancer.

Components of a Clinical Trial

Objectives

In clinical oncology research, where the disease is often fatal, the ultimate purpose of a research program is to develop a treatment plan that puts the patients into a disease-free state, reduces the risk of cancer recurrence, and allows patients to return to their normal lifestyle within a reasonable period of time. The objectives of a particular clinical trial are often more specific and less grandiose. A clinical trial attempts to answer a precisely defined set of questions with respect to the effects of a particular treatment(s) (20). These questions (objectives) form the foundation upon which the rest of the trial is built. The study objective typically incorporates 3 elements: the interventions to be evaluated, the “yardstick” to be used to measure treatment benefit (see Endpoints), and a brief description of the target population (see Eligibility Criteria). These 3 elements (i.e., “what,” “how,” and “who”) should be stated in the most precise, clear, and concise terms possible.

The choice of experimental therapy to be evaluated in a randomized clinical trial is not always easy. Both a plethora of new therapies and the absence of innovative concepts make for difficult choices. The former is problematic since many malignancies in gynecologic oncology are relatively uncommon. Definitive clinical trials may require 4 to 5 years to accrue a sufficient number of patients even in a cooperative group setting. This time-frame limits the number of new therapies that can be evaluated. The absence of new therapies is a problem since substantial increases in patient benefit are less likely to be observed in trials that merely alter doses or schedules of already acceptable therapies. An open dialogue among expert investigators remains the most effective approach for establishing the objectives of any clinical trial.

Endpoints

The endpoint of a trial is some measurable entity in the patient’s disease process that can be used to assess the effectiveness of an intervention. A study may assess more than 1 endpoint, but in these instances the endpoint of primary interest should be clearly specified or else the study design should carefully reflect the complexity of interpreting multiple outcomes. Endpoints can be a composite measure of multiple outcomes. For instance, some studies assessing quality of life aggregate patient reported scores from several related items or domains that are all considered components of a larger concept called quality of life.

Selecting endpoints that will reflect the effectiveness of an experimental therapy is not always obvious. First, endpoints should be a valid (unbiased) measure of the treatment effect on the disease process. Endpoints that are susceptible to a systematic error that favors one treatment lead to biased estimates of the treatment’s effect. For instance, trials assessing time to disease progression, in which the schedule for CT scans is different for each treatment group, are susceptible to this assessment bias. This problem is not uncommon in studies comparing two different modalities such as chemotherapy and radiation therapy. Second, the measurement of an endpoint should be reliable and not

susceptible to subjective interpretation. In some cases clinical response can be considered unreliable, since it is not uncommon for experts to disagree when interpreting the same radiograms (21). Third, endpoints that are directly relevant to the patient are preferable, although valid surrogate endpoints are considered indirectly relevant to the patient. Finally, endpoints which are not too expensive or inconvenient for the patient are preferred. It is not always possible for a single endpoint to exhibit all of these characteristics simultaneously. For example, avoiding death is extremely relevant to a patient with a lethal disease like advanced gynecologic cancer. Also, survival can be measured very reliably. However, most cancer patients will not only receive the treatments prescribed by the study, but, after exhibiting signs of disease progression, they also receive other anticancer therapies. In this case, the validity of overall survival comparisons is suspected since they not only reflect the effects of the study treatment, but also the effects of other therapies that are external to the study. For example, a meta-analysis of those trials comparing the survival of patients, who were randomized to nonplatinum versus platinum regimens for the treatment of advanced ovarian cancer, concluded that these trials appear to have underestimated the true effect of platinum on survival. The reason is that many patients who were not randomized to the platinum regimen eventually received platinum treatment (22). For this reason, progression-free survival (PFS) is often considered a reasonable endpoint in those trials, since it is unaffected by subsequent therapies (23). Nevertheless, some authors have argued that survival remains an important endpoint to be assessed in Phase III trials, even when active second-line treatments are available (24). Moreover, overall survival remains the recommended preferred endpoint in trials that explicitly compare a strategy of immediate treatment versus delayed treatment for advanced stage disease.

Endpoints may be classified as categorical (e.g., clinical response), continuous (e.g., serum CA-125 values) or time-to-event (e.g., survival time). A time-to-event endpoint includes both time (a continuous measure) and censoring status (categorical measure). The data type influences the methods of analysis.

Measurement Errors

The susceptibility of an outcome to measurement errors is an important consideration when choosing an endpoint. Both random and systematic errors are components of measurement error. Random error refers to that part of the variation that occurs among measurements that is not predictable, and appears to be due to chance alone. For example, a serum sample could be divided into 10 aliquots and submitted to the laboratory for CA-125 determinations. If the laboratory returns nearly the same value for each aliquot, then the associated random error is low, and the measurement may be deemed reproducible. On the other hand, if the CA-125 values vary considerably among aliquots, perhaps due to inconsistent laboratory procedures, then individual values may be considered unreliable. In this case, taking the average CA-125 measurement across all 10 aliquots is expected to be a better estimate of the patient’s true CA-125 value than any single measurement.

Concern for reliability is one of the reasons for incorporating several items into a quality of life questionnaire. Quality of life is a complex entity and no single question can be expected to reliably measure it. A measurement of an individual’s quality of life is therefore typically composed from an individual’s responses to several items that are all considered to be associated with quality of life. Indeed, one step toward demonstrating the usefulness of any quality of life instrument is to show that it provides reproducible results when assessing individuals under the same conditions (25).

Systematic error, also called bias, refers to deviations from the true value that occur in a systematic fashion. For example,

suppose an investigator initiates a randomized clinical trial comparing two treatments with time to disease progression being the primary endpoint. The protocol indicates that the patient should be assessed after each cycle of therapy. However, suppose that a cycle duration is 2 weeks for one treatment group, and 4 weeks for the other treatment group. Using a more intense assessment schedule for 1 treatment group would tend to detect failures earlier in that group. Therefore, the time-to-failure comparison between treatments would systematically favor the second treatment group.

When there are recognized sources of error, it is important that the study design implement procedures to avoid or minimize their effect. For example, random error in many cases can be accommodated by either increasing the number of individuals in the study, or in some cases by increasing the number of assessments performed on each individual. Systematic measurement error cannot be addressed by increasing the sample size. In fact, increasing the sample size may exacerbate the problem since small systematic errors in large comparative trials contribute to the chances of erroneously concluding that the treatment effect is “significant.” The approaches to controlling sources of systematic error tend to be procedural. For example, treatment randomization is used to control selection bias, placebos are used to control observer bias, standardized assessment procedures and schedules are used to control measurement bias, and stratified analyses are used to control biases due to confounding. For an extensive description of biases that can occur in analytic research see Sackett, 1979 (26).

Surrogate Endpoints

Surrogate endpoints do not necessarily have direct clinical relevance to the patient. Instead, surrogate endpoints are intermediate events in the etiologic pathway to other events that are directly relevant to the patient (27). The degree to which a treatment’s effect on a surrogate endpoint predicts the treatment’s effect on a clinically relevant endpoint is a measure of the surrogate’s validity. The ideal surrogate endpoint is an observable event that is a necessary and sufficient precursor in the causal pathway to a clinically relevant event. Additionally, the treatment’s ability to alter the surrogate endpoint must be directly related to its impact on the true endpoint. It is important that the validity and reliability of a surrogate endpoint be established with appropriate analyses and not simply presupposed (28,29). Surrogate endpoints are sometimes justified on the basis of an analysis that demonstrates a statistical correlation between the surrogate event and a true endpoint. However, while such a correlation is a necessary condition, it is not a sufficient condition to justify using a particular surrogate as an endpoint in a clinical trial. For example, CA-125 levels following 3 cycles of treatment of ovarian cancer have been shown to be associated with the subsequent overall survival (30). Women with newly diagnosed ovarian cancer whose serum CA-125 levels normalize at the end of 3 cycles of standard treatment tend to survive longer than those who have abnormal levels. However, it has not (yet) been demonstrated that the degree to which any particular treatment reduces CA-125 levels reliably predicts its effects on clinically relevant endpoints, like overall survival.

The most frequently cited reasons for incorporating surrogate endpoints into a study include reduction in study size and duration, decreased expense, and convenience.

Primary Endpoints in Gynecologic Oncology Treatment Trials

The Food and Drug Administration (FDA) organized a conference to consider endpoints for trials involving women diagnosed with advanced ovarian cancer (31). Meta-analyses were presented, which indicate that PFS can be considered a valid

endpoint for trials involving women with advanced ovarian cancer. It is important to recognize that while the general validity of PFS for predicting overall survival in this patient population has been established, PFS comparisons in a particular study can be biased. One source of bias arises from using different disease assessment schedules for each treatment group either intentionally or unintentionally. Delaying assessments for 1 treatment group artificially increases the apparent time to progression. Survival time is generally not susceptible to this source of bias.

Progression-free interval (PFI) may be a reasonable endpoint in trials involving patients with early or locally advanced cancer. PFI should be distinguished from PFS. The difference resides in how patients, who die without any evidence of disease progression are handled in the analysis. Patients who die without evidence of progression are censored at the time of their death in a PFI analysis, but considered an uncensored event in a PFS analysis. If deaths due to non-cancer-related causes are common, then selecting PFI as the study endpoint will generally increase the study’s sensitivity for detecting active treatments. In this case, however, the analysis needs to consider procedures that will account for treatment-related deaths, which may occur prior to disease recurrence. Simply censoring the time to recurrence in these cases can make very toxic treatments appear more effective than they actually are.

There have been a number of studies that provided evidence that a new treatment increases the duration of PFS, but not overall survival. For example, OVAR 2.2, a second-line treatment trial involving patients with platinum-sensitive ovarian cancer, indicated that carboplatin and gemcitabine significantly decreased the hazard of first progression or death (PFS) 28% (hazard ratio = 0.72, $p = 0.003$) when compared to carboplatin alone (32). However, there was no appreciable difference between the treatment groups with regard to the duration of overall survival (hazard ratio = 0.96, $p = 0.735$). Also, 3 trials evaluating maintenance bevacizumab for first- and second-line treatment of ovarian cancer reported significant prolongation in the duration of PFS (33–35), but no difference in overall survival. Therefore, while PFS may be a good surrogate for overall survival, it appears to be susceptible to a small but not insignificant chance of false-positive prediction. It is noteworthy, however, that results from PFS seldom lead to false-negative predictions. In other words, it is very rare for the results of an oncology trial to indicate that a new treatment prolongs overall survival but does not delay the onset of recurrence or progression. It seems reasonable to expect that an anticancer treatment that prolongs survival should exert its influence by delaying the onset of new or increasing disease. This has prompted some investigators to recommend using both PFS and overall survival as trial endpoints (36–38). Specifically, trials involving patients with advanced-stage cancer are designed to assess overall survival in the final analysis, but PFS is monitored at scheduled interim analyses. If the trial’s evolving evidence indicates that there is insufficient PFS benefit, then the trial may be stopped early and concluded that the treatment has insufficient activity to warrant further investigation in the target population. This procedure tends to halt trials of inactive treatments early, but continues trials of active agents to completion.

Response (disease status) assessed via reassessment laparotomy following treatment has been proposed for use as a study endpoint in ovarian cancer trials (39). The justification is that patients with no pathologic evidence of disease are more likely to experience longer survival than those with evidence of disease. The principal drawback to this endpoint is that reassessment laparotomy is a very onerous procedure for the patient, and many patients refuse reassessment surgery, or the surgery may become medically contraindicated. Even among highly motivated and very persuasive investigators the percent of patients not reassessed is typically greater than 15%. These missing evaluations can significantly undermine the interpretability of a study.

To date, PFS has not been formally validated for use in trials involving patients with advanced cervical, endometrial, or vulvar cancers. In the absence of a formally validated endpoint, overall survival or symptom relief are reasonable endpoints. Since relief from symptoms is susceptible to assessment bias, trials utilizing this endpoint should use validated instruments (See Measurement Errors) and consider blinding the study treatments whenever possible.

The endpoint selection for trials involving patients with recurrent cervical cancer has been controversial. Historically, some trials have been designed with clinical response as the primary endpoint. However, survival is a preferable primary endpoint. The rationale for this choice arises from the observation that treatments that have demonstrated an improvement in the frequency of response have not consistently prolonged survival (40–42). While subsequent therapies may have distorted the cause-effect relationship, the effect is probably at best minimal since there are no known treatments that have consistently demonstrated an ability to influence the survival time of patients with advanced or recurrent cervical cancer.

In summary, the ideal endpoint provides reasonable assurance that inference about the causal relationship between the intervention and the endpoint is valid. It is either itself clinically relevant to the patient, or predictive of a clinically relevant outcome. The ideal endpoint can be measured reliably. It should be convenient and cost-effective to measure. Unfortunately, in some trials, these features are not always available simultaneously. If a surrogate endpoint is used, then its validity should be established, not presumed.

Eligibility Criteria

The eligibility criteria serve 2 purposes in a clinical trial. The immediate purpose is to define those patients with a particular disease, clinical history, and personal and medical characteristics that may be considered for enrollment in the clinical trial. The subsequent purpose of eligibility criteria comes after the clinical trial is completed and the results are available. Physicians must then decide whether the trial results are applicable to their particular patient. A physician may consider the trial results to be applicable when the patient meets the eligibility criteria of the published study. Unfortunately, this principle is problematic. The necessary sampling procedure for selecting patients for the study (i.e., a random sample of all eligible patients) is never actually applied in clinical trials. Therefore, extrapolation of study results becomes an inherent part of medical practice.

Within the general population, there is a target population that includes those patients for whom the results of the trial are intended to apply (e.g., advanced endometrial cancer with no prior systemic cytotoxic therapies). While an investigator can typically specify an idealized definition for the target population, additional practical issues also frequently need to be considered. For example, there are varying opinions about whether patients diagnosed with an adenocarcinoma of the fallopian tube or primary peritoneal cancer in studies which target the treatment of patients with adenocarcinomas of the ovary. Some clinical investigators will argue for the need to study a “pure” study population and ignore the fact that their treatment decisions for patients with cancers originating in the fallopian tube or peritoneum frequently come from the results of trials involving patients with advanced ovarian cancer. Ideally, the size of a subgroup represented in a study should be in proportion to their presence in the target population. The degree to which a study sample reflects the target population determines the generalizability or external validity of the study results. Eligibility criteria should reflect a concern for the generalizability of the trial results. When clinicians frequently resort to extrapolating the results of a trial to patient groups that were not eligible for the trial, this may be considered a serious indictment of the study’s eligibility criteria.

The ideal situation is when every patient who meets the eligibility criteria of a clinical trial is asked to participate. This is seldom possible since not all physicians, who treat such patients, participate in the study. Also, not all patients wish to be involved in a clinical trial. Impediments in traveling to a participating treatment center further reduce the target population. The source population is the subset of patients in the target population who have access to the study. Figure 17.1 displays common restrictions that can limit the entry of patients to a clinical trial.

Restricted access to the study may contribute a biased sample from the target population, referred to as selection bias. For example, participating investigators at university hospitals might tend to enroll disproportionately more patients with cancer who have undergone very aggressive initial cytoreductive surgeries than their counterparts at community hospitals.

A potentially useful approach for determining the necessity of a particular eligibility criterion is to clearly identify its function. In addition to defining the target population, there are 4 distinct functions that an eligibility criterion may serve: benefit-morbidity equipoise (safety), homogeneity of benefit (scientific), logistic, and regulatory (43).

Eligibility criteria for safety are frequently imposed to eliminate patients for whom the risk of adverse effects from treatment is not commensurate with the potential for benefit. This concern can manifest in two ways. First, in oncology trials, there is often some concern that study treatments may be too toxic for patients with compromised bone-marrow reserves or kidney function. These patients are frequently excluded from trials when the potential benefits of treatment are not consistent with the risk associated with treatment. Second, even otherwise healthy cancer patients may be eliminated from the study when the risks from treatment are considered too great. For example, chemotherapy after hysterectomy is normally considered excessive treatment for a patient with Stage IA cervical cancer, since even without this treatment the risk of relapse is relatively small, but the morbidity of this combined modality following hysterectomy may be substantial. Therefore, eligibility criteria that eliminate these patients can be justified.

Eligibility criteria may be warranted when there is a scientific or biologic rationale for a variation in treatment benefit across patient subgroups. There is no scientific reason to expect that the effect of treatment is entirely the same across all subgroups of patients included in the study. The effect of a new therapy may be expected to have such dramatic inconsistencies across the entire spectrum of the target population that statistical power is compromised (43). One example of this type of exclusion criterion is found in GOG Protocol 152 (A Phase 3 Randomized Study of Cisplatin [NSC#119875] and Taxol [Paclitaxel] [NSC#125973] with Interval Secondary Cytoreduction versus

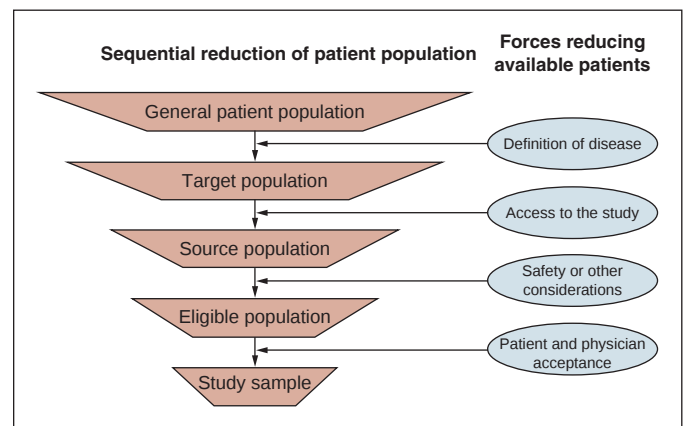


FIGURE 17.1. Sequential reduction of patient population.

Cisplatin and Paclitaxel in Patients with Suboptimal Stage III & IV Epithelial Ovarian Carcinoma). This study was designed to assess the value of secondary cytoreductive surgery in patients with Stage III ovarian cancer. All patients who entered into this study were to receive 3 courses of cisplatin and paclitaxel. After completing this therapy they were then randomized to either 3 additional courses of chemotherapy or interval secondary cytoreductive surgery followed by 3 additional courses of chemotherapy. The eligibility criteria exclude those patients who had only microscopic residual disease following their primary cytoreductive surgery since there is no scientific reason to expect that interval cytoreduction would be of any value to patients with no gross residual disease.

Clinical investigators frequently implement eligibility criteria in order to promote homogeneity in patient prognoses. The desire to attain a study population with homogeneous prognoses is a common reason for excessive eligibility criteria. However, the concept is both unattainable and overemphasized. This notion may arise from an investigator's attempt to duplicate the experimental method conducted in the laboratory. It is standard practice in laboratory experiments on animals to use inbred strains in an effort to control genetic variability. In large-scale clinical trials, this approach seldom has merit in light of the cost to generalizability. Eligibility criteria should be as broad as possible in order to enhance generalizability. For example, GOG Protocol 165 (A Randomized Comparison of Radiation Plus Weekly Cisplatin versus Radiation plus PVI [Protracted Venous Infusion] 5-FU in Patients with Stage II-B, III-B and IV-A Carcinoma of the Cervix) includes patients with no surgical sampling of the paraaortic lymph nodes. Previous GOG trials required sampling of these nodes. However, there is no evidence or sound biological justification to support the notion that the relative treatment benefit depends on the extent of surgical staging. This is not to say whether or not surgical staging is itself beneficial.

Eligibility criteria can be justified on the basis of logistic considerations. For example, a study that requires frequent clinic visits for proper evaluation or toxicity monitoring may restrict patients who are unable to arrange reliable transportation. The potential problem with such a restriction is how it is structured. A criterion requiring that the patient have a car at her disposal is probably too restrictive in a trial of women with advanced cervical cancer, since patients from this target population tend toward poorer socio-economic status (SES) and may not have access to private transportation. Such a restriction erodes the generalizability of the trial by over sampling patients with higher SES and may prolong study accrual. Moreover, complicated eligibility criteria are more likely to function ineffectively. In general complicated eligibility restrictions should be avoided.

Eligibility criteria based on regulatory considerations include institutional and governmental regulations that require a signed and witnessed informed consent and study approval by the local Institutional Review Board. These restrictions are required in most research settings and are not subject to the investigator's discretion.

Currently many biostatisticians believe that eligibility criteria in oncology trials tend to be too restrictive and complicated (43,44). Overly restrictive or complex eligibility criteria hamper accrual, prolong the study's duration, and delay the reporting of results. The Medical Research Council has demonstrated that it is possible to conduct trials with simple and few eligibility criteria (45). The ICON3 (International Collaborative Ovarian Neoplasms) trial compares standard carboplatin or cisplatin adriamycin cyclophosphamide regimen with paclitaxel plus carboplatin in women with newly diagnosed ovarian cancer. This trial has 6 eligibility criteria, 3 of which are for safety: (a) fit to receive, and no clear contraindication to, chemotherapy, (b) Absence of sepsis, and (c) bilirubin less than twice the normal level for the center. This is in sharp contrast to GOG Protocol 162 (A Phase 3 Randomized Trial of Cisplatin [NSC #119875]

with Paclitaxel [NSC #125973] Administered by Either 24-Hour Infusion or 96-Hour Infusion in Patients with Selected Stage III and Stage IV Epithelial Ovarian Cancer), which compares 2 different paclitaxel infusion durations in patients with advanced ovarian cancer and has 34 eligibility criteria.

Phases of Drug Development trials

The traditional approach to identifying and evaluating new drugs has relied on sequential evidence from Phase 1, 2, and 3 clinical trials. Each of these study designs stems from very distinct study objectives. Phase 2 trials build on the evidence gathered from Phase 1 trial results, and similarly Phase 3 trials build on Phase 2 and Phase 1 trial results. The investigation of a given treatment may be halted at any phase, either due to safety and/or efficacy issues. Depending upon the underlying investigation, the time from the initiation of a Phase 1 trial for a given treatment to the completion of a Phase 3 trial often spans several years.

Phase 1 Trials

The purpose of a Phase 1 therapeutic trial in cancer-related research is to determine an acceptable dose or schedule for a new therapy as determined by toxicity and/or pharmacokinetics. A Phase 1 trial marks the first use of a new experimental agent in humans. Most Phase 1 trials escalate the dose or schedule of the new agent after either a pre-specified number of consecutive patients has been successfully treated or within an individual as each dose is determined to be tolerable. The usual Phase 1 trial of a cytotoxic agent attempts to balance the delivery of the greatest dose intensity against an acceptable risk of dose limiting-toxicity (DLT). The conventional approach increases the dose after demonstrating that a small cohort of consecutive patients (3 to 6) is able to tolerate the regimen. However, once an unacceptable level of toxicity occurs (e.g., two or 3 patients experiencing DLT), the previously acceptable dose level is used to treat a few additional patients in order to provide additional evidence that the current dose has an acceptably low risk of DLT. If this dose is still regarded as acceptable, it becomes the dose and schedule studied in subsequent trials and it is referred to as the recommended dose level (RDL). The RDL should not be confused with the maximum tolerated dose (MTD). The MTD is a theoretical concept used to design a Phase 1 trials, while the RDL is an *estimate* of the MTD, which may or may not be accurate. Due to the limited number of patients involved in a Phase 1 trials outcome measures such as response and survival are not the primary interest in these studies. When these outcomes are reported, they are considered anecdotal evidence of treatment activity. Eligibility criteria for Phase 1 trials in oncology often limit accrual to patients in whom conventional treatments have failed.

Alternative strategies for estimating the MTD have been proposed. The primary motivation for these newer strategies is to reduce the number of patients treated at therapeutically inferior doses and to reduce the overall size of the study. One of these alternatives implements a Bayesian approach and is referred to as the continual reassessment method (CRM) (46). It has the attractive feature of determining the dose level for the next patient based on statistically modeling the toxicity experience of the previously treated patients. While the traditional approach has been criticized for treating too many patients at subtherapeutic doses and providing unreliable estimates of the MTD, CRM has been criticized for tending to treat too many patients at doses higher than the MTD (47). Refinements to CRM have been proposed (48) and found to have good properties when compared to alternative dose-seeking strategies (49). Another family of designs termed the accelerated titration design (ATD) allows doses to be escalated within each patient and incorporates toxicity or

pharmacologic information from each course of therapy into the decision of whether to further escalate or not (50). Both the modified CRM and ATD designs can provide significant advantages over the conventional Phase 1 design.

Special Phase I study designs are often recommended for targeted agents. These studies will often incorporate a biomarker endpoint that signals either the activation or deactivation of a targeted pathway. As the dose is increased for small cohorts of individuals, the biomarker is measured and toxicity is monitored simultaneously. Then, statistical models are used to determine a safe dose where the targeted pathway is consistently activated or inhibited (51).

Even though the majority of Phase 1 trials in cancer research follow what was described above, it should be mentioned that alternative Phase 1 trials may arise in other settings such as medical device trials, prevention trials, education intervention trials, and behavior modification trials, where the first phase of investigation may actually utilize healthy subjects, such as studies interested in determining the utility of a new educational intervention on smoking cessation. The Phase 1 trial may simply be utilized as an approach towards gaining some experience with the intervention prior to moving forward to the next phase of investigation.

Phase 2 Trials

Once a dose and schedule for a new regimen has been deemed acceptable, a reasonable next step is to seek evidence that the new regimen is worthy of further evaluation in a particular patient population. The principal goal of a Phase 2 trial is to prospectively quantify the potential efficacy of the new therapy. Since a Phase 2 trial treats more patients at the RDL than a Phase 1 trial, it also provides an opportunity to more reliably assess toxicities. A Phase 2 trial is often referred to as a drug-screening trial because it attempts to judiciously identify active agents worthy of further study in much the same way a clinician screens a patient for further evaluation. The study should have adequate sensitivity to detect active treatments and adequate specificity for rejecting inactive treatments. A Phase 2 trial may evaluate a single new regimen, or incorporate randomization to evaluate several new therapies or treatment schedules simultaneously.

There are several concerns that need to be considered when weighing the decision to conduct a single-arm versus a multi-arm randomized Phase 2 study. While the required sample size is smaller for the single-arm trial, this design is susceptible to several sources of biases (52). Single-arm trials often assume that the probability of response to standard treatment in the target population is known with certainty. However, this assumption is often suspect. There are often unanticipated or unknown differences between the study sample and the historical sample which can introduce significant biases into the comparisons. For instance, there may be differences in the patients' prognoses unintentionally introduced by the study's eligibility criteria or changes in patient referral patterns. Differences in the response assessment schedule, the modalities for evaluation, or the definition of response may change over time and therefore distort comparisons with historical results. Generally, randomized controlled Phase 2 studies are preferred over single-arm studies. However, when the probability of response to standard treatment is widely accepted to be very low (e.g., <5%), it may be reasonable to conduct a single-arm studies. Investigators who conduct Phase 2 studies in rare diseases often argue in favor of single-arm designs; however, these are often the cases where the historical data is usually least understood and most susceptible to the previously mentioned biases.

Phase 2 trials can have a single-stage or multistage design. In a single-stage design, a fixed number of patients is treated with the new therapy. The goal of the single-stage design is to achieve a predetermined level of precision in estimating the endpoint.

While precision is one important goal in cancer trials, there is also a concern for reducing the number of patients treated with inferior regimens. For this reason many Phase 2 cancer trials use multistage designs. Multistage designs implement planned interim analyses of the data and apply predetermined rules to assess whether there is sufficient evidence to warrant continuing the trial. These rules, which are established prior to initiating the study, tend to terminate those trials with regimens having less than the desired activity, and tend to continue to full accrual of those trials with regimens having at least a minimally acceptable level of activity. Two-stage designs that minimize the expected sample size when the new treatment has a clinically uninteresting level of activity have been proposed for single-arm studies (53) and multiarm studies (54). In the cooperative group setting, there is often a need for flexibility in specifying exactly when the interim analysis will occur. This is due to the significant administrative and logistic overhead of coordinating the study in several clinics. Therefore, designs that do not require that the interim analyses occur after a precise number of patients is entered, are useful in the multi-institutional setting (55).

Regardless of the measure of treatment efficacy, most designs treat toxicity as merely a secondary observation. This approach is not likely to be appropriate in Phase 2 trials of very aggressive treatments, such as high-dose chemotherapy with bone-marrow support. In these trials, stopping rules that explicitly consider both response and the cumulative incidence of certain toxicities may be more appropriate (56–58). Bayesian designs, which permit continuous monitoring of both toxicity and response, have also been proposed (59).

Phase 3 Trials

The goal of a Phase 3 trial is to prospectively and definitively determine the effects of a new therapy relative to a standard therapy in a well-defined patient population. Phase 3 trials are also used to determine an acceptable standard therapy when there is no prior consensus on the appropriate standard therapy. Some Phase 3 trial methodologies such as randomization and blocking have origins in comparative agricultural experiments. However, in clinical trials the experimental unit is a human being and consequently, there are 2 very important distinctions. First, each individual must be informed of the potential benefits as well as the risks and must freely consent to participate before enrollment in the study. Second, an investigator has very limited control over the patient's environment during the observation period. This later distinction can have a profound statistical implication, which will be discussed later.

Phase 3 Trials with Historical Controls

The strict definition of a Phase 3 trial does not necessitate concurrent controls (i.e., prospectively enrolled patients assigned the standard treatment) or randomization (i.e., random treatment allocation). However, these 2 features are almost synonymous with Phase 3 trials today. The principal drawback from inferring treatment differences from a historically controlled trial is that the treatment groups may differ in a variety of characteristics that are not apparent. Differences in outcome, which are in fact due to differences in characteristics between the groups, may be erroneously attributed to the treatment. While statistical models are often used to adjust for some potential biases, adjustments are possible only for factors that have been recorded accurately and consistently from both samples. Shifts in medical practice over time, differences in the definition of the disease, eligibility criteria, follow-up procedures or recording methods can all contribute to a differential bias. Unlike random error, this type of error cannot be reduced by increasing the sample size. Moreover, the undesirable consequences of moderate biases may be exacerbated with larger sample sizes. When a trial includes *concurrent*

controls, the definition of disease and the eligibility criteria can be applied consistently to both treatment groups. Also, the standard procedures for measuring the endpoint can be uniformly applied to all patients. Inclusion of prospectively treated controls within the clinical trial requires a method of assigning the treatments to patients. Randomization and its benefits are discussed in a later section.

It is useful to distinguish Phase 3 objectives as having an efficacy, equivalency, or noninferiority design consideration. An efficacy design is characterized by the search for an intervention strategy that provides a therapeutic advantage over the current standard of care. An equivalency trial seeks to demonstrate that 2 interventions can be considered sufficiently similar on the basis of outcome that 1 can be reasonably substituted for the other. Noninferiority trials seek to identify new treatments that reduce toxicity, patient inconvenience, or treatment costs without significantly compromising efficacy.

Efficacy trials. Efficacy designs are very common in oncology trials. Examples include: trials that assess the benefit of adding chemotherapy to radiation for the treatment of early-stage cervical cancer or trials that compare standard versus dose intense platinum regimens for treating ovarian cancer. In each of these cases, the trial seeks to augment the standard of care in order to attain a better treatment response. From the outset of these trials it is recognized that the treatment benefit may be accompanied by an increased risk of toxicity, inconvenience, or financial cost. However, it is hoped that the benefits will be sufficiently large to offset these drawbacks. Suppose treatment A is the standard of care for a particular target disease population. The quantitative difference between treatments with respect to a particular outcome ($B-A$) can be described on a horizontal axis as in Figure 17.2. If we are reasonably certain that the difference between treatments is less than 0 (left of 0) then we would consider treatment A to be better. On the other hand, if the treatment difference is greater than 0 (right of 0) then we would conclude that the new treatment, B, is better. Furthermore, we can use dotted lines to demarcate on this graphic a region in which the difference between A and B is small enough to warrant no clinical preference for A or B. Consider the results from a trial expressed as the estimated difference between treatments and the corresponding 95% or 99% confidence interval superimposed on this graph. The confidence interval depicts those

values of the treatment difference that can be reasonably considered consistent with the data from the trial. An inconclusive trial is characterized by having such broad confidence intervals that the data cannot distinguish between A being preferred or B being preferred (see Figure 17.2). This is a typical consequence of a small trial. On the other hand, if the confidence interval entirely excludes the region where A is better than B, then we can conclude that B is significantly better than A (see Fig. 17.2). Note that in this case the lower bound of the confidence interval may extend into the region of clinical indifference, but the confidence interval must exclude the region below (left of) 0 difference.

Equivalency trials. The equivalency study design is perhaps a misnomer, since it is actually impossible to generate enough data from any trial to definitively claim that the 2 treatments are equivalent. Instead, an investigator typically defines the limits for treatment differences that can be interpreted as clinically irrelevant. If it is a matter of opinion for what differences in effect sizes can be considered clinically irrelevant, this issue can become a major source for controversy in the final interpretation of the trial results. Survival or progression-free survival endpoints are seldom used in equivalency trials; however, bio-equivalency designs are sometimes used for drug development. For example, if 1 agent is known to influence a particular biologic marker, then it may be desirable to design a trial to determine whether a new agent is as effective at modifying the expression of this biomarker. In this case, an investigator has some notion about the acceptable range of activity that can be considered clinically biologically equivalent. These studies are designed so that, within tolerable limits, the treatments can be considered equivalent.

Notice that the results from the inconclusive trial in Figure 17.2 cannot be interpreted as demonstrating equivalency. Even though the estimated difference between the treatments is nearly 0, the confidence interval cannot rule out treatment differences that would lead to preferring A or B. Caution should be exercised in interpreting the results from studies that conclude “therapeutic equivalency” when only a small difference between treatments with regard to the outcome is observed and it is declared to be not statistically significant. Even results from moderately large trials, which suggest therapeutic equivalence, may in fact be due to inadequate statistical power to detect clinically relevant differences.

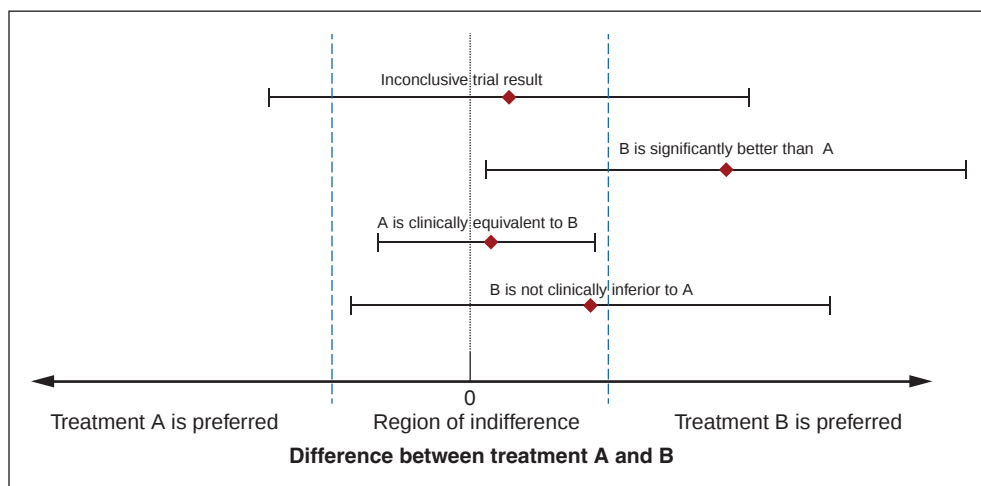


FIGURE 17.2. Graphical representation of the point estimates and confidence intervals describing the results from 4 hypothetical trials.

Noninferiority trials. A noninferiority study design may be considered when the currently accepted standard treatment is associated with significant toxicity and a new and less toxic treatment becomes available. The goal of this type of study is to demonstrate that substituting the new treatment for the current standard treatment does not compromise efficacy appreciably (60–63). Referring to Figure 17.2, the trial seeks to provide sufficient evidence to be reasonably certain that the difference between A and B lies above the lower boundary of the indifference region. This lower boundary is often called the “noninferiority margin.”

The justification for the noninferiority margin selected in a particular study is often controversial. If this margin is set too low, then the study has an unacceptably high probability of recommending an inferior treatment. If it is too high, then the trial utilizes too many clinical and financial resources. In order to select an appropriate margin of noninferiority, it is important to recognize that even though a noninferiority trial may explicitly compare only 2 treatments, implicitly there is a third treatment to be considered. For example, suppose that several historical studies indicate that treatment A is better than a placebo for treating a specific disease. In this case, the goal of a noninferiority study is to demonstrate that a new experimental treatment, B, does not significantly compromise efficacy when compared to currently accepted active standard treatment, A. However, it should also demonstrate that B would have been better than a placebo, if it had been included in the current trial. In other words, the current trial will directly estimate the effectiveness of B relative to A, but it must also indirectly consider the effectiveness of B relative to the previous control treatment (placebo in this case). This indirect comparison relies on obtaining a reliable and unbiased estimate of the effectiveness of the current active control to the previous control from previous trials. Sometimes the margin of noninferiority is expressed as a proportion of the effectiveness of A relative to the previous standard treatment. For example, a noninferiority study could be designed to have a high probability of concluding that a new treatment retains at least 50% of the activity of the standard regimen, A. Note that an investigator may decide that she is unwilling to give up any of the benefit attributed to the current standard treatment. In this case, the margin of noninferiority is set at 0 (see Fig. 17.2) and the design is the same as the efficacy trial. Indeed an efficacy trial can be considered a study in which the investigator is willing to accept the new treatment B, only if the trial results indicate that B is superior to A.

Obtaining reliable estimates for the activity of the currently accepted active standard treatment can be a very troublesome aspect of noninferiority oncology trials. For example, cisplatin 75 mg/m² and paclitaxel 135 mg/m² infused over 24 hours was the first platinum-taxane combination to demonstrate activity in the treatment of advanced ovarian cancer (64). Subsequently, several trials were conducted to assess whether carboplatinum could be safely substituted for cisplatin (65–67) or whether taxotere could be substituted for paclitaxel (68). However, there has been some controversy about the size of the benefit provided by paclitaxel (69). An investigator can reasonably ask, “What is the effect size of paclitaxel, and how much of this effect can I reasonably be certain is preserved by taxotere?”

Randomized Phase 3 Trials

There are several design features that may be considered for Phase 3 trials. Some are more pertinent than others to gynecologic oncology trials. The most important feature to be considered is treatment randomization. A study with this feature, a randomized clinical trial (RCT), has several scientific advantages. First, both the known and unknown prognostic factors tend to be distributed similarly across the treatment groups when a trial implements randomized treatments. Second, a potential source of differential selection bias is eliminated. This bias could

occur when there is an association between treatment choice and prognosis. It need not be intentional. When a physician's interest in a trial or a patient's decision to participate in the trial depends on the assigned treatment, a nonrandom association between treatment and prognosis can be introduced. Finally, randomization provides the theoretical underpinning for the significance test (70). In other words, the probability of a false-positive trial as stated in the study design is justified with randomization. It is important to recognize that these advantages, which are provided by randomizing the study treatments, are forfeited when all of the randomized patients are not included in the final analyses.

It is sometimes argued that since many factors that influence prognosis are known, perhaps other approaches to allocating treatments can be considered, and statistical models should be used to adjust for any imbalances in prognosis. However, the conclusions from this type of trial must be conditioned on the completeness of knowledge about the disease and the acceptability of the modeling assumptions. If the disease is moderately unpredictable with regard to the outcome, or the statistical model is inappropriate, then the conclusions are suspect. Results from nonrandomized studies can polarize the medical community. They frequently provide enough evidence for those who already support the conclusions but insufficient evidence for those who are skeptical.

Kunz and Oxman (71) have compared the results from overviews of randomized and nonrandomized clinical trials that evaluated the same intervention. They reported that the nonrandomized studies tended to overestimate the treatment effect from the randomized trials by 76% to 160%. Schulz et al. (72) compared 33 randomized controlled trials that had inadequate concealment of the random treatment assignments to studies that had adequate concealment. They found that studies with inadequate concealment tended to overestimate the treatment effect (relative odds) by 40%. Some investigators do not appreciate the importance of concealment and will go to considerable lengths to subvert it (73). When the randomization technique requires pregenerated random treatment assignments, one must guarantee that the investigators, who are enrolling patients, do not have access to the assignment lists.

The patient–physician relationship can occasionally be challenged by introducing the concept of treatment randomization (74). Patients may prefer a sense of confidence from their physician regarding the “best” therapy for them. However, physicians involved in a RCT must honestly acknowledge that the best therapy is unknown and that a RCT is preferred to continued ignorance. One survey of 600 women seen in a breast clinic suggests that 90% of women prefer their doctor to admit uncertainty about the best treatment option, rather than give them false hope (75).

Randomization techniques. The simplest approach to randomization is to assign treatments based on a coin flip, sequential digits from random number tables, or computerized pseudo-random number generators. On average, each patient has a defined probability of being allocated to a particular study treatment, when he or she enters the study. While this approach is simple, the statistical efficiency of the analyses can be enhanced by constraining the randomization so that each treatment is allocated an equal number of times. Permuted block randomization is sometimes used to promote equal treatment-group sizes. A block can be created by shuffling a fixed number of cards for each treatment and then assigning the patients according to the random order of the deck. After completing each block there are an equal number of patients assigned to the treatment groups. For example, consider a trial comparing treatments A and B. There are 6 possible ways the block can be ordered when the block size is 4: AABB, ABBA, BBAA, BABA, ABAB, and BAAB. A sufficient number of assignments for a RCT can be created by

randomly selecting a series of blocks from the 6 distinct possibilities. There are 3 features of blocked randomization that may be problematic. First, the probability of a particular treatment being allocated is not the same throughout the study, as in simple randomization. Taking the example above, every 4th treatment is predetermined by the previous 3 allocations. Second, the use of small blocks in a single-clinic study may undermine concealment and allow an investigator to deduce the next treatment. This potential problem can be corrected by continually changing the block size throughout the assignment list. Third, large block sizes can subvert the benefits of blocking. As block sizes increase, the procedure resembles simple randomization.

The statistical efficiency of the study can be further enhanced by stratifying patients into groups with similar prognoses and using separate lists of blocked treatments for each stratum. This procedure is called stratified block randomization. It is worth noting that using simple randomization within strata would defeat the purpose of stratification, since this is equivalent to using simple randomization for all patients. Likewise, trials that stratify on too many prognostic factors are likely to have many uncompleted treatment blocks at the end of the study, which also defeats the intent of blocking (76).

When it is desirable to balance on more than a few prognostic factors, an alternative is dynamic treatment allocation; one particular type being minimization. Whereas stratified block randomization will balance treatment assignments within each combination of the various factor levels, minimization tends to balance treatments within each level of the factor separately. Each time a new patient is entered into the study, the number of individuals who share any of the prognostic characteristics of the new patient is tabulated. A metric, which measures the imbalance of these factors among the study treatments, is computed as if the new patient were allocated to each of the study treatments in turn. The patient is then allocated to the treatment that would favor the greatest degree of balance. In the event that the procedure indicates equal preference for two or more possible treatment allocations, simple randomization can be used to determine the patient's treatment assignment.

Masking Treatments

Concealment Concealment refers to the procedure in which the assigned study treatment is not revealed to the patient or the investigator until after the subject has successfully enrolled in the study. The purpose of concealment is to eliminate a bias which can arise from an individual's decision to participate in the study depending on the treatment assignment (77). Concealment is an essential component of randomized clinical trials.

Blinding Blinding is a procedure that prevents the patient or physician from knowing which treatment is being used. In a single-blinded study the patient is unaware of which study treatment she is receiving. A double-blinded study results in a situation in which neither the patient nor the health care provider is aware of that information. One purpose of blinding is to avoid measurement bias, particularly differential measurement bias (see Endpoints section). This type of bias occurs when the value of a measurement is influenced by the knowledge of which treatment is being received (see Historical Perspective section). It can occur when the measurement of an endpoint is in part or totally subjective. Most methods for assessing pain are subjective and require treatment blinding in order to promote the study's validity.

Oncology trials frequently do not implement blinding for several reasons. It is rather difficult to blind treatments when various treatment modalities are used (e.g., surgery versus radiation therapy, or intravenous versus oral administrations), when good medical practice is jeopardized (e.g., special tests are required to monitor toxicity due to particular treatments),

or when it is logistically difficult (e.g., the evaluating physician must be kept isolated from the treatment of the patient). In the absence of blinding, care should be taken that the method of measuring the endpoint is precisely stated in the protocol and consistently applied to each patient uniformly. Trials that assess quality of life or relief from symptoms should give serious consideration to treatment blinding.

Schulz et al. (78) have reviewed 110 randomized clinical trials published between 1990 and 1991 from 4 journals dedicated to obstetrics and gynecology. Thirty-one of these trials reported being double-blinded. Schultz et al. conclude that blinding should have been used more often, despite frequent impediments. Moreover, blinding seemed to have been compromised in at least 3 of the trials where it was implemented.

Placebo A placebo is an inert treatment. Placebos blind the patient, and usually the physician as well, to the knowledge of whether an experimental or an inert treatment is being given. Placebos are frequently used in trials where there is no accepted standard treatment and the endpoint is susceptible to measurement bias. The use of a placebo is also important when the endpoint can be affected by the patient's psychological response to the knowledge of receiving therapy combined with a belief that the therapy is effective. This phenomenon is aptly named the "placebo effect." In such circumstances, the use of a placebo provides a treatment-to-control comparison that measures only the therapeutic effect. Note that the "placebo effect" is a distinctly different type of measurement bias from those that have been previously discussed. Careful ethical considerations must precede the use of a placebo or sham procedure in any clinical trial (79).

GOG Protocol 137 (A Randomized Double-Blinded Trial of Estrogen Replacement Therapy versus Placebo in Women with Stage I or II Endometrial Adenocarcinoma) was a randomized double-blinded comparison of estrogen replacement therapy versus a placebo in women who had a total abdominal hysterectomy and bilateral salpingo-oophorectomy for early-stage endometrial cancer. One primary reason for the use of a placebo in this trial was the potential for differential measurement bias being introduced by the physician monitoring patients on estrogens much more closely due to the anticipation of adverse events.

Factorial Designs

Factorial designs are used when several interventions are to be studied simultaneously. The term *factorial* arises from historical terminology in which the treatments were referred to as factors. Each factor has corresponding levels; for example, an investigator may wish to compare a study agent administered at 3 dose levels: high-dose, medium-dose, and none. The total number of factor combinations being studied is the product of the number of levels for each factor or treatment. For example, a trial that evaluates treatment A at three levels and treatment B at 2 levels is called a 3-by-2 (denoted 3×2) factorial design. If the relative effects due to the various levels of treatment A are independent of the levels of B, the two treatments (A and B) can be evaluated simultaneously. The factorial design provides a significant reduction in the required sample size when compared to a study that evaluates all levels of A and B separately. The key assumption necessary for a factorial design is that all treatments can be given simultaneously without interaction or interference.

The most commonly utilized factorial design is the 2×2 factorial design that includes 2 distinct treatment regimens at each of 2 factor levels. For example, suppose individuals entering a cancer prevention trial are randomly assigned to receive vitamin E and beta carotene while the respective factor levels are placebo-A or 50 mg/day for vitamin E, and placebo-B or 20 mg/day for beta carotene. There are 4 treatment

combinations. In a standard 2×2 design the main effect of vitamin E can be ascertained by utilizing information from each of the 4 treatment groups. In some studies, however, the main effects may be of secondary importance compared to the “interaction” between each factor. An interaction exists when the effect due to 1 of the factors (i.e., treatment A) depends on the level of the other factor (treatment B). In drug discovery, a “positive” interaction may imply a synergistic effect of 2 drugs in combination, that is, the effect of the combination therapy is greater than the sum of the individual additive effects. Reliable tests of an interaction require a relatively large number of patients in each of the 4 treatment groups. If potential treatment interaction cannot reasonably be ruled out or there is interest in possible interactions, then attention to the statistical power of such tests is an important part of designing and interpreting the study results (80).

Hypothesis Test

A hypothesis is a conjecture based on prior experiences that leads to refutable predictions (81). A hypothesis is frequently framed in the context of either a null or an alternative hypothesis. A null hypothesis may postulate that a treatment does not influence patients’ outcomes. The alternative hypothesis is that a particular, well-defined treatment approach will influence the patients’ outcomes to a prespecified degree. These hypotheses cast the purpose of the trial into a clear framework. During the study design the investigators select a test statistic from an appropriate statistical procedure (e.g., an F-statistic from an analysis of variance, or a chi-square statistic from a logistic model) that evaluates the degree to which the study data support the null hypothesis. A Type I error is committed when the null hypothesis is in fact true, but the test statistic leads the investigator to incorrectly conclude it is false. Committing the Type I error would be disastrous if it means discontinuing the use of an active control treatment that is well tolerated and substituting an experimental therapy that is more toxic but, in reality, not better. A Type II error is committed when the null hypothesis is not true, but the test statistic leads the investigator to erroneously conclude that it is true. Type II errors commonly occur in studies that involve too few subjects to reliably estimate clinically important treatment effects. Prospectively specifying the null hypothesis, the appropriate statistical method for the analysis, the test statistic and quantifying the acceptable probabilities of Type I error (i.e., α -level) and Type II error are essential elements for determining the appropriate design and sample size for a particular trial.

p-Value

At times statisticians play the role of the conservative physician, cautiously prescribing a significance test only when it is appropriate. There is a general concern that the p -value is overused, even abused, and overemphasized. A common misconception is that the p -value is the probability that the null hypothesis is true. The null hypothesis is either true or false, and so it is not subject to a probability statement. It is the inference that an investigator makes, based on his or her data, that is susceptible to error. The p -value is simply the probability that the test statistic would be as extreme or even more extreme, if the null hypothesis was in fact true (see hypothesis test section).

Misconceptions about the p -value may arise in part from a poor distinction between the p -value and the α -level of a study (82). The α -level is the probability of the test statistic rejecting the null hypothesis when it is true. It is specified during the design phase of the study, and is unaltered by the results obtained. The p -value results from a statistical test performed on the observed data.

Translational Research

Many modern clinical trials often involve the systematic collection and banking of biologic materials from the participants. The materials may include serum, plasma, urine, buccal cells, or tumor tissue, which are collected and stored in a bank. The biologic materials together with the clinical data can then be used to understand how a biologic effect translates into the treatment effect on the patient population. This translation gives rise to the concept of translational research (TR). In translational research, discoveries in laboratory science are translated into practical applications. The flow of information from TR studies is a 2 way street: 1) more complete understanding of tumor biology and 2) more effective treatments for patients.

The goal in this section is to provide clinical and laboratory scientists with some fundamental information needed to design, implement, and analyze the data from TR studies. The following sections develop the concepts for: (a) biomarker discovery and verification, and (b) biomarker validation. In short, these steps are presented in Figure 17.3 (Discovery and Test Validation Stage). We provide insights into what goals and expectations a researcher can have when performing a biomarker study. With this knowledge, the reader can avoid some of the errors and biases that have plagued translational research and led to false, misreported, or misleading reports.

Biospecimen Collection

A widely used definition of a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention” (83). Biomarkers can be measurements of macromolecules (DNA, RNA, proteins, lipids), cells, or processes that describe a normal or abnormal biologic state in a patient. From the paradigm of translational research described above, biomarkers can inform investigators about a patient’s diagnosis, prognosis, prediction of response to therapy (i.e., effect modifier), or prediction of a clinical outcome (i.e., surrogate endpoint).

Generally speaking, biomarkers can be diagnostic or prognostic. A diagnostic biomarker is designed to identify the presence of a disease or other condition, while a prognostic biomarker is an indicator that helps researchers in predicting the course of a patient’s disease. Prognostic biomarkers are used to estimate the risk of a future clinical outcomes, and examples include stage of the disease, histology of the tumor, or patient’s performance status. A biomarker may also be deemed predictive, and as such, it can be used to modify the estimated risk of a future outcome, but only when a particular type of treatment is taken. In breast cancer patients, examples of predictive biomarkers are estrogen receptor status when the treatment is tamoxifen or *Her2/neu* status when the treatment is trastuzumab. The phrase “treatment selection marker” has become the preferred terminology for a predictive biomarker to avoid confusion with other uses of the word “predictive”. For our immediate purposes here we will view predictive markers as a special class of prognostic markers and primarily focus on prognostic biomarker studies. Only in the section describing studies involving targeted therapies will the distinction be made.

The biologic specimens used in a study are typically gathered either prospectively or retrospectively. In the prospective approach, patients are identified and then followed forward in time. There are several advantages to the prospective approach. First, patient enrollment can focus on enrolling only individuals from the intended target population. Second, the procedures for collecting and preparing specimens can be tailored to the intended laboratory procedures. Third, the quality

Biomarker Development for High-throughput Technologies**Classifier Development Phase**

- **Probe Discovery:** Identify a subset of genes/proteins associated with the clinical outcome of interest.
- **Probe Verification:** Confirm measurements on selected genes/proteins using alternate laboratory techniques, like IHC or Rt-PCR.
- **Classifier Development:** Use the confirmed genes/proteins to develop a model (classifier) that appears to predict clinical outcome.

Classifier Verification Phase

- **Model Verification:** Confirm the model's properties using a small independent sample of individuals or cross-classification techniques.
- **Document Classifier:** Document the computational procedures and criteria for interpreting the lock-down model.

Classifier Validation

- **Validation:** Evaluate the model's predictive accuracy in a sample of individuals representative of the target population. Any changes to the procedures or the lock-down model to improve the classifier will require further validation.

For additional information see National Research Council. *Evolution of Translational Omics: Lessons Learned and the Path Forward*. Washington, DC: The National Academies Press, 2012 (147).

FIGURE 17.3. Biomarker development for high-throughput technologies.

control procedures for collecting the clinical data can target those data items that are required for the specific study objectives. Fourth, the patient's treatment and follow-up assessments can be standardized and optimized in accordance with the goals of the study. When samples are retrospectively collected, the laboratory analysis is performed using previously archived specimens that may have been originally collected for another purpose. The investigator using a retrospective approach is a prisoner to the procedures that were set down before the current study goals were contemplated and therefore, they may not be optimal for his intended objectives. For instance, the samples may have come from patients who are not representative of the target population. This reduces the generalizability of the study results. The specimens may have been obtained, prepared or stored using outdated or less than optimal procedures for his laboratory tests. This could introduce biases in the measurements or reduce the power of the study.

Biomarker Development Process

In the following sections, we discuss a common TR study design for a biomarker: (a) biomarker discovery and (b) biomarker validation. In short, these steps are presented in Figure 17.3 (Discovery and Test Validation Stage).

Discovery Phase

Regardless of whether the samples were retrospectively or prospectively collected, many studies are designed to discover biomarkers with clinical utility, from among many potentially useful biomarkers.

Since the invention of microarray technology and related high-throughput technologies, researchers have been able to compile large amounts of information and an enormous pool of potential biomarkers. These so called high-throughput platforms have become commonly used experimental platforms in the biologic realm (84). A high-throughput platform is designed to measure large numbers (thousands or millions) of signatures in a biologic organism at a given time point. These platforms are a function of the postgenomic era and are often used to determine how genomic expression is regulated or involved in

biologic processes. The technologies in Table 17.1 use hybridization and sequence-based platforms such as gene expression microarrays and RNA-Seq to obtain data matrices.

Several of the common high-throughput assay platforms used in experiments designed for cancer diagnosis are listed in Table 17.1. These platforms were chosen to illustrate the diversity of platforms available for interrogating deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins.

Preprocessing High-Throughput (HT) Platforms

In short, pre-processing algorithms are required in nearly all high-throughput technologies listed in Table 17.1. This is due to the fact that HT platforms measure both biologic signal and technical signal. Therefore, the goal of preprocessing algorithms is removal of the technical signal. This technical signal can be considered in terms of background correction and normalization to adjust across experiments. The background corrections and normalization account for technical artifacts that can occur due to either the array construction or laboratory procedures that introduce systematic errors in the signal on individual arrays or across arrays. Often these pre-processing techniques are specific to the platform employed (see, for example, Miecznikowski et al. [85]) and therefore it is impractical to review all of the available pre-processing methods here.

Type I Error and Multiple Testing

The experiments performed in the HT discovery phase often have a goal of simply narrowing down the genome or proteome to a subset of potentially relevant biomarkers. In this sense, the scientists are performing a data reduction where the goal is to choose a subset of markers from the high-throughput scope that are related or associated with clinical outcome. The association with the outcome is assessed using a null hypothesis for each biomarker and summarizing “significance” with a p -value. In this case, the interpretation of each p -value differs slightly from a study with a single null hypothesis (See Hypothesis Test and p -value sections).

When the Type I error is limited to 5% for a single hypothesis, then there is only a 1-in-20 chance of rejecting that null hypothesis, if it is in fact true. This is a relatively uncommon

Table 17.1 A Summary of Discovery Platforms, The Material Analyzed in the Platform and Recent Cancer Biomarker Discovery Studies Using the Given Platform

Platforms	Material	Cancer Studies
aCGH microarray	DNA	(86,88–95)
Gene expression microarray	mRNA	(96–105)
RNA—Seq	Transcriptomics	(106,107)
DNA methylation	DNA	(108)
Mass spectrometry	Peptide/proteomics	(109–114)

occurrence. When there are 10,000 null hypotheses tested, as may be typical for some HT studies, even if all of the null hypotheses were true, one would expect 500 null hypotheses to be rejected at the 5% significance level. The chance of committing a Type I error over the entire study should no longer be considered an uncommon occurrence.

Therefore, during the discovery phase of a HT experiment the goal is to limit the Type I error rate. That is, HT studies are designed to limit the number of false positives, denoted by V in Table 17.2A. Table 17.2B lists some alternative approaches to controlling the Type I error rate during the discovery phase of the experiment. Statistically significant or interesting markers are determined from hypothesis testing in light of controlling one of the Type I error rates listed in Table 17.2B.

Confirmation and Verification

In order to have reasonable power in light of multiple testing, the Type I errors in Table 17.2A tend to be more liberal (more likely to reject null hypotheses) than standard scientific significance testing procedures. Thus, any markers from the discovery phase should be confirmed or verified using other methods, such as immunohistochemical (IHC) assays or reverse transcription polymerase chain reaction (RT-PCR). These verification platforms could use either the same samples from the discovery phase or a new independent set of samples. The goal for this step is to confirm that the biomarker signal from the discovery platform is accurately measuring the expression of the desired gene, protein or RNA.

Including a confirmation step ensures researchers that their discovery markers can be confirmed using other platforms. This provides some reassurance in the ability of the markers to be confirmed on independent samples from possibly different institutions with, possibly, differing methods of assessment. Methods that describe how to correlate RT-PCR and IHC signals with their microarray counterparts can be found in Press et al. (115), van den Broek and van de Vijver (116), McShane et al. (117), Esteban et al. (118).

Table 17.2A A summary of results from analyzing multiple hypothesis tests.

	H_0 Retained	H_0 Rejected	Total
H_0 True	U	V	M_0
H_0 False	T	Q	M_1
	M—R	R	M

M_0 and M_1 are considered as fixed (unknown) parameters representing the number of true nulls and the number of true alternatives, respectively. The random variables U and Q represent the number of the correct decisions, while the random variables T and V represent the number of incorrect decisions. V is the number of false positives.

In certain immunohistochemistry assays the results should be performed by at least 2 different observers who are blinded to the clinical data. This may alleviate the subjectivity in these experiments since IHC assays require selection of best regions to score and subjective measurements of staining intensity and percentage of stained cells.

Validation Phase

Various statistical models can be fit using the data in the discovery phase. At the end of the discovery phase there should be a complete specification of the marker assay method and model, and thorough documentation of the (final) lock-down model. The fully specified precise lock-down model will be evaluated using a validation dataset. Note, for example, this must include specifying all coefficients in the classification model and any of the rules for deciding the level of a biomarker.

Validation in biomarker experiments should always involve an independent dataset, that is, data from patients that were not included in any of the discovery dataset(s). Note that internal validation procedures such as cross-validation, boot strapping, or other data resampling methods are useful to give insights into issues such as bias and variance of regression parameter estimates and stability of the model derived. In these internal validation procedures, some portion of the data is held out (test set), while a model is built on the remaining portion (training set). A limitation of these internal procedures is that there may be biases that affect the training and test sets equally. For example, if the set of specimens for confirmation are collected in the same laboratory, processed by the same technician, and run on the same equipment, then peculiarities of that data (equipment, lab, technician) will be shared between the samples used to develop the computational model and the samples used to evaluate the model.

Table 17.2B Summary of Type I Errors

Abbreviation	Name	Quantity
FWER	Family Wise Error Rate	$\Pr(V > 1)$
k-FWER	Generalized Family Wise Error Rate	$\Pr(V > k)$
FDR	False Discovery Rate	$E[V/R]$
k-FDR	Generalized False Discovery Rate	
PCER	Per comparison error rate	$E[V]/M$
TPPPF	Tail probabilities for the proportion of false positives	$\Pr(V/R) > q$

Summaries of Type I errors using random variables defined in Table 2a. See similar tables in Nichols and Hayasaka [2003] (Nichols and Hayasaka 2003) and Table 15.1 in Gentleman et al. [2005] (Gentleman, Carey et al. 2005). Note that $I(\cdot)$ in the equation for k-FDR denotes the indicator function and $\max(\cdot)$ denotes the maximum operator. Further note that q in TPPPF should be determined prior to testing. $\Pr(\cdot)$ denotes probability, and $E[\cdot]$ denotes expectation.

Even with the requirement of an independent dataset, there may still be levels of validation evidence. For example, a lower level of validation evidence may be independent sets of specimens and clinical data collected at a single institution using carefully controlled protocols, with samples from the same patient population. Meanwhile, a higher level of validation evidence would be independent sets of specimens and clinical data collected at multiple institutions.

Additionally, it should be stressed that the independent validation dataset must be relevant to the intended use of the candidate biomarker test. Patients in the independent dataset should have the same type of disease, the same stage and same clinical setting for which the candidate test is intended to be used in the future. Ideally, the specimens for independent confirmation will have been collected at a different point in time, at different institutions, from a different patient population, with samples processed in a different laboratory to demonstrate that the test has broad applicability and is not overfit to any particular situation.

Publicly Available Data

These datasets can help with the development process, and further they can complete the puzzle in systems biology, for example, provide the proteomics story if you only have genomic data. They can be used in an integrative analysis and a meta-analysis. These meta-analyses can strengthen the conclusions drawn from an individual researcher's study. They may also offer insights from other study populations.

As deoxyribonucleic acid (DNA) microarray technology has been widely applied to detect gene activity changes in many areas of biomedical research, development and curation of online microarray data repositories are at the forefront of research endeavors to use and reuse this mounting deluge of data. Several representative repositories of microarray datasets are ArrayExpress at the webpage <http://www.ebi.ac.uk/arrayexpress/>, Gene Expression Omnibus (GEO) (119) at the webpage <http://www.ncbi.nlm.nih.gov/geo/>, Stanford Microarray Database (SMD) at the webpage <http://smd.stanford.edu/> and Center for Information Biology Gene Expression Database (CIBEX) (120) at the webpage <http://cibex.nig.ac.jp/index.jsp>. Also a new database called Anduril which has been recently developed and described in Ovaska et al. (121) now provides comprehensive storage of the massive data including single base pair mutation, copy number change or deletions of genes, differential gene expression, and epigenetic changes like methylation profiles. A somewhat recent comparison of the available microarray databases was provided in Gardiner-Garden and Littlejohn (122). Statistical packages in R have also been created that allows users to easily import data from databases like ArrayExpress into Bioconductor packages (123).

Concordant with the development of online data repositories, researchers have developed specific data standards required for microarray analysis. The data standard concept describes the minimum information about a microarray experiment (MIAME) that is needed to enable the interpretation of the results of the experiment and to potentially reproduce the experiment (124). MIAME compliance will ensure that biological properties of the samples and the phenotypes that were assayed were correctly recorded, thus, ensuring, that the data can be quickly assessed for its suitability in studying new questions. The public repositories including ArrayExpress (146), GEO (125), and CIBEX (120) are all designed to hold MIAME compliant microarray data.

Especially exciting for oncologists, multiple platforms of microarray data from The Cancer Genome Atlas (TCGA) are now available through the data portal at <http://tcga-data.nci.nih.gov/tcga/tcgaHome2.jsp>. The TCGA project is further described in Stratton et al. (126), but in short, represents one of the first large-scale attempts to study the multiple types of genetic mutations involved in multiple cancer types from

different cohorts of patients. Initially, the pilot projects studied glioblastoma multiforma (GBM) and cystadenocarcinoma of the ovary, but have now expanded to cover roughly 20 different cancer types. For each cancer type, the patient cohorts (collected from different sites) include several hundred individuals and the platform techniques include gene expression profiling, copy number variation profiling, SNP genotyping, methylation profiling, and microRNA profiling. These data will be made publicly available, making the TCGA dataset a great resource for future research using meta-analysis and integrative analysis techniques that were not previously available.

Developing Translational Research Studies and Reporting Results

Guidelines have been developed to promote accurate and complete reporting of results from biomarker studies. Throughout this section, the importance of having well-defined questions for the proposed data is stressed. In other words, serious thought, planning, and discussions amongst a team of scientists are necessary to successfully perform biomarker analysis, including discovery, verification, and validation.

In the discovery phase it is important that the proposed technology has been validated, see for example, technical replication studies in Strand et al. (127), Callesen et al. (128); Leyland-Jones et al. (129), De Cecco et al. (130), Hicks et al. (131), Benton et al. (132), Freidin et al. (133), and Lawrie et al. (134). During the discovery phase, it is also important to consider differences in material preparation, for example, frozen tissue samples versus paraffin embedded tissues as discussed in Nowak et al. (135), and Mittempergher et al. (136). During the verification phase, these issues also may play a role; however, other concerns may arise such as the level of concordance in signal necessary between the discovery platform and the verification platform. Ultimately, after discovery and verification, a lockdown model is carried forth to validation. This, so called, lockdown model can be interpreted in a decision theoretic setting; each future sample must be classified or the outcome predicted based only on the model and a given sample signal from the intended technology.

In the validation phase, it is important to note that there is a major difference between answering *a priori* defined hypotheses and providing conclusions from exploratory analyses. Conclusions drawn from exploratory data analysis are descriptive results and typically need to be confirmed in a validation dataset, while *a priori* hypothesis lead to stronger conclusions and do not necessarily need an external validation. Care should be given in reporting unanticipated significant effects, as these are most likely due to chance and thus unlikely to be validated in other studies. Most importantly, researchers should keep in mind that, in the long term, the success of biomarker studies should be measured by the clinical improvement in patient outcomes.

There have been a prodigious number of biomarker studies reported in the literature; however, a surprising number of these results are irreproducible. The reasons for these discrepancies may lie in the differences in methodological procedures, inadequate control of false-positive findings, improper validation procedures, variability in the patient sampling, or any number of other differences in study design, conduct, or analytical procedures. Many published studies lack adequate information that would allow an evaluation of quality or comparability. In order to promote clear and complete reporting of biomarker studies, the REMARK guidelines have been developed (137). These guidelines make specific recommendations for preparing translational research presentations, reports, and publications with regard to describing patient and sample characteristics, assay methodology, study design, methods of data analysis, and results. While these recommendations have been distilled into bullets in Table 17.3, useful additional information can be found in the REMARK document (137).

Table 17.3 **REMARK Criteria: Reporting Recommendations for Tumor MARKer Prognostic Studies**

Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK)

Introduction

1. State the marker examined, the study objectives, and any prespecified hypotheses.

Materials and methods

Patients

2. Describe the characteristics (e.g., disease stage or comorbidities) of the study patients, including their source and inclusion and exclusion criteria.
3. Describe treatments received and how chosen (e.g., randomized or rule-based).

Specimen characteristics

4. Describe type of biologic material used (including control samples) and methods of preservation and storage.

Assay methods

5. Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.

Study design

6. State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.
7. Precisely define all clinical endpoints examined.
8. List all candidate variables initially examined.
9. Give rationale for sample size; if the study was designed to detect a specific effect size, give the target power and effect size.

Statistical analysis methods

10. Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.
11. Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.

Results

Data

12. Describe the flow of patients through the study, including the number of patients participating in each stage of the analysis (a diagram may be helpful), and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the number of patients and the number of events.
13. Report distribution of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.

Analysis and presentation

14. Show the relation of the marker to standard prognostic variables.
15. Present univariate analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.
16. For key multivariate analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.
17. Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.
18. If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.

Discussion

19. Interpret the results in the context of the prespecified hypotheses and other relevant studies, and include a discussion of limitations of the study.
20. Discuss implications for future research and clinical value.

Source: Reprinted with permission from REMARK Criteria: REporting Recommendations for Tumor MARKer Prognostic studies. Mitterpergher L, de Ronde JJ, Nieuwland M, et al. Gene expression profiles from formalin fixed paraffin embedded breast cancer tissue are largely comparable to fresh frozen matched tissue. *PLoS One*. 2011;6(2):e17163.

Clinical Trials Involving Targeted Therapies

As previously mentioned, biomarkers can be used to diagnose a disease, to assess prognosis, to select appropriate treatments (predictive), or to assess treatment outcome (surrogate endpoint). Thus, biomarkers can be incorporated into many aspects of clinical practice and research once validated. There are 2 types of biomarker validation to consider: analytic and clinical validation. Analytic validation refers to obtaining evidence that the biomarker assay result is reproducible under a variety of conditions and that the assay is shown to accurately measure the intended analyte. Some aspects of analytic validation are presented in the Translational Research section. Analytic validation of the biomarker assay is essential before a biomarker can be clinically validated. Clinical validation involves demonstrating that the biomarker is “fit for purpose.” That is, it functions properly for its intended use as a diagnostic, prognostic, treatment selective, or surrogate marker. The rigor needed to evaluate the clinical utility of a biomarker has recently been emphasized in light of several failed attempts at validating complex biomarkers (138–140). This section will focus on trial design considerations for evaluating the clinical utility of a predictive biomarker. The term *predictive* biomarker has been used to differentiate a biomarker’s properties, over and above that of being prognostic. A predictive biomarker is prognostic when a particular treatment (or class of treatments) is prescribed. For example, *Her2/neu* is considered a predictive biomarker for Herceptin in the treatment of women diagnosed with breast cancer. There has been a movement toward using the term “treatment selection biomarker” in the literature instead.

A clinically useful treatment selection biomarker will identify patients with diseases that are either resistant or sensitive to a specific targeted therapy. These markers can be used to improve the efficiency of a study. Suppose the probability of response to standard treatment is 20% in the general patient population. Furthermore, suppose that 20% of the individuals in the general patient population are very responsive to a new targeted treatment, such that, when the targeted agent is added to the standard treatment, the probability of response is 60% among this sensitive subgroup, but unchanged in the nonsensitive subgroup. If the new treatment is combined with the standard treatment in the general population, regardless of their sensitivity status, then the expected probability of response would only be 28% (ie., 20% of the population have 60% response rate, and 80% have 20% response rate = $0.20 \times 0.60 + 0.80 \times 0.20 = 0.28$). If a randomized trial was now designed to compare standard treatment versus standard treatment with the new agent, then over 1000 patients would need to be enrolled in order to reliably detect this size of a treatment effect (Table 17.4). On the other hand, if the study used a perfectly accurate biomarker (sensitivity = 100% and specificity = 100%) to restrict enrollment to treatment-sensitive patients, then only 60 patients would be needed for the study (Table 17.4) and the expected number of patients needed to be screened would be about 300. However, biomarkers are seldom perfect. If a biomarker has only 80% sensitivity and 80% specificity, it could still be used to increase the prevalence of treatment-sensitive patients from 20% in the general population to 50% (also called the positive predictive value [PPV]) in the biomarker-enriched study population (Fig. 17.4). In this case the probability of response to the standard regimen with the new targeted agent in the enriched study population would be 40% ($0.50 \times 0.60 + 0.50 \times 0.20 = 0.40$). The two-arm trial designed with this imperfect biomarker to select sensitive patients would require 220 enrolled patients to reliably detect the difference in response rates (Table 17.4), and the expected number of patients needed to be screened would be about 688.

Table 17.4 Required Sample Size for a Randomized Trial with a Target Prevalence = 20%

Patient Population	Probability of Response		Sample Size
	Standard Therapy	Standard + Targeted Therapy	
Ideal Target Population ^a	0.20	0.60	60
General Population	0.20	0.28	1022
Enriched Population ^b	0.20	0.40	220

Design parameters: $H_0: P_0 \geq P_1$, $\alpha = 0.05$, $\beta = 0.10$.

^aSensitivity = 100%; specificity = 100%; number needed to screen = 300.

^bSensitivity = 80%; specificity = 80%; number needed to screen = 688.

In any study design where a biomarker is used to enrich the study sample with individuals considered most likely to respond, it may not be possible to differentiate between a failed treatment and a failed biomarker. Misspecification of the treatment target and misclassification of the tumor state are fundamental reasons for study failure. There can be a mismatch between the agent and the patient selection process in an enrichment design due to inadequate understanding of the true molecular target of the agent under study or use of an invalid surrogate endpoint biomarker (Fig. 17.5). A successful study depends on the degree to which the biomarker accurately measures the true state of the treatment’s target(s). Ideally, measuring the agent’s effect through the biomarker should measure the agent’s effect through the targeted pathway (highlighted in Fig. 17.5). If the treatment can influence the disease through pathways that are not captured by the biomarker, then the activity of the agent will be underestimated and potentially missed. For example, ovarian cancer mutations in the *BRCA1* and *BRCA2* genes identify tumors likely to respond to a class of agents referred to as Poly-ADP ribose polymerase inhibitors (PARPi). However, responses to PARPi have been observed among patients with no *BRCA* mutations (141). This suggests that markers of other biologic pathways will be needed to identify PARPi-sensitive tumors, such as markers for methylation of the *BRCA* genes or other types of dysfunction in the homologous recombination mechanism. Therefore, if the biomarkers that are used to define PARPi sensitivity included only *BRCA* mutation status, then sensitivity is sacrificed. On the other hand, if the markers for determining PARPi sensitivity include inconsequential mutations in the *BRCA* genes, then specificity is diminished. In enrichment studies, loss in sensitivity and specificity decreases the predictive value of the marker, which in turn decreases the chances that a study will identify active targeted agents (Table 17.4 and Fig. 17.4).

There are several alternative randomized trial designs for targeted therapies (142). One approach randomizes all patients from the target population and prospectively stratifies the random treatment assignment based on discrete values of the biomarker value. This design assesses a treatment effect in each of the discrete biomarker levels. Other designs randomize between treatment strategies, such as, assay-directed treatment versus standard therapy. These designs can be very inefficient and are generally not recommended (143). Study designs that adaptively modify the patient population when a planned interim analysis indicates that the biomarker identifies a subgroup of patients who are unlikely to respond or that utilize surrogate endpoints a lead-in randomized Phase II (seamless

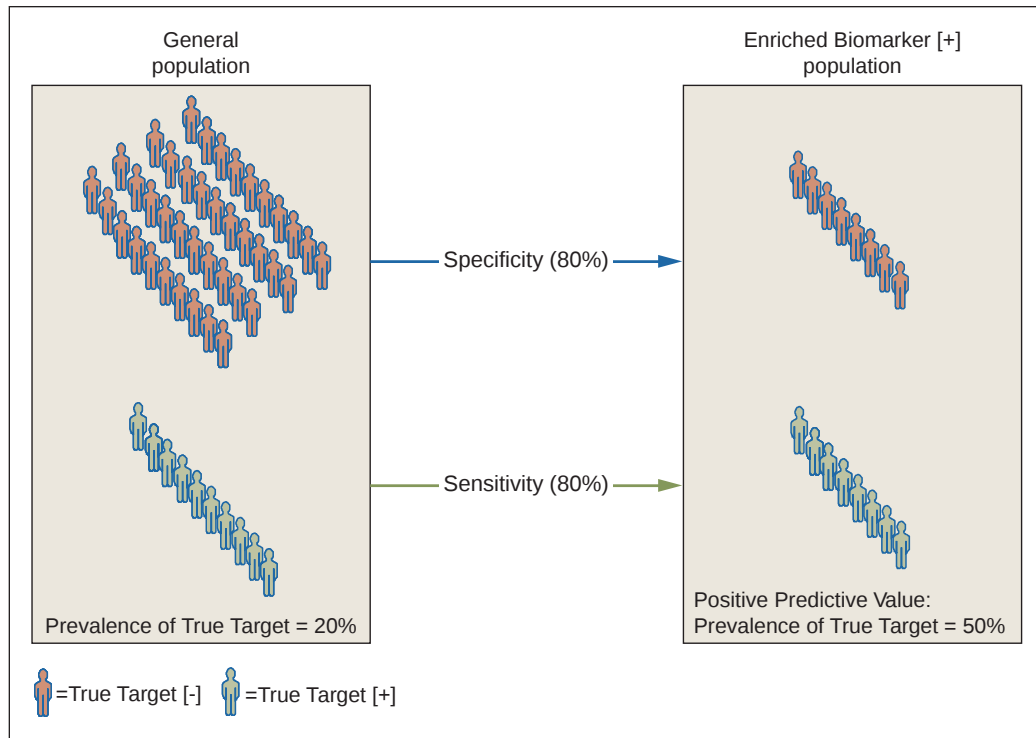


FIGURE 17.4. Hypothetical biomarker-based enrichment study.

Phase II/III) study have also been proposed (144, 145). Currently, adaptive designs for targeted therapies are an area of intense biostatistical research.

Careful planning is necessary for incorporating biomarkers into clinical trials. The appropriate choice of the trial design

that incorporates a biomarker into a clinical trial depends on 1) the study objectives, 2) how well the agent's mechanism of action is understood, 3) how well the role of the target is understood, and 4) how well the selected biomarker captures the state of the target.

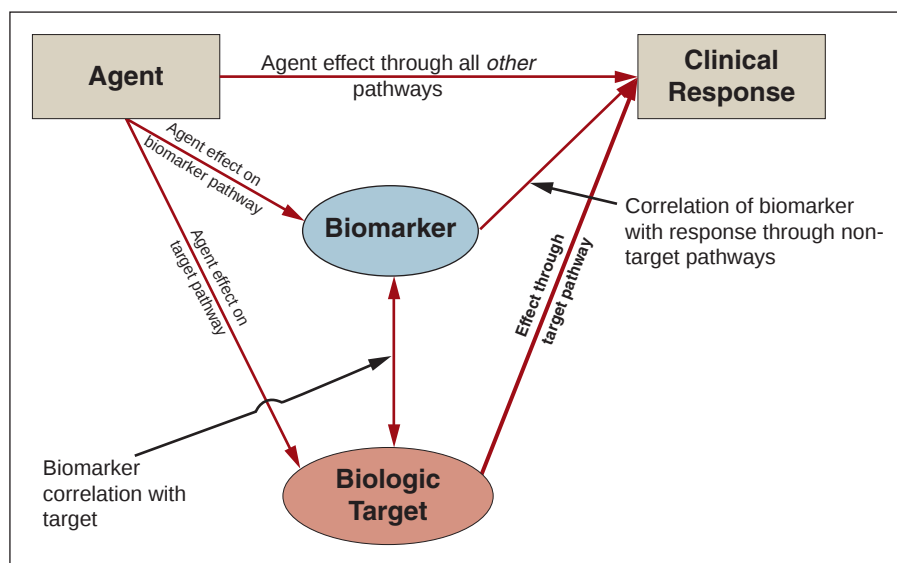


FIGURE 17.5. Schematic of the causal relationships and correlations between treatment, biomarker, biologic target, and clinical outcome.

CONCLUSION

The complexity of clinical trial design, conduct, analysis, and reporting has increased considerably over the past 60 years

since randomized treatment trials and public screening trials first began. It is difficult for a single clinician to consider initiating a clinical study since a study often requires extensive collaboration with other physicians, as well as with professionals from other disciplines such as biology, statistics, ethics, psychology, and economics.

REFERENCES

- Piantadosi S. *Clinical Trials: A Methodologic Perspective*. Hoboken, New Jersey: John Wiley and Sons, Inc.; 2005.
- Green S, Benedetti J, Smith A, et al. *Clinical Trials in Oncology*. Boca Raton, FL: Chapman and Hall/CRC; 2003.
- Bull JP. The historical development of clinical therapeutic trials. *J Chronic Dis*. 1959;10(3):218–248.
- Meinert CL, Tonascia S. *Clinical Trials: Design, Conduct and Analysis*. New York, NY: Oxford University Press; 1986.
- Kapchik TJ. Intentional ignorance: a history of blind assessment and placebo controls in medicine. *Bull Hist Med*. 1998;72(3):389–433.
- Fibiger J. Om Serumbehandling af difteri. *Hospitalstidende*. 1898;6:765–769.
- Hrobjartsson A, Gotzsche PC, Gluud C. The controlled clinical trial turns 100 years: Fibiger's trial of serum treatment of diphtheria. *Brit Med J*. 1998;317:1243–1245.
- Neuhauser D, Diaz M. Shuffle the deck, flip that coin: randomization comes to medicine. *Qual Saf Health Care*. 2004;13(4):315–316.
- Hinshaw H, Feldman W. Evaluation of chemotherapeutic agents in clinical tuberculosis: a suggested procedure. *Am Rev Tuberc*. 1944;50:202–213.
- Medical Research Council Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment for pulmonary tuberculosis. *Brit Med J*. 1948;ii:769–782.
- Yoshioka A. Use of randomisation in the Medical Research Council's clinical trial of streptomycin in pulmonary tuberculosis in the 1940's. *Brit Med J*. 1998;317:1220–1223.
- Paterson R, Russell M. Clinical trials in malignant disease. Breast cancer: value of radiation of the ovaries. *J Faculty Radiologists*. 1959;10:130–133.
- Fisher B. Winds of change in clinical trials—from Daniel to Charlie Brown. *Controlled Clin Trials*. 1982;4:65–73.
- Frei III E, Holland JF, Schneiderman MA, et al. A Comparative study of two regimens of combination chemotherapy in acute leukemia. *Blood*. 1958;13:1126–1148.
- Gehan EA, Schneiderman MA. Historical and methodologic developments in clinical trials at the National Cancer Institute. *Stat Med*. 1990;9:871–880.
- Zubrod CG, Schneiderman M. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *J Chronic Dis*. 1960;11:7–33.
- Abrams J, Mooney M. (2011). U10 Cooperative Agreement for NCI Clinical Trials Network. from <http://deainfo.nci.nih.gov/advisory/bsa/bsa1111/130%20Mooney%20Abrams.pdf>. Accessed August 6, 2012.
- Lewis GC, Blessing J, Kellner JR. *Clinical Trials in Gynecology Oncology: Cooperative Group Research*. Boston, MA: Martinus Nijhoff Publishers; 1983.
- Kelsey JL, Hildreth NG. *Breast and Gynecologic Cancer Epidemiology*. Boca Raton, FL: CRC Press Inc.; 1983.
- Buyse ME, Staquet MJ, Sylvester RJ, eds. *Cancer Clinical Trials, Methods and Practice*. New York, NY: Oxford University Press; 1984.
- Therasse P. Measuring the clinical response. What does it mean? *Eur J Cancer*. 2002;38(14):1817–1823.
- Advanced Ovarian Cancer Trialist Group (1991). Chemotherapy in advanced ovarian cancer; an overview of randomised clinical trials. *Brit Med J*. 1991;303:884–893.
- Vermorken J, Parmar M, Brady MF, et al. Clinical trials in ovarian carcinoma: study methodology. *Ann Oncol*. 2005;16(S8):viii20–viii29.
- Korn EL, Freidlin B, Abrams JS. Overall survival as the outcome for randomized clinical trials with effective subsequent therapies. *J Clin Oncol*. 2011;29(17):2439–2442.
- Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. *J Chronic Dis*. 1987;40(2):171–178.
- Sackett DL. Bias in analytic research. *J Chronic Dis*. 1979;32(1–2):51–63.
- Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125(7):605–613.
- Buyse M, Molenberghs G, Burzykowski T, et al. The validation of surrogate endpoints in meta-analyses of randomized experiments. *Biostatistics*. 2000;1(1):49–67.
- Lesko LJ, Atkinson Jr AJ. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. *Annu Rev Pharmacol Toxicol*. 2001;41:347–366. <http://unglamorousseatingdisorders.blogspot.com/>.
- Skaznik-Wikiel ME, Sukumvanich P, Beriwal S, et al. Possible use of CA-125 level normalization after the third chemotherapy cycle in deciding on chemotherapy regimen in patients with epithelial ovarian cancer: brief report. *Int J Gynecol Cancer*. 2011;21(6):1013–1017.
- FDA, ASCO, FDA, the American Society of Clinical Oncology (ASCO), with co-sponsorship by the American Association for Cancer Research (AACR) Public Workshop on Endpoints for Ovarian Cancer. 2006. from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/CancerDrugs/ucm094586.htm>. Accessed August 23, 2012.
- Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer. An Intergroup trial of the AGO-OVAR, the NCIC CTG, and EORTC GCG. *J Clin Oncol*. 2012;30(24):4699–4707.
- Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365(26):2473–2483.
- Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365(26):2484–2496.
- Aghajanian C, Blank S, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled Phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30(17):2039–2045.
- Royston P, Parmar MK, Qian W. Novel designs for multi-arm clinical trials with survival outcomes with an application in ovarian cancer. *Stat Med*. 2003;22(14):2239–2256.
- Parmar MK, Barthel FM, Sydes M, et al. Speeding up the evaluation of new agents in cancer. *J Natl Cancer Inst*. 2008;100(17):1204–1214.
- Oza AM, Castonguay V, Tsores D, et al. Progression-free survival in advanced ovarian cancer: a Canadian review and expert panel perspective. *Curr Oncol*. 2011;18(suppl 2):S20–S27.
- Creasman WT. Second-look laparotomy in ovarian cancer. *Gynecol Oncol*. 1994;55(3 Pt 2):S122–S127.
- Omura GA, Blessing JA, Vaccarello L, et al. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecology Oncology Group Study. *J Clin Oncol*. 1997;15(1):165–171.
- Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol*. 2004;22(15):3113–3119.
- Moore KN, Herzog TJ, Lewin S, et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. *Gynecol Oncol*. 2007;105(2):299–303.
- George SL. Reducing patient eligibility criteria in cancer clinical trials. *J Clin Oncol*. 1996;14(4):1364–1370.
- Begg CB, Engstrom PF. Eligibility and extrapolation in cancer clinical trials. *J Clin Oncol*. 1987;5(6):962–968.
- ICON Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet*. 2002;360(9332):505–515.
- O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase I clinical trials in cancer. *Biometrics*. 1990;46:33–48.
- Korn EL, Midhune D, Chen TT, et al. A comparison of two phase I trial designs. *Stat Med*. 1994;13:1799–1806.
- Goodman SN, Zahurak ML, Piantadosi S. Some practical improvements in the continual reassessment method for phase I studies. *Stat Med*. 1995;14:1149–1161.
- Ahn C. An evaluation of phase I cancer clinical trial designs. *Stat Med*. 1998;17:1537–1549.
- Simon R, Freidlin B, Rubinstein L, et al. Accelerated titration designs for phase I clinical trials in oncology. *J Natl Cancer Inst*. 1997;89:1138–1147.

51. Mandrekar SJ, Qin R, Sargent DJ. Model-based phase I designs incorporating toxicity and efficacy for single and dual agent drug combinations: methods and challenges. *Stat Med*. 2010;29(10):1077–1083.
52. Mandrekar SJ, Sargent DJ. Randomized phase II trials: time for a new era in clinical trial design. *J Thorac Oncol*. 2010;5(7):932–934.
53. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clin Trials*. 1989;10:1–10.
54. Wieand S, Therasneau T. A two-stage design for randomized trials with binary outcomes. *Controlled Clin Trials*. 1987;8:20–28.
55. Chen TT, Ng TH. Optimal flexible designs in phase II clinical trials. *Statist Med*. 1998;17:2301–2312.
56. Jennison C, Turnbull BW. Group sequential tests for bivariate response: interim analyses of clinical trials with both efficacy and safety endpoints. *Biometrics*. 1993;49:741–752.
57. Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. *Biometrics*. 1995;51:1372–1383.
58. Conaway MR, Petroni GR. Designs for the phase II trials allowing for a trade off between response and toxicity. *Biometrics*. 1996;52:1375–1386.
59. Thall P, Simon R, Estey EH. New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. *J Clin Oncol*. 1996;14(1):296–303.
60. Durrleman S, Simon R. Planning and monitoring of equivalence studies. *Biometrics*. 1990;46:329–336.
61. Senn S. Inherent difficulties with active control equivalence studies. *Statist Med*. 1993;12:2367–2375.
62. Wiens B. Choosing an equivalence limit for non-inferiority or equivalence studies. *Control Clin Trials*. 2002;23:2–14.
63. Rothmann M, Li N, Chen G, et al. Design and analysis of non-inferiority mortality trials in oncology. *Stat Med*. 2003;22(2):239–264.
64. McGuire WP, Hoskins WJ, Brady MF, et al. A phase III trial comparing cisplatin/cytosine and cisplatin/paclitaxel in advanced ovarian cancer (abstract 808). *Proc Am Soc Clin Onc*. 1993;12:808.
65. Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol*. 2000;18(17):3084–3092.
66. du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst*. 2003;95(17):1320–1329.
67. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21(17):3194–3200.
68. Vasey PA. Role of docetaxel in the treatment of newly diagnosed advanced ovarian cancer. *J Clin Oncol*. 2003;21(suppl. 10):136–144.
69. Sandercock J, Parmar MK, Torri V, et al. First-line treatment for advanced ovarian cancer: paclitaxel, platinum and the evidence. *Br J Cancer*. 2002;87(8):815–824.
70. Byar DP, Simon RM, Friedewald WT, et al. Randomized clinical trials. Perspectives on some recent ideas. *N Engl J Med*. 1976;295:74–80.
71. Kunz R, Oxman A. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *Brit Med J*. 1998;317:1185–1190.
72. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *J Am Med Assoc*. 1995;273(5):408–412.
73. Schulz KF. Subverting randomization in controlled trials. *J Am Med Assoc*. 1995;274(18):1456–1458.
74. Emanuel EJ, Patterson WB. Ethics of randomized clinical trials. *Journal of Clinical Oncology*. 1998;16(1):365–371.
75. Ellis PM, Coates AS. Ethics of randomized clinical trials. *J Clin Oncol*. 1998;16(7):2570.
76. Therasneau TM. How many stratification factors are “too many” to use in a randomization plan? *Control Clin Trials*. 1993;14(2):98–108.
77. Schulz KF, Altman DG, Moher D. Allocation concealment in clinical trials. *JAMA*. 2002;288(19):2406–2407; author reply 2408–2409.
78. Schulz KF, Grimes DA, Altman DG, et al. Blinding and exclusions after allocation in randomized controlled trials: survey of published parallel group trials in obstetrics and gynaecology. *Brit Med J*. 1996;312:742–744.
79. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med*. 1994;331(6):394–398.
80. Green S, Liu PY, O’Sullivan J. Factorial design considerations. *J Clin Oncol*. 2002;20(16):3424–3430.
81. Last JM, ed. *A Dictionary of Epidemiology*. New York, NY: Oxford University Press; 1995.
82. Goodman SN. p values, Hypothesis tests, and likelihood: implications for epidemiology of a neglected historical debate. *Am J Epidemiol*. 1993;137(5):485–499.
83. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89–95.
84. Rajan S, Djambazian H, Dang HC, et al. The living microarray: a high-throughput platform for measuring transcription dynamics in single cells. *BMC Genomics*. 2011;12:115.
85. Miecznikowski JC, Gaile DP, Liu S, et al. A new normalizing algorithm for BAC CGH arrays with quality control metrics. *J Biomed Biotechnol*. 2011;2011:860732.
86. Albertson DG, Ylstra B, Seagraves R, et al. Quantitative mapping of amplicon structure by array CGH identifies CYP24 as a candidate oncogene. *Nat Genet*. 2000;25(2):144–146.
87. Hodgson G, Hager JH, Volik S, et al. Genome scanning with array CGH delineates regional alterations in mouse islet carcinomas. *Nat Genet*. 2001;29(4):459–464.
88. Pollack JR, Sorlie T, Perou CM, et al. Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors. *Proc Natl Acad Sci USA*. 2002;99(20):12963–12968.
89. Albertson DG, Collins C, McCormick F, et al. Chromosome aberrations in solid tumors. *Nat Genet*. 2003;34(4):369–376.
90. Hackett CS, Hodgson JG, Law ME, et al. Genome-wide array CGH analysis of murine neuroblastoma reveals distinct genomic aberrations which parallel those in human tumors. *Cancer Res*. 2003;63(17):5266–5273.
91. Garnis C, Coe BP, Zhang L, et al. Overexpression of LRP12, a gene contained within an 8q22 amplicon identified by high-resolution array CGH analysis of oral squamous cell carcinomas. *Oncogene*. 2004;23(14):2582–2586.
92. Veltman JA, Fridlyand J, Pejavar S, et al. Array-based comparative genomic hybridization for genome-wide screening of DNA copy number in bladder tumors. *Cancer Res*. 2003;63(11):2872–2880.
93. Pinkel D, Albertson DG. Array comparative genomic hybridization and its applications in cancer. *Nat Genet*. 2005;37 Suppl:S11–S17.
94. Rossi MR, Conroy J, McQuaid D, et al. Array CGH analysis of pediatric medulloblastomas. *Genes Chromosomes Cancer*. 2006;45(3):290–303.
95. Idubai H, Marie Y, Lucchesi C, et al. BAC array CGH distinguishes mutually exclusive alterations that define clinicogenetic subtypes of gliomas. *Int J Cancer*. 2008;122(8):1778–1786.
96. Ramaswamy S, Tamayo P, Rifkin R, et al. Multi-class cancer diagnosis using tumor gene expression signatures. *Proc Natl Acad Sci USA*. 2001;98(26):15149–15154.
97. Gordon GJ, Jensen RV, Hsiao LL, et al. Translation of microarray data into clinically relevant cancer diagnostic tests using gene expression ratios in lung cancer and mesothelioma. *Cancer Res*. 2002;62(17):4967–4977.
98. Tibshirani R, Hastie T, Narasimhan B, et al. Diagnosis of multiple cancer types by shrunken centroids of gene expression. *Proc Natl Acad Sci USA*. 2002;99(10):6567–6572.
99. Statnikov A, Aliferis CF, Tsamardinos I, et al. A comprehensive evaluation of multicategory classification methods for microarray gene expression cancer diagnosis. *Bioinformatics*. 2005;21(5):631–643.
100. Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. *BMC Genomics*. 2006;7:278.
101. van’t Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002;415(6871):530–536.
102. Sotiriou C, Neo SY, McShane LM, et al. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. *Proc Natl Acad Sci USA*. 2003;100(18):10393–10398.
103. Michiels S, Koscielny S, Hill C. Prediction of cancer outcome with microarrays: a multiple random validation strategy. *Lancet*. 2005;365(9458):488–492.
104. Barrier A, Boelle PY, Roser F, et al. Stage II colon cancer prognosis prediction by tumor gene expression profiling. *J Clin Oncol*. 2006;24(29):4685–4691.
105. Miecznikowski JC, Wang D, Liu S, et al. Comparative survival analysis of breast cancer microarray studies identifies important prognostic genetic pathways. *BMC Cancer*. 2010;10:573.
106. Levin JZ, Berger MF, Adiconis X, et al. Targeted next-generation sequencing of a cancer transcriptome enhances detection of sequence variants and novel fusion transcripts. *Genome Biol*. 2009;10(10):R115.
107. Pflueger D, Rickman DS, Sboner A, et al. N-myc downstream regulated gene 1 (NDRG1) is fused to ERG in prostate cancer. *Neoplasia*. 2009;11(8):804–811.
108. Portela A, Esteller M. Epigenetic modifications and human disease. *Nat Biotechnol*. 2010;28(10):1057–1068.
109. Pawletz CP, Trock B, Pennanen M, et al. Proteomic patterns of nipple aspirate fluids obtained by SELDI-TOF: potential for new biomarkers to aid in the diagnosis of breast cancer. *Dis Markers*. 2001;17(4):301–307.
110. Koopmann J, Zhang Z, White N, et al. Serum diagnosis of pancreatic adenocarcinoma using surface-enhanced laser desorption and ionization mass spectrometry. *Clin Cancer Res*. 2004;10(3):860–868.
111. Kolch W, Neuss C, Pelzing M, et al. Capillary electrophoresis-mass spectrometry as a powerful tool in clinical diagnosis and biomarker discovery. *Mass Spectrom Rev*. 2005;24(6):959–977.

112. Diamandis EP. Analysis of serum proteomic patterns for early cancer diagnosis: drawing attention to potential problems. *J Natl Cancer Inst.* 2004;96(5):353–356.
113. Diamandis EP. Mass spectrometry as a diagnostic and a cancer biomarker discovery tool: opportunities and potential limitations. *Mol Cell Proteomics.* 2004;3(4):367–378.
114. Lan KKG, Rosenberger WF, et al. Sequential monitoring of survival data with the Wilcoxon statistic. *Biometrics.* 1995;51(3):1175–1183.
115. Press MF, Hung G, Slamon DJ. Sensitivity of HER-2/neu antibodies in archival tissue samples: potential source of error in immunohistochemical studies of oncogene expression. *Cancer Res.* 1994;54(10):2771–2777.
116. van den Broek LJ, van de Vijver MJ. Assessment of problems in diagnostic and research immunohistochemistry associated with epitope instability in stored paraffin sections. *Appl Immunohistochem Mol Morphol.* 2000;8(4):316–321.
117. McShane LM, Aamodt R, Cordon-Cardo C, et al. Reproducibility of p53 immunohistochemistry in bladder tumors. National Cancer Institute, Bladder Tumor Marker Network. *Clin Cancer Res.* 2000;6(5):1854–1864.
118. Esteban J, Baker J, Cronin M, et al. Tumor gene expression and prognosis in breast cancer: multi-gene rt-pcr assay of paraffin-embedded tissue. *Proc Am Soc Clin Oncol.* 2003;22.
119. Edgar R, Domrachev M, Lash AE. Gene expression omnibus: NCBI gene expression and hybridization array data repository. *Nucleic Acids Res.* 2002;30(1):207–210.
120. Ikeo K, Ishi-I J, Tamura T, et al. CIBEX: center for information biology gene expression database. *C R Biol.* 2003;326(10–11):1079–1082.
121. Ovaska K, Laakso M, Haapa-Paananen S, et al. Large-scale data integration framework provides a comprehensive view on glioblastoma multiforme. *Genome Med.* 2010;2(9):65.
122. Gardiner-Garden M, Littlejohn TG. A comparison of microarray databases. *Brief Bioinform.* 2001;2(2):143–158.
123. Fred Hutchinson Cancer Research Center. Bioconductor: Open source software for bioinformatics. 2012, from <http://www.bioconductor.org>.
124. Brazma A, Hingamp P, Quackenbush J, et al. Minimum information about a microarray experiment (MIAME)-toward standards for microarray data. *Nat Genet.* 2001;29(4):365–371.
125. National Center for Biotechnology Information. GEO: Gene Expression Omnibus. 2012. From <http://www.ncbi.nlm.nih.gov/geo/>. Accessed August 23, 2012.
126. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature.* 2009;458(7239):719–724.
127. Strand C, Enell J, Hedenfalk I, et al. RNA quality in frozen breast cancer samples and the influence on gene expression analysis—a comparison of three evaluation methods using microcapillary electrophoresis traces. *BMC Mol Biol.* 2007;8:38.
128. Callesen AK, Vach W, Jørgensen PE, et al. Reproducibility of mass spectrometry based protein profiles for diagnosis of breast cancer across clinical studies: a systematic review. *J Proteome Res.* 2008;7(4):1395–1402.
129. Leyland-Jones BR, Ambrosone CB, Bartlett J, et al. Recommendations for collection and handling of specimens from group breast cancer clinical trials. *J Clin Oncol.* 2008;26(34):5638–5644.
130. De Cecco L, Musella V, Veneroni S, et al. Impact of biospecimens handling on biomarker research in breast cancer. *BMC Cancer.* 2009;9:409.
131. Hicks DG, Kushner L, McCarthy K. Breast cancer predictive factor testing: the challenges and importance of standardizing tissue handling. *J Natl Cancer Inst Monogr.* 2011;(42):43–45.
132. Benton P, Want E, Keun HC, et al. Intra- and inter-laboratory reproducibility of uplc-tof-ms for urinary metabolic profiling. *Anal Chem.* 2012;29(4):2424–2432.
133. Freidin MB, Bhudia N, Lim E, et al. Impact of collection and storage of lung tumor tissue on whole genome expression profiling. *J Mol Diagn.* 2012;14(2):140–148.
134. Lawrie CH, Ballabio E, Soilleux E, et al. Inter- and intra-observational variability in immunohistochemistry: a multicentre analysis of diffuse large B-cell lymphoma staining. *Histopathology.* 2012;61(1):18–25.
135. Nowak NJ, Miecznikowski J, Moore SR, et al. Challenges in array comparative genomic hybridization for the analysis of cancer samples. *Genet Med.* 2007;9(9):585–595.
136. Mittempergher L, de Ronde JJ, Nieuwland M, et al. Gene expression profiles from formalin fixed paraffin embedded breast cancer tissue are largely comparable to fresh frozen matched tissue. *PLoS One.* 2011;6(2):e17163.
137. McShane LM, Altman DG, Sauerbrei W, et al. REporting recommendations for tumor MARKer prognostic studies (REMARK). *Nat Clin Pract Oncol.* 2005;2(8):416–422.
138. Ransohoff DF. Lessons from controversy: ovarian cancer screening and serum proteomics. *J Natl Cancer Inst.* 2005;97(4):315–319.
139. IOM. *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease.* 2010. <http://www.iom.edu/Reports/2010/Evaluation-of-Biomarkers-and-Surrogate-Endpoints-in-Chronic-Disease.aspx>.
140. Goozner M. Duke scandal highlights need for genomics research criteria. *J Natl Cancer Inst.* 2011;103(12):916–917.
141. Sessa C. Update on PARP1 inhibitors in ovarian cancer. *Ann Oncol.* 2011;22(suppl. 8):viii72–viii76.
142. Simon R. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. *Per Med.* 2010;7(1):33–47.
143. Freidlin B, McShane LM, Korn EL. Randomized clinical trials with biomarkers: design issues. *J Natl Cancer Inst.* 2010;102(3):152–160.
144. Wang SJ, O'Neill RT, Hung HM. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. *Pharm Stat.* 2007;6(3):227–244.
145. Jenkins M, Stone A, Jennison C. An adaptive seamless phase II/III design for oncology trials with subpopulation selection using correlated survival endpoints. *Pharm Stat.* 2011;10(4):347–356.
146. European Bioinformatics Institute. 2012. “ArrayExpress.” from <http://www.ebi.ac.uk/arrayexpress/>.
147. National Research Council. *Evolution of Translational Omics: Lessons Learned and the Path Forward.* Washington, DC, The National Academies Press; 2012.

18 Comparative Effectiveness Research in Gynecologic Oncology

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OVERVIEW OF COMPARATIVE EFFECTIVENESS RESEARCH

Introduction

Comparative effectiveness research (CER) is defined by the Institute of Medicine (IOM) as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care.” With this definition, the IOM provides a framework for CER to exist, for example, in the development of a model to better understand the potential impact of an intervention (generation of evidence), or in the form of the comparison of 2 existing treatments of a condition (synthesis of evidence). As such, CER can take on various forms in differing clinical conditions.

The purpose of CER is “to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels” (1). In an effort to develop meaningful results from CER studies, the IOM recognized that “the most important priority of all should be the building of a broad and supportive infrastructure to carry out a sustainable CER strategy.” Furthermore, the IOM was mandated by the Obama administration to both define and establish priorities for CER. According to the IOM’s definition, CER is a way to identify what works for which patients and under what circumstances. Congress, in the American Recovery and Reinvestment Act (ARRA) of 2009, appropriated \$1.1 billion to jump-start the nation’s efforts to accelerate CER. Furthermore, ARRA created the Patient-Centered Outcomes Research Institute (PCORI), a public-private organization charged with setting national priorities for CER. In ARRA, IOM was also asked to recommend national priorities for research questions to be addressed by CER and supported by ARRA funds. The IOM provided its “100 Initial Priority Topics for Comparative Effectiveness Research,” which were then included in ARRA for priority funding (1). Many of these priorities are pertinent to gynecologic cancer research and are listed in Table 18.1. Although not comprehensive, this list provides insight into potential opportunities to utilize techniques and resources to study CER in gynecologic cancer. Despite the emphasis and funding to support CER, this field is not widely utilized in gynecologic cancer research, mainly due to the need for special

understanding of the tools for performing and analyzing CER and a relative lack of understanding of the application of CER in gynecologic cancer practice. Nonetheless, the field of CER has been gaining momentum within the gynecologic cancer community and has resulted in impactful information that continues to move the field forward.

History of CER

The concept of comparing interventions based on best available data is not new. Over the last 50 years, the ability to deliver health care of high quality and value has continued to be a conceptual priority that has been variably named. In the 1970s, new health care technologies were evaluated through the U.S. Congress Office of Technology Assessment. In the 1980s and 1990s, the terms “Effectiveness Research” and “Outcomes Research” were commonly utilized when evaluating the quality of health care interventions, and were often associated with the Agency for Health Care Policy and Research (which eventually became more formally organized as the Agency for Healthcare Research and Quality [AHRQ], now charged with improving “the quality, safety, efficiency, and effectiveness of health care for all Americans”). Despite the changes in names and focus, the ultimate goal of these groups and initiatives was to provide data to support the rational development and utilization of health care interventions. The formal process of developing a CER focus was initiated in the 2003 Medicare Modernization Act, which appropriated \$50 million to conduct research to address the needs and priorities related to improve outcomes, clinical effectiveness, and appropriateness of certain services and treatments. Data from these earlier efforts began to become integrated into coverage for these interventions in 2006, when the Centers for Medicare and Medicaid Services (CMS) provided support to the concept of inclusion of evidence-based decision-making and research into coverage determination policies. As the field has moved forward and become integrated into health care policy and coverage decisions, there has concurrently been an increasing concern that the field of CER will lead to rationing and denial of certain health care interventions. As the percentage of gross domestic policy spent on health care continues to rise beyond what is considered sustainable for the future, it is anticipated that CER will have a greater impact in establishing cost-effective and high-quality care.

Table 18.1 Priority Topics for Comparative Effectiveness Research Pertinent to Gynecologic Cancer Research

1. Compare the effectiveness of imaging technologies in diagnosing, staging, and monitoring patients with cancer, including positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT).
2. Compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating ovarian cancer.
3. Compare the effectiveness of interventions (e.g., community-based multilevel interventions, simple health education, and usual care) to reduce health disparities in cancer.
4. Compare the effectiveness of different benefit design, utilization management, and cost-sharing strategies in improving health care access and quality in patients with cancer.
5. Compare the effectiveness of robotic assistance surgery and conventional surgery.
6. Compare the effectiveness of surgical resection, observation, or ablative techniques on disease-free and overall survival, tumor recurrence, quality of life, and toxicity in patients with liver metastases.
7. Compare the effectiveness of hospital-based palliative care and usual care on patient-reported outcomes and cost.

CER Methodology: “Real World” versus Randomized Controlled Trials

In practical terms, CER aims to compare 2 or more treatment strategies, either in clinical care or through modeling. This process of comparing strategies has historically been different from that of a conventional randomized controlled clinical trial (RCT), in which the subjects are carefully selected and many excluded from participation due to intercurrent illness or prior history. In CER, data is derived from “real world” subjects, settings, and treatments and is thus more apt to be generalizable to the overall population with a specific condition. Furthermore, RCTs tend to be of short duration and are underpowered to detect unexpected adverse effects or heterogeneity of treatment effects. Importantly, RCTs can be prohibitively expensive to complete and sometimes are not feasible to perform. While RCTs may be the best means by which one can assess whether an intervention works, it is an ineffective means to assess who will benefit from the intervention (2). CER methodologies often employ large clinical databases that are not restricted in their sample size, take into account those who do not participate in a research study, and are associated with a longer follow-up compared with RCTs. Given that these databases often have information regarding disease severity and subject comorbidity, a more complex analysis of the heterogeneity of treatment effects is feasible with database studies. Given the limitations of RCTs in the generalizability of an intervention and the strengths of CER in addressing this issue, there has been increasing interest in “pragmatic clinical trials,” which aim to combine the strengths of a RCT but are performed as larger population trials. These trials incorporate “real world” treatments, often include multiple outcomes, and are able to evaluate subgroup differences (3). It is anticipated that these trials will become increasingly important as the field of CER progresses.

CER and Cost-Effectiveness

While CER is broadly defined as any methodology that compares the benefits and harms of alternative strategies in health care, the most common CER studies fall within the field of

health economics. Health economic studies address the optimal allocation of economic resources in health care. The most common type of health economic evaluation is a cost-effectiveness analysis (CEA), a tool for comparing the relative values of 2 or more medical interventions. Therefore, a CEA fits under the umbrella of CER through its ability to inform decision-making regarding the financial implications of health care.

Summary

Comparative effectiveness research is becoming increasingly utilized by patients, providers, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels. With increasing pressure to control the costs and improve the quality of health care, CER will be an important means by which different treatments can be critically evaluated. While in its relative infancy, CER in gynecologic cancer is a field ready for development.

PRINCIPLES OF HEALTH ECONOMIC ANALYSES

This section will introduce basic types of health economic studies. The term “cost-effectiveness analysis” is commonly used as a catch-all term for any health economic analysis. In fact, there are several distinct forms of health economic evaluation, including CEA, cost-utility analysis (CUA), cost-minimization analysis (CMA), and cost-benefit analysis (CBA). CEA and CUA are the most frequently used health economic analyses. CEAs compare alternative interventions using a cost per unit of effectiveness such as a year of life gained (4). CUAs examine cost, effectiveness, and preferences for health outcomes. CMAs compare only cost. CBAs are less commonly used in health care and compare the total expected cost of each option against the total expected monetary benefit (4).

Cost-Effectiveness Analyses

CEA is defined by the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) as an economic study design in which the consequences of different interventions are measured using a single outcome (e.g., years of life gained, deaths avoided) (5). A CEA is used to help prioritize the allocation of resources and to decide between one or more treatments or interventions. It compares a standard of care strategy to its more costly alternatives in terms of the additional cost per unit of effectiveness. Units of effectiveness in oncology CEA are most commonly expressed as additional survival time, but may be expressed in other terms such as the number of adverse events or additional procedures avoided or the number of cases of cancer prevented. This type of study is commonly used when a decision or health policy maker is operating within a given budget and is considering a limited range of options (4). When an intervention costs more and is also more effective than its alternative, the cost-effectiveness comparison is expressed as an incremental cost-effectiveness ratio (ICER) or the ratio of the difference in costs to the difference in effectiveness between 2 strategies.

Cost-Minimization Analyses

In some cases, alternative medical decisions have approximately equivalent effectiveness but potentially different costs. In such cases, the effectiveness component of a CEA may not be needed. CMAs assume comparable effectiveness between strategies and

choose a preferred strategy based on the mean cost of each (6). For example, a recent decision analysis comparing the costs of three different surgical approaches to endometrial cancer staging assumed equal survival outcomes between strategies and therefore did not incorporate effectiveness (7).

Cost-Utility Analyses

CUA is a form of CEA in which effectiveness is adjusted based on the quality of life that is associated with each strategy. In CUAs, *utilities* are the measurement used for quality of life and represent the preferences of an individual or a society for a particular health outcome. A utility is a number between 0 and 1, with 1 representing perfect health and 0 representing death. The most common metric used for comparison of strategies in a CUA is a quality-adjusted life year (QALY). The QALY quantifies both differences in survival and in quality of life between strategies. In an oncology CUA, the QALY is usually derived as the product of the length of survival in a specific health state and the utility representing the quality of life in that state. For example, 1 year of additional survival in a health state of utility 0.8 is equivalent to 0.8 QALYs. CUAs are preferred when both morbidity and mortality are affected by the proposed medical intervention or when quality of life related to the intervention being examined is a major concern. QALYs are the recommended outcome for health economic analyses if utility scores are available (8).

Cost-Benefit Analyses

CBA is a more global type of economic analysis than CEA and CUA in that it can be used to evaluate programs outside the realm of health care, such as general public policy decisions. A CBA measures both the costs and the consequences of each intervention in monetary units. The outcome of a CBA can be expressed as a ratio of benefits to costs. Unlike CEA and CUA, which define costs and effects by comparing at least two strategies and choosing one as the winner, a CBA estimates the absolute monetary benefit of a proposed health care intervention or program. A key characteristic of a CBA performed in the field of health care is the need to assign monetary values to health outcomes. Such an exercise is considered controversial by some due to the placement of monetary value on human life (4).

Methods for Development of a Health Economic Decision Model

This section will address specific methods used in the development of a health economic decision model, with an emphasis on the two most common types of models, CEA and CUA.

Define the model's perspective The perspective of a health economic model is the first important consideration as costs are calculated differently based on the perspective taken. Most CEAs are performed from a third-party payer or a societal perspective. In a third-party payer perspective model, costs assumed by an insurance company or by Medicare are incorporated. These may include professional fees for encounters and procedures, reimbursements to the hospital or ambulatory surgical center for postoperative care, or reimbursements for home health or rehabilitation care. A societal perspective is usually most appropriate as it accounts not only for all costs included from a third-party payer perspective, but also costs related to a patient's lost productivity and the caregiver's expense. For example, if one surgical approach results in a faster return to work, this will be associated with less cost that is due to lost productivity. Use of the societal perspective has led to the recognition that minimally

invasive surgery results in cost savings to society (7,9,10). Other perspectives of health economic models include the *patient* and *hospital* perspectives. A hospital perspective model might be used to inform the decision to purchase expensive equipment such as robotic surgery platforms or an intraoperative radiotherapy facility.

Define the question Once the model's perspective has been determined, the clinical problem, standard approach, and any alternatives must be defined (11). The alternatives to the intervention of interest should always include a standard of care approach or even a "do nothing" approach. Next, a conceptual model for the analysis is developed, which outlines the possible consequences of each intervention. Decision models are often used as the conceptual framework for CEAs and have become an integral part of CEA studies.

Develop a decision tree A simple decision tree begins with a *decision node* representing the primary clinical decision being examined. Two or more strategies may be examined using one decision tree. The subsequent nodes in the tree are termed *chance nodes*, and define the probability of each possible clinical event that follows from the initial decision. For example, if the decision node concerns the clinical question of whether to accept a blood transfusion, the first chance node may define the probability that the patient will be infected with a blood-borne infection such as HIV if she accepts. Another chance node may define the risk of death if transfusion is refused (Fig. 18.1). Probabilities defined at chance nodes are usually derived from the literature or from clinical trial data. At the end of each branch of a decision tree is the *terminal node*, at which a payoff representing the effectiveness of that strategy occurs. In the blood transfusion example, the terminal nodes define 3 states: Life, death, or life with a blood-borne infection such as HIV. The payoff for life is 1, for death is 0, and for infection is a utility representing a lifetime spent with the infection. The expected value of each strategy, or its effectiveness, is calculated as the weighted average of the probabilities and payoffs associated with each terminal branch of the tree. The strategy resulting in the highest expected value is said to be the most effective. The payoff in an oncology model is usually expressed as a survival time. In a CUA, the effectiveness might be the product of survival time and the quality of life-based preference score, or utility.

Once all possible clinical events and their probabilities and payoffs have been defined by chance nodes, the costs of tests, treatments, and adverse events may be incorporated at each node. The cost associated with each strategy is calculated as a weighted average of the costs and probabilities associated with each branch of the tree.

Analysis of model After cost and effectiveness information have been collected and incorporated into the model, the analysis is performed. Results of cost-effectiveness models are expressed in terms of a comparison of 2 or more strategies. When one strategy is both more costly and less effective than an alternative strategy, it is said to be *dominated* and should not be considered. Likewise, a strategy that is both more effective and less costly is considered to be *dominant* and should be the treatment of choice. In these 2 cases, numeric cost-effectiveness quantification is not needed. When one strategy is both more costly and more effective than an alternative, an ICER is calculated. This is expressed as the difference in the mean cost divided by the difference in the mean effectiveness between strategies.

The ICER for comparison of intervention A compared to intervention B is defined as:

$$\frac{\text{Cost}_A - \text{Cost}_B}{\text{Effect}_A - \text{Effect}_B}$$

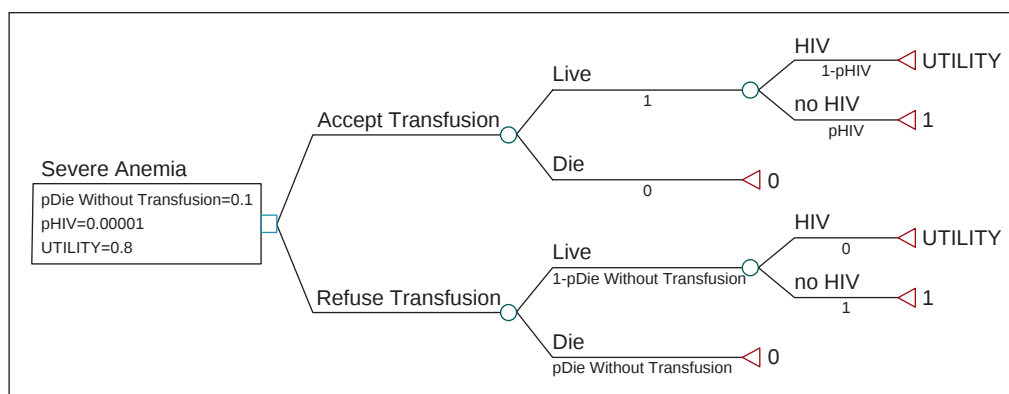


FIGURE 18.1. Simple decision tree representing the choice to accept or refuse a blood transfusion for severe anemia. The blue square is the decision node, green circles are chance nodes, and the red triangles are terminal nodes. Probabilities of events are depicted beneath each branch. Payoffs are listed to the right of terminal nodes. Three parameters are modeled as variables and have been given numeric values defined beneath the decision node. pHIV is the probability of being infected with HIV should the patient accept a transfusion. pDieWithoutTransfusion is the probability of death from severe anemia without a transfusion. Utility is the quality-of-life-related value of living with HIV, where 0 represents death and 1, perfect health.

It is important to note that the ICER is *not* estimated by dividing the cost of one intervention by the measure of its own effectiveness. This average cost-effectiveness ratio is not comparable to the ICER and is not a useful metric in cost-effectiveness analyses (12).

In the United States, an intervention has traditionally been considered cost-effective relative to an alternative strategy if the ICER is less than \$50,000 per quality-adjusted life year (QALY) (6). While ICER thresholds of \$50,000 per QALY are theoretically used in decision making, they are not strictly applied. Social norms may raise this value such that interventions costing up to \$100,000 or even greater per QALY have sometimes been considered cost-effective (13). The term “cost-effective” does not mean that a strategy saves money but rather that the additional cost of the intervention is worthwhile, usually from the perspective of society.

Sensitivity Analyses

Uncertainty in health economic analyses may exist about such input parameters as cost, survival, or clinical probabilities. To assess the impact of such uncertainty on the findings of a decision model, a sensitivity analysis can be performed. The simplest form of sensitivity analysis is a one-way analysis. Estimates are varied one parameter at a time to evaluate the impact made by the changes on the outcome or conclusions of the model (14). For example, in the simple model describing the decision to accept or refuse a blood transfusion, varying the probability of death due to anemia or the utility related to quality of life with HIV has an impact on the expected value of each decision (Fig. 18.2A–B). Likewise, a two-way sensitivity analysis can be performed to evaluate the impact of varying two model parameters simultaneously (Fig. 18.2C). When variation in the key parameters of a model over their confidence intervals or expected range of values does not change the model’s results, the model is said to be insensitive to these variations and its conclusions can be more strongly interpreted. Models whose outcomes change significantly when key estimates are varied over a clinically reasonable range should be interpreted with caution.

Most clinical models are fairly complex and may warrant the use of multiple simultaneous sensitivity analyses. In a Monte Carlo probabilistic sensitivity analysis, each variable in the model can be sampled from a probability distribution representing its value (15). Sampling parameter values from probability distributions (rather than from a simple range of values) places greater weight on likely combinations of parameter values.

Multiple sampling simulations of the model may then be run, each of which results in an individual cost-effectiveness comparison or estimate. Multiple simulations allow for construction of a cost-effectiveness scatterplot and the ability to express confidence intervals around the ICER estimate (Fig. 18.3), which effectively allows quantification of the total impact of uncertainty on the model and the confidence that can be placed in the analysis results.

INPUT DEVELOPMENT FOR HEALTH ECONOMIC MODELS

The following section details methods for the development of input data for health economic models.

Estimation of Costs

Cost definitions The costs incorporated into a CEA depend on the study’s perspective. The standard CEA or CUA is performed from a societal perspective (6). However, alternative perspectives include those of the patient, hospital, or a third-party payer. In a societal perspective analysis, the costs included are all of those borne by society and should therefore include both direct and indirect costs. Direct costs include direct medical costs (e.g., professional and hospital costs, diagnostic tests and procedures) and direct nonmedical costs (such as travel to receive care). Indirect costs account for lost productivity due to time off work for illness, both for the patient and any caregivers. When a health economic model is performed from a non-societal perspective, the scope of the costs included may be narrower. For example, in an analysis performed from a third-party payer perspective, lost productivity would not be included.

Which costs to include When developing a model to compare two strategies, it is important to remember that all medical costs do not necessarily need to be incorporated if it can reasonably be assumed that they do not differ between strategies. For example, for a comparison of 2 alternative surgical approaches to a disease, the cost of identical preoperative evaluation and laboratory testing need not be incorporated. Likewise, for a cost comparison of a Phase III clinical trial, the costs and consequences of adverse events that do not differ significantly between treatment arms may be omitted. Conversely,

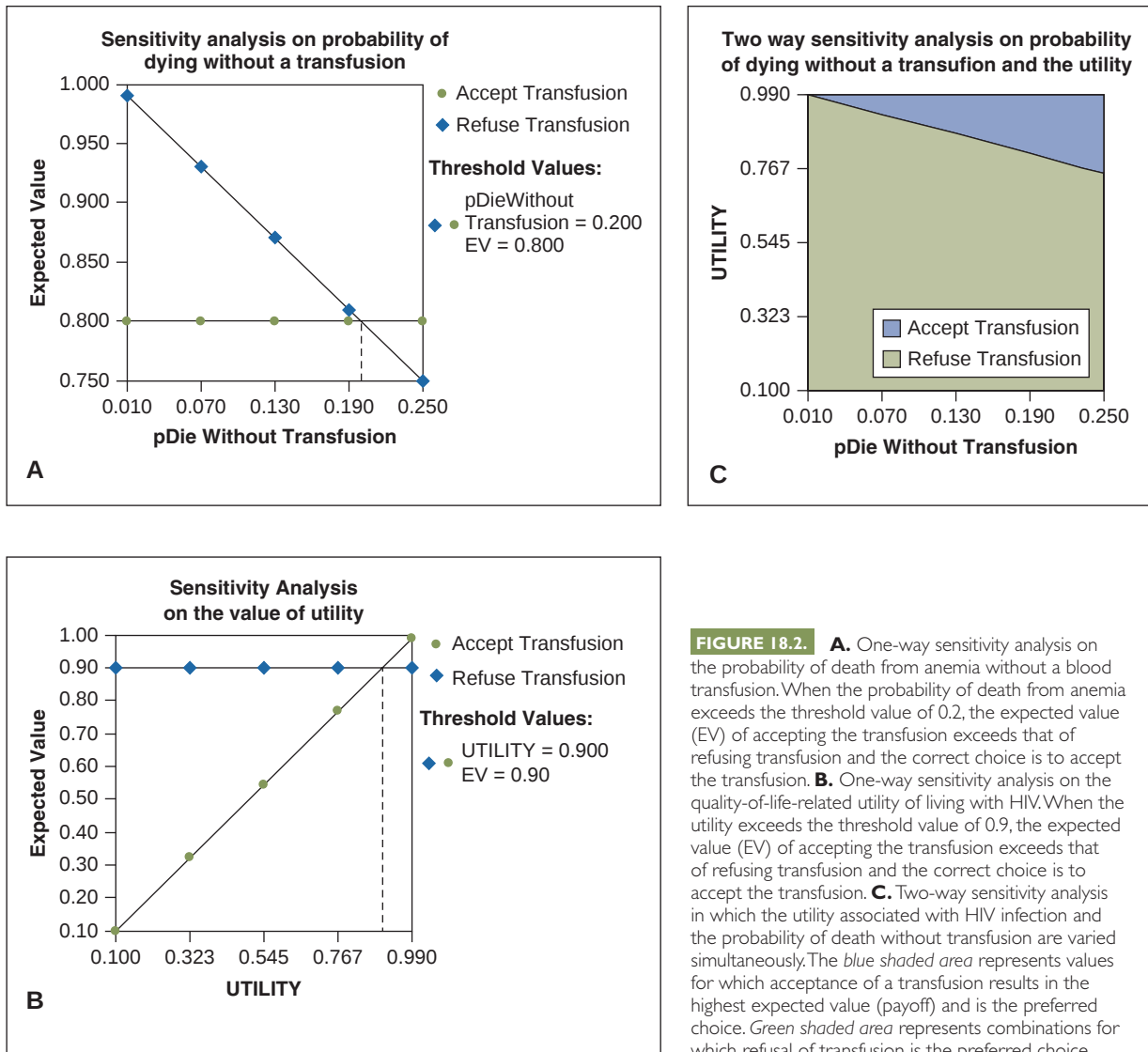


FIGURE 18.2. **A.** One-way sensitivity analysis on the probability of death from anemia without a blood transfusion. When the probability of death from anemia exceeds the threshold value of 0.2, the expected value (EV) of accepting the transfusion exceeds that of refusing transfusion and the correct choice is to accept the transfusion. **B.** One-way sensitivity analysis on the quality-of-life-related utility of living with HIV. When the utility exceeds the threshold value of 0.9, the expected value (EV) of accepting the transfusion exceeds that of refusing transfusion and the correct choice is to accept the transfusion. **C.** Two-way sensitivity analysis in which the utility associated with HIV infection and the probability of death without transfusion are varied simultaneously. The blue shaded area represents values for which acceptance of a transfusion results in the highest expected value (payoff) and is the preferred choice. Green shaded area represents combinations for which refusal of transfusion is the preferred choice.

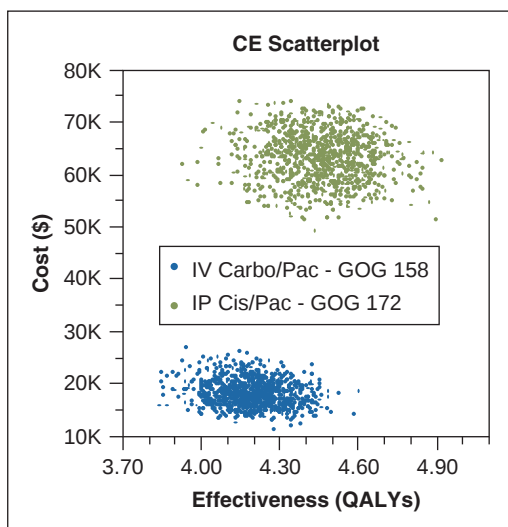


FIGURE 18.3. Cost-effectiveness scatterplot resulting from a Monte Carlo probabilistic sensitivity analysis for a model comparing intravenous carboplatin/paclitaxel to intraperitoneal cisplatin/paclitaxel and intravenous paclitaxel for advanced ovarian cancer. The simulation was repeated 10,000 times with sampling of key model parameters (cost, survival, and probability of adverse events) from probability distributions. This simulation resulted in an estimate of 95% confidence intervals to surround the primary incremental cost-effectiveness ratio estimate.

Source: Reprinted with permission from Havrilesky LJ, Alvarez-Secord A, Darcy KM, et al. Cost effectiveness of intraperitoneal compared with intravenous chemotherapy for women with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2008;26(25):4144-4150. (114)

Abbreviation: CE, cost-effectiveness; QALY, quality-adjusted life year.

if there are global downstream effects on health care costs that result from an intervention, such as fewer subsequent hospitalizations or emergency department visits, these should be incorporated.

Costs versus charges When performing a health economic analysis, it is important to distinguish costs from charges. Charges represent what the provider or hospital asks an individual to pay for a service, and not the reimbursement provided by either a private third-party payer or Medicare. Because reimbursements by the CMS are generally considered to approximate the cost of providing a service, it is standard to use national Medicare reimbursements to approximate the costs of medical tests, procedures, or services in a health economic analysis (16). If a Medicare reimbursement is not available for a particular aspect of medical costs, charges may be used to calculate costs using a cost-charge ratio. Cost-charge ratios allow a calculation of the proportion of hospital charges that represent cost to the hospital. Cost-charge ratios are specific to individual hospital departments and may be available from CMS (<http://www.cms.gov>).

Surgical costs Health economic analyses in gynecologic oncology may include an estimate of the costs of surgical procedures. CMS reimbursements may be used to approximate these costs from a societal perspective. Direct surgical costs include professional fees (surgeon, anesthesiologist, and pathologist), the cost of hospital recovery, and the costs of any tests or procedures performed in the postoperative period. Postoperative outpatient care is usually part of a global fee that includes the first 90 days of postoperative care, and is therefore not included separately. Likewise, the reimbursement for recovery in the hospital or ambulatory surgery center is usually determined by a CMS code, and this reimbursement covers tests and inpatient care. However, additional procedures performed postoperatively are associated with additional professional fees.

Costs of hospitalization The cost of a hospitalization may be estimated for health economic models using the Diagnosis Related Group (DRG), a CMS code that takes into account the primary diagnosis and the patient's comorbidities, and is used to determine the reimbursement Medicare provides to the hospital. An alternative method for estimating the cost of an inpatient hospital stay is to use the AHRQ's Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) (<http://www.hcup-us.ahrq.gov/>). This large all-payer public database provides inpatient data from a national sample of over 1,000 hospitals in 44 states and is released annually. Mean and median charges and costs of all hospitalizations for a specific primary or secondary diagnosis can be obtained by entering ICD-9 codes. Results can be stratified by demographic information.

Outpatient treatment costs Outpatient treatments in gynecologic oncology often refer to chemotherapy. Cost tabulation should include the CMS reimbursements for the individual chemotherapy drugs and any other medications infused based on the designated J code for each drug. Tests performed routinely over the course of a cycle of treatment should also be included. Finally, the costs of infusion at an outpatient facility should be included using appropriate CPT codes.

Adverse events When 2 or more strategies are compared using a health economic model, it is critical that the adverse events associated with each strategy be accounted for. Specifically, when severe adverse events result in additional medical or nonmedical costs, these costs should be incorporated as well. For example, if one chemotherapy strategy results in a higher

rate of febrile neutropenia, the cost of a hospitalization for this diagnosis should be incorporated into the cost of each strategy in proportion to the probability of the event in each treatment group. Adverse events whose frequencies are not significantly different between strategies or that do not generate additional cost (e.g., grade 1 anemia) may reasonably be omitted from a CEA. However, models should adjust for quality of life differences resulting from adverse events.

Cost collection as a component of Phase III trials While many cost-effectiveness studies are performed following completion of the clinical trials from which the data is derived, such analyses are ideally planned and executed in conjunction with prospective Phase III trials. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices recommends that collection of health economic data should be fully integrated into Phase III studies (16). In a Phase III trial, prospective economic data is usually collected by accounting for differences in health resource utilization between treatment groups. Ideally this might include an accounting of all health-related encounters in each treatment group. However, logistical considerations during trial planning often require prioritization as to which data elements will be collected. Therefore, it is often appropriate to choose to focus on "big ticket" items as well as resources that are expected to differ between treatment arms. Resource utilization collection is accomplished by means of subject diaries in which outpatient and inpatient encounters as well as travel and caregiver time may be recorded. Once resource utilization collection is accomplished, national fee schedules and reimbursements are generally used to assign costs to each element.

Modeling Effectiveness

Effectiveness in CER should be reported in units of relevant clinical outcomes. For example, in oncology studies, effectiveness might be expressed as the number of cases of cancer prevented, the number of unnecessary surgical procedures avoided, or the number of cancer recurrences prevented. However, it is most common in oncology CER to quantify effectiveness using survival. Thus, in cost-effectiveness analyses the comparison of alternative strategies might be described in terms of the cost per additional year of life, or QALY, saved. While overall survival is a standard outcome in both CER and clinical trials, progression-free survival (PFS) may also be reported.

Modeling survival Survival outcomes may be modeled in several ways. One simple method is to assign a survival time (e.g., mean survival in years) to each relevant branch of a simple decision tree. While this method accomplishes the assignment of a survival "value" to each branch of the model, it does not account for additional costs or changes in quality of life that may need to be applied only to subjects who are still alive at a later time. For example, it may be useful to apply the cost of additional cycles of treatment or adverse events to only those individuals remaining alive or progression-free at a specific time point. An alternative, and more common, method is to use a modified Markov state transition model to represent survival (see the section *Construction of a Markov natural history model* below). When a modified Markov approach is used, costs of events that are applied only if a subject is alive or has relapsed may be applied at each relevant time point. Likewise, changes in quality of life during or after treatment may also be quantified. In the context of comparing effectiveness results of a prospective clinical trial, raw survival data can be used to model Kaplan-Meier survival curves directly (Fig. 18.4).

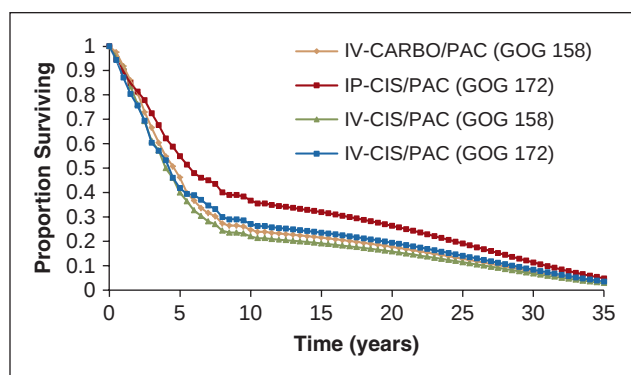


FIGURE 18.4. Survival curve output from a modified Markov state transition model designed to compare the cost-effectiveness of chemotherapy regimens studied in 2 randomized Phase III trials.

Source: Reprinted with permission from Havrilesky LJ, Alvarez-Secord A, Darcy KM, et al. Cost-effectiveness of intraperitoneal compared with intravenous chemotherapy for women with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2008;26(25):4144–4150. (114)

Modeling Quality of Life

Medical interventions in oncology may improve quality of life without extending life, or may extend life but worsen quality during treatment. Economic analyses that are based only on cost and efficacy do not fully account for the value of many treatments and interventions. CUAs account for the morbidity, physical well-being, and emotional well-being associated with medical treatments. CUAs may be used when the interventions being considered affect both quality of life and survival, or when there is no expected difference in survival but a difference in quality of life is anticipated (4).

In CUAs, quality of life is represented by a utility. A utility is a measure of the desirability or preference that individuals or societies place on a given health outcome (17,18). Utility scores are usually linked to judgments about the value of a particular health state. The anchor health states are 0 for death and 1 for perfect health. Applying utility scores to a cost-effectiveness model allows the outcome of the economic analysis, now the CUA, to be reported in QALYs.

Eliciting preferences for calculation of utility scores Use of utility scores in a cost utility model requires a defined health state for each distinct outcome of the intervention and its alternative (19). For example, health states of interest in ovarian cancer CUA may include: (a) newly diagnosed ovarian cancer starting primary chemotherapy; (b) completed primary therapy, no evidence of disease; (c) progressive disease on treatment; or (d) end-stage ovarian cancer. Descriptions of health states are needed for deriving utilities. The description of each health state includes information about levels of physical health, emotional health, activities of daily living, and overall well-being (20). Because psychological studies report that only a limited number of items can be simultaneously considered by an individual, it is recommended that each health state contain no more than 5 to 9 separate aspects (18,19). A rater provides preferences for each health state and a utility score is created.

Raters are selected according to the perspective of the study. For example, if a societal perspective is taken, then representatives of the population should be used to score the preference (6). The preferences of individuals with conditions of interest (such as patients) or of physicians are important ancillary information that might be incorporated into studies performed from alternative perspectives, but these cannot be substituted for societal preferences when the model's perspective is societal (11). Several rigorous formal approaches to the direct

measurement of preferences and calculation of utility scores for health states have been developed, of which the most commonly used are the standard gamble (SG) and the time-trade off (TTO) methods.

The *TTO* method presents the rater with a choice between 2 health states, both of which have a certain outcome (21). Raters choose between a set number of years of life in a certain health state (i.e., with disease) and a shorter number of years of life in perfect health. The shortest period of time in perfect health that a rater would accept in exchange for a lifetime in the diseased state determines the utility score. For example, if the rater would accept living the next 20 years (but no less) in perfect health instead of living the next 30 years in the diseased health state, the utility score for the health state would be 20/30 or 0.67. The *TTO* method is relatively easy for raters to comprehend.

In the *SG*, raters are asked to choose between two alternatives: one with a guaranteed outcome, and an alternative containing uncertainty or a “gamble.” The guaranteed outcome is the less-than-perfect health state that is being rated. The alternative consists of a treatment that has 2 possible results: Perfect health, with a probability of p , or a worst state (such as death) with a probability $1-p$. The value of p is then varied until the rater is indifferent between the choices of the alternative outcome (Fig. 18.5). Visual aids are often used to help the rater understand this exercise, but even with visual aids, some raters have difficulty thinking in terms of probability (19). While there is some debate concerning consistency of results between the *SG* and *TTO*, they are both considered standard methods to elicit utilities (18,19,22).

A simple *visual-analog scale* (VAS) is sometimes used to determine preferences for health states. A rater is shown a line with the anchor states (death, perfect health) at either end. The rater places a mark on this line to demonstrate a preference for the health condition being described. The utility is calculated as the position of the mark on the line divided by the length of the line. Although easy for raters to understand, this method is not “preference-based” due to the lack of the notion of sacrifice that is inherent in the *SG* and *TTO* methods (23). The validity of the visual analog method has therefore not been established, and these scales are only moderately correlated with the results from the *SG* and *TTO* methods (11).

Use of quality of life instruments and health status classification systems to derive utilities for comparative effectiveness research Measuring preferences for health outcomes using the direct *SG* and *TTO* methods is not a simple exercise and is beyond the scope of most clinical trials for which a CUA might be desirable. There exist a number of prescored health status classification systems to allow indirect assignment

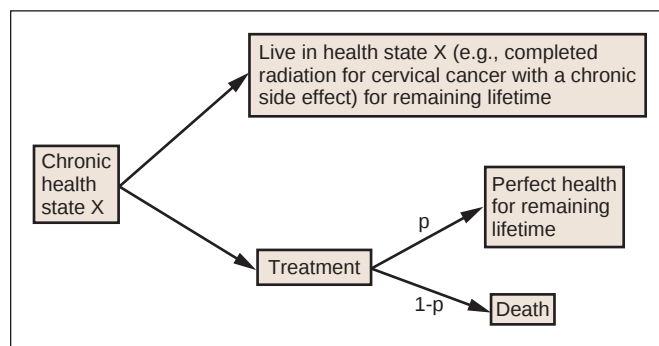


FIGURE 18.5. Schematic describing the standard gamble method to elicit preferences for health states for incorporation into health economic models. “ p ” is the probability that the proposed treatment will result in restitution of perfect health that will last for the remainder of the subject's lifetime.

of utilities based on questionnaires, and calibrated using prior studies of societal preferences. Several of these indirect methods for eliciting utilities are described below.

Health utilities index (HUI) is a family of generic health profiles and preference-based systems that measure health status, report health-related quality of life, and produce utility scores. In the commonly used HUI mark 3 classification systems, attributes for which ratings are provided are vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. In the multi-attribute approach used for HUI, a respondent completes a questionnaire providing information about her health status that is then scored using a multi-attribute scoring function derived from community preference measures for health states (24). While the HUI is considered a highly valid approach for deriving utilities, it has seldom been used in gynecologic cancer clinical trials.

EuroQoL-5D (EQ-5D) is a simple questionnaire in which raters report no problem, some problem, or a major problem in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety and depression (25,26). The ratings are scores from 0 (dead) to 1 (perfect health) and have been measured against the TTO technique on a random sample of 3,000 members of the adult population in the UK (27). The score obtained from the EQ-5D may be directly applied to health economic models and is the method preferred by the UK NICE.

Short form-6D (SF-6D) is a utility instrument based on responses to the longer and widely used SF-36 and SF-12 quality of life questionnaires (28,29). The classification system is based on physical functioning, role limitations, social functioning, pain, mental health, and vitality. The scoring model used for the SF-6D was developed based on the standard gamble utility measurements using a random sample of the UK general population. A scoring table is used to compute utilities from questionnaire responses (4).

Functional assessment of cancer therapy (FACT) is a 33-item scale developed to measure quality of life in patients undergoing cancer treatment (30). It is commonly used in RCTs conducted by the Gynecologic Oncology Group (GOG). The FACT consists of a core instrument (FACT-G) that can be supplemented by various subscales based on the malignancy of interest. While conversion of FACT scores to utilities has been studied (31,32), these methods have not been fully validated. Recent data from the GOG has further evaluated the ability to convert FACT scores to utilities in patients with ovarian cancer, arguing for a prospective trial attempting to address this issue [Hess LM, Brady WE, Havrilesky LJ, Cohn DE, Monk BJ, Wenzel L, Cella D. Comparison of methods to estimate health state utilities for ovarian cancer using quality of life data: A Gynecologic Oncology Group study. *Gynecol Oncol*. 2012 Oct 30. pii: S0090-8258(12)00851-7. doi: 10.1016/j.ygyno.2012.10.024. [Epub ahead of print]]

To date, the TTO and SG methods are the most accepted methods to develop utility scores. While the use of quality of life instruments eases the labor-intensiveness of collecting preferences using the TTO and SG methods, many question the validity of the use of indirect methods such as quality of life instruments to construct CUAs. At present, there is no clearly superior method for determining utility scores either directly or indirectly. Moreover, some believe that utilities should best be derived from patients as they best know their disease condition (33). Others feel that the preferences of the general public are most relevant because society as a whole must delegate distribution of its health care resources (34). As economic analyses evolve, the limitations of preference ratings should be examined and a consistent method of developing utility scores should be determined to allow for better comparisons to be made across cost-utility studies.

COMPARATIVE EFFECTIVENESS OF SCREENING FOR GYNECOLOGIC CANCERS

In the following section, methods for development of cancer natural history models and their use in screening decision analyses will be described. The current state of evidence for cervical and ovarian cancer screening as informed by comparative effectiveness research will then be reviewed.

Modeling the Natural History of Cancer

To evaluate the comparative effectiveness of a proposed cancer screening test for which no Phase III clinical trials have been completed, a model must be created that simulates the natural history of the disease with and without screening. The simplest model is a decision tree. Although decision trees are useful for modeling outcomes that occur over a short period of time, they can become unwieldy when trying to model a disease that occurs over a longer period or that involves recurrent events such as multiple episodes of screening or multiple cycles of treatment. Consider the decision to perform cancer screening on a woman with a family history of *BRCA1/2* mutation. A decision tree could be used to model her likelihood of developing breast or ovarian cancer by 15 years or of dying from another cause over that same time period, but this will not tell us when the woman developed cancer during the given time period, information that may impact the total cost of her care. Another type of model is usually needed to address issues of time dependency when modeling cancer. Markov models are used for events that recur or occur in a predictable manner over time (35). They are particularly well suited to depicting the events associated with cancer, especially cancers that have a screening component.

Construction of a Markov natural history model For creating a Markov model, the natural history of a cancer is broken up into a defined, mutually exclusive, and exhaustive set of states. For cervical cancer, these states would include: well, human papillomavirus (HPV) infection, preinvasive disease, undetected invasive cancer (Stages I through IV), detected invasive cancer (Stages I through IV), cancer death, and death from other causes. For epithelial ovarian cancer, which does not have a universal preinvasive state, natural history states might include: well, undetected and detected invasive cancer (Stages I through IV), cancer death, and death from other causes (Fig. 18.6). Once the states have been defined, movement (usually referred to as “transition”) between the states is defined based on knowledge of the cancer’s natural history. For example, a woman cannot enter Stage II cervical cancer without first having been in Stage I. The arrows in Figure 18.6 depict allowed transitions between states that have been defined for an ovarian cancer natural history model (36). Once the states and allowed transitions have been identified, probabilities of moving from one state to another over a fixed period of time are needed to populate the model. During each “cycle” of the model, allowed transitions between states occur. The cycle length of the model is a time period chosen to correspond to a period that takes into account the natural history of the disease as well as the timing of screening, diagnosis, and treatment recommendations. For most cancers a year is sufficient, although shorter or longer time periods can be used. The probabilities corresponding to the chosen time period for the model (referred to as a Markov cycle) are usually obtained from the epidemiologic literature, an analysis of an epidemiologic study, or expert opinion. Together, the states, allowed transitions, and probabilities constitute the model. Once programmed, the model can be used to calculate different outcomes. Usually, the outcomes are calculated for a cohort

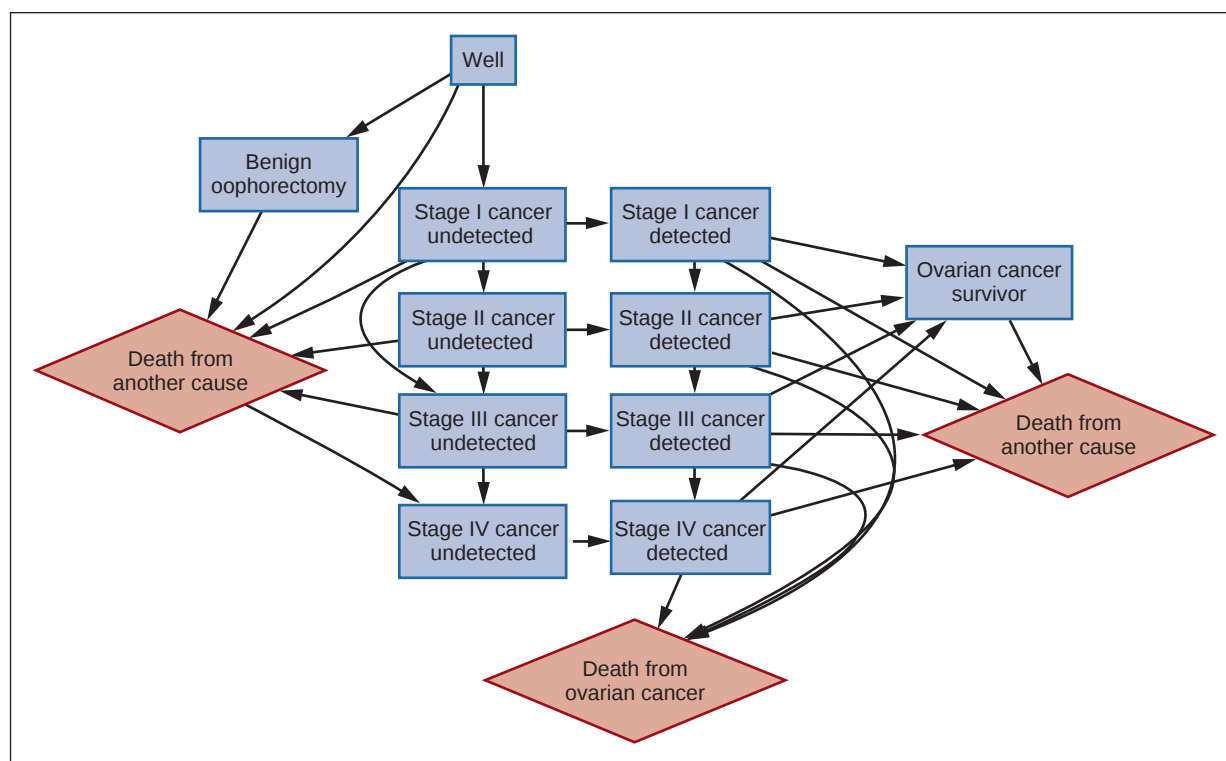


FIGURE 18.6. Influence diagram for models of the natural history of ovarian cancer. Arrows represent allowed transitions between health states. Diamonds represent terminal states.

Source: Reprinted with permission from Havrilesky LJ, Sanders GD, Kulasingam S, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity: implications for potential mortality reduction. *Cancer*. 2011;117(3):545–553. (36)

(or cohorts) of women who are assumed to enter the model at a given age and then followed until death or a later age (i.e., 100 years).

Calibration An important step in developing a model is obtaining probabilities or estimates for key variables (referred to as parameters) from the literature. However, often there are few available estimates, estimates of varying degrees of quality, or even no existing estimates for a given model parameter. The selection of a given clinical estimate is important since this affects the credibility of the model's aggregate result. Calibration is a process that involves comparing the model-predicted results to observed data to ensure a reasonably good fit of one to the other. Model calibration involves several steps: (a) identification of calibration endpoints (for cancer this usually means age-specific cancer incidence, but can also include stage distribution and age-specific mortality curve); (b) establishment of criteria for determining how well the model-predicted data fit the observed data. This may be visual inspection or use of a statistical goodness of fit test; (c) adjustment of the set of model input parameters (i.e., probabilities); and (d) comparison of model-predicted outcomes to observed outcomes using the pre-specified criteria and repeating steps 3 and 4 until a satisfactory calibration is achieved (37).

Figures 18.7 and 18.8 show the calibration results for 2 models (ovarian and cervical) that used visual inspection to achieve calibration (36,38). Another calibration method uses goodness of fit statistics and then selects parameter sets that best fit the observed cancer incidence curve. This latter method improves upon visual inspection in a few ways: (a) the calibration goal is formally stated, which can aide with reproducibility and (b) instead of one good fitting set, multiple sets are used, which can account for parameter uncertainty (39).

Validation Model validation (confirming that a calibrated model predicts results that are consistent with observed results from screening trials) can be achieved in a number of ways. The most robust method is to compare model-predicted outcomes with actual outcomes. For example, Havrilesky et al. constructed a natural history model accounting for the observed heterogeneity of epithelial ovarian cancers. Validation was performed by simulating the published prevalence phase of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) by entering the age and prevalence of disease from the trial population as well as the reported sensitivity and specificity of the trial's multimodality screening algorithm. The model predicted the stage distribution of cancers detected by screening and the positive predictive value of the multimodality prevalence screen within their reported 95% confidence intervals (36). To the degree that simulated results do not reproduce those observed in a clinical trial, the question arises whether there are key input parameters or model structural differences that affect the conclusions. A model can then be revised to determine whether the prediction is improved in an iterative process. Usually, the initial decision to conduct a modeling study is based on the fact that there are no observed data that exist to answer a given question. In this case, model validation is achieved by comparing the results from models built by different, independent groups, to evaluate for similarity. This approach has been adopted by Cancer Intervention and Surveillance Modeling Network (CISNET). CISNET is a consortium of National Cancer Institute (NCI)-sponsored investigators that uses statistical modeling to study cancer control interventions in prevention, screening, and treatment and their effects on population trends in incidence and mortality. The models in this consortium were independently developed and have been calibrated to US data. The U.S. Preventive Services Task Force has used the results from modeling studies conducted

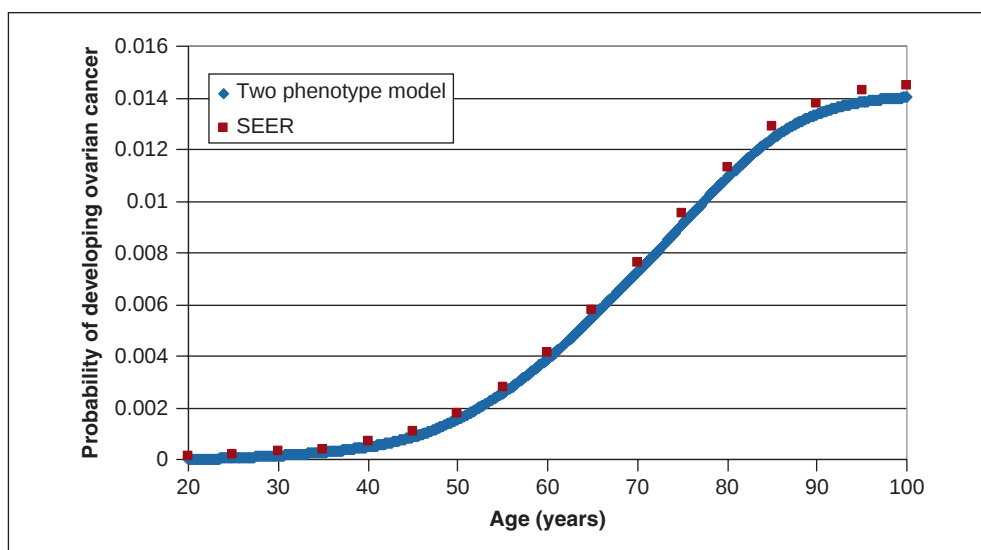


FIGURE 18.7. Calibration of ovarian cancer natural history model on the age-related incidence of ovarian cancer in the US. *Blue line* represents model output; *red dots* represent SEER data.

Source: Reprinted with permission from Havrilesky LJ, Sanders GD, Kulasingam S, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity: implications for potential mortality reduction. *Cancer*. 2011;117(3):545–553. (36)

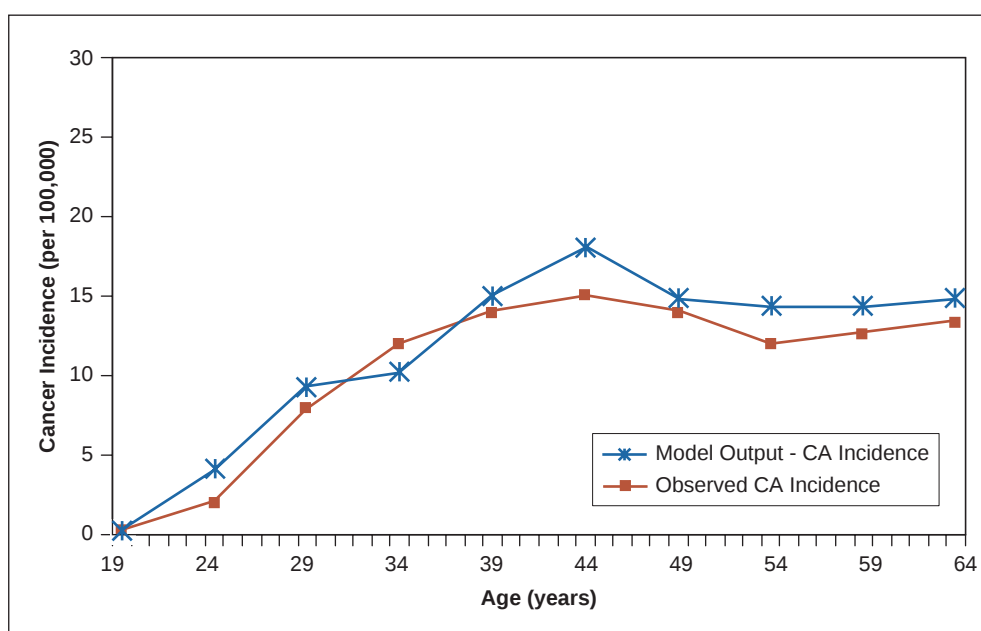


FIGURE 18.8. Calibration of a model of the natural history of cervical cancer on the age-related incidence of cervical cancer in Canada.

Source: Reprinted with permission from Kulasingam SL, Rajan R, St Pierre Y, et al. Human papillomavirus testing with Pap triage for cervical cancer prevention in Canada: a cost-effectiveness analysis. *BMC Med*. 2009;7:69. (38)

by this group to inform their recommendations for colorectal and breast cancer (40,41).

Simulation of Screening

The impact of screening, diagnosis, and treatment can be tracked using a Markov model. Markov models can be programmed to keep count of the outcomes associated with diagnosis, treatment, and screening. Examples include the average number of false-positive or false-negative screening test results, the number of diagnostic procedures such as colposcopy or laparoscopy performed, number of preinvasive lesions detected, and treatments.

Other important outcomes include cancer incidence, stage distribution, and mortality. If the cohort of women is modeled over a sufficiently long period of time, the model can be used to calculate life expectancy, lifetime costs, and quality-adjusted life expectancy.

Cervical Cancer

For cervical cancer, modeling has played a particularly prominent role in informing decisions regarding which screening and triage tests to adopt, how frequently women should be screened, and whether the addition of vaccination to screening is cost-effective. This prominent role is due to the fact that trials of new screening

tests include follow-up and treatment that often differ from clinical practice, or are conducted in non-US populations with different screening histories. Modeling studies can also be used to project both short- and long-term results from trials. For example, trials for the HPV vaccines used cervical intraepithelial neoplasia (CIN) grade 2 or higher as primary outcomes. However, cancer incidence and death are more important outcomes for policy makers. Modeling has been used to estimate the potential cost-effectiveness of adding vaccination to screening. More recently, modeling has been used to justify the expanded coverage of HPV vaccines to include boys. The following sections describe how natural history models of HPV and cervical cancer are constructed, and how such models have been used to inform policies regarding screening and vaccination for cervical cancer prevention.

Natural history of cervical cancer Natural history models have primarily used the CIN nomenclature to characterize progression from HPV infection through preinvasive disease to invasive cancer. CIN 1 is usually modeled as a separate category from CIN 2 or 3, to reflect the general consensus that this lesion represents a self-limited infection that has a high likelihood of spontaneously regressing. However, while some have combined CIN 2 and 3 into a single category (42–47), others have separated these 2 categories (48–50). Separating CIN 2 and 3 in modeling is based on the findings of a large trial that suggested that CIN 2 may be a self-limited lesion, especially in young women (51). Moreover, ongoing and recently completed trials examining the potential role of HPV DNA testing in screening have chosen CIN 3 as the surrogate endpoint for cancer (52). By separating CIN 2 and 3, these models are able to predict the extent to which the detection and treatment of CIN 3 will lead to reductions in cancer incidence and mortality.

Until recently, models have based progression and regression rates between the different states on estimates that were averaged across different HPV types (53). However, models that can quantify the impact of type-specific infection have now been developed, prompted by several factors: (a) the availability of HPV vaccines that are targeted at a few HPV types; (b) the U.S. Food and Drug Administration approval of type-specific HPV tests; and (c) guidelines that allow for triage to immediate treatment based on type-specific HPV infection. These more recent models have stratified progression and regression between different CIN states by HPV type. For example, Sanders and Taira grouped HPV into low- and high-risk types (54), Goldie et al. grouped HPV into low-risk, high-risk, and HPV 16 and 18 (55), and Elbasha et al. modeled 4 HPV types only: HPV 6, 11, 16, and 18 (50). A more recent model by Kim and Goldie (2008), designed to assess vaccine strategies in the US, stratified HPV infection by HPV 16, HPV 18, and other high-risk and low-risk types (56,57). Of note, to assess the potential impact of vaccines with more HPV types than those currently available, Brisson et al. have further stratified an HPV model using 18 HPV types. As our understanding of the natural history of each type grows, HPV type-specific testing is becoming more common and vaccines are being expanded to include additional HPV types. In this changing environment, models will need to further stratify by HPV type to better predict the expected benefits and harms of type-specific testing and vaccination.

Questions Addressed by Cervical Cancer Models

Appropriate age to begin/end and screening interval with cytology A mathematical model of cervical cancer, developed in the 1980s by David Eddy, was used to examine the relationship between screening interval using Pap smears and cancer incidence (58). This modeling study showed that screening every 2 or 3 years would result in 95% to 99% of the cancer reduction benefit of screening every year, but with lower costs and fewer procedures.

In terms of the age to begin and end screening, these have for the most part been based on epidemiologic data showing that cancer incidence peaks in the late 30s to mid-40s, but that the incidence of CIN peaks in the 20s. Given this, guidelines have usually called for screening in the late teens and early 20s, although there has been a shift toward a recommendation to begin screening in the 20s in more recent years (59,60). Canfell et al. modeled the impact of changing the UK screening guidelines to begin at 25 years of age, instead of 21 years (61). They found that if the age to start screening was delayed until 25, the lifetime risk of cancer would be minimally affected (cumulative lifetime incidence decreasing from 0.63% to 0.61%) due to the low incidence of cancer in young women (61). More recently, Kulasingam et al. modeled the impact of varying the age to begin screening in 1-year increments from age 15 years to age 25 years on cancer incidence and mortality (62). They showed that screening in the teens was associated with a high number of additional diagnostic procedures and small reductions in lifetime risk of cancer compared to delaying screening until the 20s. In terms of the age to end screening, Canfell et al. showed that further reductions in lifetime incidence of cancer (from 0.63% to 0.56%) could be achieved if screening were extended from age 64 to 79 and conducted at 5-year intervals (61). Kulasingam et al. estimated the impact of continuing to screen women who had been screened every 3 years since age 21 beyond age 65 years, and showed small incremental reductions in cancer but large increases in additional procedures (62). Although the differences in conclusions between the 2 modeling studies are presumably due to differences in screening intervals modeled, other differences that may play a role include benign hysterectomy rates, deaths from other causes, or cohort effects in screening. Importantly, these studies illustrate how modeling can be used to examine issues related to age that epidemiologic studies may not be able to answer.

Liquid-based cytology versus conventional cytology

Models are particularly useful for predicting the impact of the adoption of new screening tests or treatments on cancer incidence and mortality. However, model conclusions are heavily dependent on the quality of the data used to inform key parameters such as test sensitivity and specificity. An example is the modeling that compared the cost-effectiveness implications of conventional cytology smears to liquid-based cytology smears (63,64). These early studies used estimates of test accuracy from nonrandomized studies. These studies suggested that liquid-based cytology had a higher sensitivity and comparable specificity to conventional cytology. As a result, adoption of liquid-based cytology for cervical cancer screening in the U.S. was predicted to be cost-effective compared to screening with conventional cytology. More recently, however, RCTs and meta-analyses have concluded that there is no significant difference in test performance between liquid cytology and conventional cytology (52).

Use of HPV testing in screening A number of randomized trials (both ongoing and recently completed) have shown that HPV DNA testing is more sensitive but less specific than cytology for detection of CIN 3+ (52). A number of studies have examined the cost-effectiveness of adding HPV DNA testing (with either PCR-based tests or hybrid capture 2) to screening programs (65). Strategies examined include co-testing (simultaneous testing with both cytology and HPV DNA, with referral for treatment if either is abnormal), primary testing with HPV followed by triage using cytology if the HPV DNA test is abnormal, primary testing with HPV only, and primary testing with cytology followed by triage using HPV DNA for those with abnormal cytology results. Across a range of settings, these studies suggest that the cost-effectiveness of adding HPV DNA to cytology-based screening depends on whether the interval between screening tests can be increased as well as the follow-up for women with discordant test results.

Of the different HPV and cytology strategies that have been compared for cost-effectiveness, one strategy in particular shows promise across a range of analyses and settings. HPV DNA testing followed by triage based on cytology for women with positive HPV results has been identified as a potentially cost-effective strategy compared to both cytology alone and the co-testing strategies (66,67). This strategy, which uses a sensitive test first (HPV), followed by a specific test (cytology), allows one to maximize detection of high-grade disease, while potentially minimizing false-positives, thereby reducing the costs of screening. Results from ongoing trials, such as the HPV-FOCAL trial in Canada, which has recently reported preliminary validation of this strategy, will be needed to confirm whether the modeling predictions are correct (68).

Quantifying the impact of HPV vaccination Two types of models have been used to explore HPV vaccine effectiveness: Markov state transition cohort models (described above) and dynamic transmission models, with a third category – hybrid models – that use a combination of the two (69). Dynamic models track population changes over time by taking into account births as well as deaths. Importantly, dynamic transmission models also explain how infection with HPV depends on patterns of sexual behavior and the distribution of infection in the population (70). As such, a strength of dynamic models is that they can be used to determine herd immunity, explore the relative value of vaccinating boys in addition to girls, and explore how sexual mixing patterns (how men and women form partnerships and how these affect transmission) affect the age at which vaccination should begin and age(s) for catch-up programs (i.e., vaccination offered to girls and/or women who are not part of the optimal age group but who may still derive a benefit). These indirect effects are not captured by Markov models; as a result, Markov models may underestimate the effect of vaccination. Hybrid models use both approaches – generating HPV incidence under different vaccination scenarios from a dynamic model, which is then used as an input to the Markov model. A recent modeling study conducted using multiple, independently developed HPV and cervical cancer models concluded that vaccination of girls prior to the age of sexual debut has the potential to considerably reduce the burden of CIN and cervical cancer (71). This is especially true if a long duration of vaccine efficacy and high vaccine coverage are modeled. Vaccine price has also consistently been shown to impact the cost-effectiveness of adding vaccination to screening or adding HPV vaccines to existing vaccine programs. Indeed, if HPV vaccines are priced below certain thresholds for different countries, HPV vaccination could potentially be cost-saving compared to not screening (72). Of note, across a range of analyses, vaccination of girls only prior to onset of sexual activity, as opposed to vaccination of boys and girls plus catch-up vaccination, has been shown to have the most attractive cost-effectiveness profile. However, under conditions of low coverage, as has occurred in the US, extending vaccination to boys is potentially cost-effective (73). On the basis of these results, and survey data showing low uptake of the HPV vaccines in the U.S., the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices decided to extend HPV vaccine recommendations to include boys in addition to girls (http://www.immunize.org/acip/acipvax_hpv.asp). In terms of which vaccine to use (bivalent or quadrivalent), modeling from the UK suggests that the bivalent vaccine (which is targeted at 2 carcinogenic HPV types, 16 and 18) would need to be less costly than the quadrivalent vaccine (which protects against the same HPV types, 16 and 18, as well as 2 types associated with >90% of genital warts) to be equally cost-effective (66,74).

Screening in the era of HPV vaccines The issue of whether and how screening should change in the era of HPV vaccines is complex and will depend on a number of factors that are

still unknown. These include, but are not limited to, the performance of cytology and HPV tests such as hybrid capture 2 that are not type-specific, whether predicted reductions in CIN and cancer are achieved, and whether vaccination will affect screening behavior, in particular, screening participation. Under the assumption that vaccines will markedly reduce cancer incidence and mortality, potentially cost-effective approaches to screening vaccinated cohorts of women include strategies that use a less frequent screening interval, delayed age of first screening, and/or use of a strategy based on HPV DNA testing followed by cytology (66,75). Preliminary modeling to examine the impact of cross-protection and broad spectrum vaccines (such as the Merck octavalent vaccine that is currently in early trials) suggests that far fewer screens than are currently recommended will be needed to achieve significant reductions in cervical cancer (76).

Modeling has been used extensively in cervical cancer to inform how we should approach screening and add HPV vaccination programs to screening programs. Given the development of new tests for cervical cancer and new vaccines that cover more HPV types than the first generation of HPV vaccines, modeling will continue to play a key role in determining the most effective and cost-effective strategies for prevention of cervical cancer.

Ovarian Cancer

Because the majority of ovarian cancers are diagnosed at an advanced stage, there has been considerable interest in designing screening strategies to diagnose and treat women earlier, in the hopes of improving survival outcomes. While screening for breast and colon cancer has been proven to reduce mortality, no screening test for ovarian cancer has yet been proven effective. Several key parameters may impact the success of any cancer screening program: (a) availability of effective treatment for screen positive individuals; (b) sufficiently high disease prevalence; (c) existence of an effective screening test; and (d) acceptable cost or cost-effectiveness of the screening program. Each of these parameters is addressed below in the context of development of a screening test for epithelial ovarian cancer.

Effectiveness of treatment Pathologic and genetic data now suggest that epithelial ovarian cancer is a heterogeneous disease, with a number of different precursor lesions. Many high-grade serous ovarian cancers likely originate in the fallopian tubes, while some clear cell and endometrioid lesions may originate in endometriosis. Because there is no universal, clearly defined precursor lesion for all epithelial ovarian cancer, the target lesion for the screening tests that are currently in Phase III trials is stage I disease. Targeting early-stage disease is appropriate because survival from epithelial ovarian cancer diagnosed at stage I is encouraging. Women with stage I disease with low-risk features may be cured without the need for adjuvant treatment, while those with higher risk stage I disease may still achieve excellent outcomes following 3 to 6 cycles of platinum-and taxane-based chemotherapy (77).

Disease prevalence Perhaps the biggest challenge to the development of a successful ovarian cancer screening program is the low prevalence of this disease. The lifetime incidence of ovarian cancer in the U.S. is approximately 1.4%. In postmenopausal women, the most likely target population for a screening program, its prevalence is approximately 40 per 100,000 women. Disease prevalence has a direct impact on the achievable positive predictive value of a screening test, which defines the number of diagnostic procedures or surgeries that would be required to diagnose one case of ovarian cancer. Expert opinion suggests that the minimal acceptable positive predictive value

for an ovarian cancer screening test should be 10%. To achieve this value in the postmenopausal population, a screening test needs to have a specificity exceeding 99.6%.

Effectiveness of screening test To date, no screening test for ovarian cancer has been proven effective in reducing mortality from this disease. Two large randomized trials have recently been performed to evaluate screening strategies utilizing the CA-125 serum test and transvaginal ultrasound. The Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial randomized 78,216 women to either usual care or a combination of annual CA-125 for 6 consecutive years and annual transvaginal ultrasound for 4 consecutive years (78). Follow-up of test results was determined by each subject's primary physician. After a median follow-up of 12.4 years, there was no difference in stage distribution at diagnosis of ovarian cancer (77%–78% stage III–IV) and no difference in ovarian cancer mortality between the screened and unscreened groups. However, there was evidence of possible harm due to the screening intervention, in the form of a 15% rate of serious adverse events among women with false-positive screening tests who underwent surgical procedures. The authors concluded that simultaneous screening with CA-125 and ultrasound does not reduce ovarian cancer mortality and may introduce harm (79).

A second large screening trial, the UKCTOCS study, randomized 202,638 postmenopausal women to no intervention, annual transvaginal ultrasound, or a multimodality algorithm incorporating annual CA-125 and second-line transvaginal ultrasound. In the prevalence round of screening, the multimodality screening algorithm had a sensitivity of 89.5% and specificity of 99.8% and resulted in a more favorable stage distribution than the no-intervention group, with over 47% of ovarian cancers diagnosed at stage I or II. While mortality results from this trial are pending, the authors concluded that the prevalence screen data were encouraging regarding the feasibility of this screening program (80).

Comparative effectiveness of screening Several groups have used mathematical modeling to determine the likely success and cost-effectiveness of screening strategies. Skates and Singer designed the first reported stochastic simulation model of the natural history of ovarian cancer. This model, which assumed orderly progression from stage I to stage IV and estimated the mean time spent in stage I at 9 months based on the expert opinion of gynecologic oncologists, suggested that screening using CA-125 could potentially save 3.4 years of life per case of cancer detected (81). Urban et al. subsequently modified the Skates and Singer model and performed a cost-effectiveness assessment of several screening strategies. The authors reported that multimodality screening with CA-125 followed by transvaginal ultrasound only if CA-125 was positive or doubling was potentially cost-effective compared to single test strategies and no screening (82).

More recent screening models have incorporated new data about the pathophysiology and progression of ovarian cancer. Havrilesky et al. constructed a natural history model that, based on the physical proximity of the ovaries to upper abdominal organs such as small bowel and omentum, allowed progression of stage I cancers either to stage II or directly to stage III (83). Disease incidence, mortality, and stage distribution were calibrated to reflect Surveillance Epidemiology and End Results (SEER) data. A modified version of this model was designed to account for the heterogeneity of ovarian cancer by modeling aggressive and indolent phenotypes with different rates of progression (36). These models highlighted factors that are important to the success of a screening program. For example, increasing the frequency of screening had a more favorable impact on reducing cancer mortality than increasing the sensitivity of the individual screening test. However, due to the increased cost

of screening more frequently, increasing the frequency actually reduced cost-effectiveness. Both models reinforced the important link between specificity and positive predictive value. An annual screening test with a sensitivity of 85% and specificity of less than 99% would have a positive predictive value not exceeding 4%. However, at a specificity of 99.9%, the positive predictive value for annual screening was excellent at 22%. Annual screening of a population of women aged 50 to 85 years at average risk of ovarian cancer with a test at 85% sensitivity and 95% specificity was predicted to improve life expectancy 2.92 days on average, with an ICER of \$73,469/YLS compared to no screening. However, simulated screening of a “high-risk” population of women aged 50 to 85 years with a relative risk of developing ovarian cancer of 2 resulted in an improvement in the ICER to \$36,025/YLS when compared to no screening. In sensitivity analysis, key factors in achieving a cost-effective screening test (defined as an ICER of less than \$50,000/YLS) were an inexpensive test, a very high test specificity, and infrequent (annual or less) testing. Screening appeared to be potentially most cost-effective when the test specificity was well above 99% and the testing interval was annual or less frequently (83).

These prior models confirm that very high test specificity is required to achieve acceptable positive predictive values and that population-based screening may not be cost-effective in the form currently being evaluated in clinical trials. However, annual screening for ovarian cancer appears to be potentially cost-effective in high-risk populations and at very high screening test specificities. Both mortality data and final analysis of the costs of the multimodality screening algorithm in the UKCTOCS trial are critical to any assessment of the costs, benefits, and potential cost-effectiveness of currently available screening strategies. Moreover, because none of the health economic models of screening performed to date have taken quality of life into account, any health economic assessments of ovarian cancer screening would be premature.

Primary prevention in high-risk women Women who are carriers of genetic mutations in *BRCA1* or *BRCA2* are at markedly increased risk for ovarian cancer; the average risk of developing ovarian cancer by age 70 is 39% (95% confidence interval [CI], 18%–54%) for *BRCA1* mutation carriers and 11% (CI, 2.4%–19%) for *BRCA2* mutation carriers (84). Likewise, women with Lynch syndrome-associated *MLH1* and *MSH2* mutations have up to 20% (CI, 1%–65%) and 24% (CI, 3%–52%) risk, respectively, of developing ovarian cancer by the same age (85). Although the prevalence of genetic mutations predisposing women to ovarian cancer in the general population is low, the high risk of cancer among women who are mutation carriers underscores the importance of modifying their likelihood of developing cancer.

The choice of a risk-reduction strategy for women at elevated risk is an individual one and commonly includes screening strategies and prophylactic surgery. Unfortunately, screening high-risk women with available modalities has not yet proven successful (86–88). In a *BRCA1/2* mutation-carrying population, bilateral salpingo-oophorectomy (BSO) has been demonstrated to reduce the risk of ovarian, tubal, or peritoneal cancers by 80% and the risk of breast cancer by 50% (89). In addition, several groups have designed health-economic decision models demonstrating that prophylactic surgery is both effective and cost-effective in women at high genetic risk for ovarian cancer (90–93). However, surgical prophylaxis performed prior to menopause is accompanied both by potential harm and the certain premature loss of ovarian function and is not generally recommended in the general population (94,95). Despite the effectiveness of prophylactic BSO, some women at high risk prefer alternatives that are less invasive, do not result in early menopause, and preserve fertility. The GOG is currently completing a nonrandomized

prospective trial comparing longitudinal screening with CA-125 and ultrasound to risk-reducing BSO in a high genetic risk population (96). This trial includes both subsequent cancer diagnoses and quality-of-life assessments, and may be informative from a comparative effectiveness standpoint.

COMPARATIVE EFFECTIVENESS OF THERAPEUTICS IN GYNECOLOGIC CANCERS

The comparative effectiveness literature regarding therapeutic interventions for gynecologic malignancies is reviewed in the next section.

Ovarian Cancer

Chemotherapy for newly diagnosed ovarian cancer The standard treatment for ovarian cancer is primary surgical staging with maximum possible cytoreduction followed by chemotherapy. Intravenous chemotherapy usually consists of a taxane and a platinum agent for 3 to 6 cycles; patients with advanced intraperitoneal disease are often candidates for intraperitoneal chemotherapy (97). The addition of bevacizumab to primary chemotherapy followed by consolidation bevacizumab has been found to provide a short-term additional benefit in Phase III trials (98,99). Likewise, dose-dense paclitaxel was associated with clinical benefit in one Phase III trial and is now under investigation by the GOG (100). As novel chemotherapy regimens for primary treatment emerge, some consideration should be given not only to the number of months of survival benefit, but to the costs and effects on quality of life of each.

Introduction of taxanes The first cost-effectiveness studies in ovarian cancer chemotherapy were performed in response to the introduction of taxanes into the frontline chemotherapy regimen for this disease. Two independent RCTs, conducted by the GOG 111 and a European-Canadian Intergroup (OV-10), demonstrated that cisplatin plus paclitaxel as primary chemotherapy is superior to previous therapy of cisplatin plus cyclophosphamide in clinical response rate, progression-free survival, and overall survival (101–103). Three Phase III RCTs subsequently proved similar efficacy of paclitaxel in combination with either carboplatin or cisplatin for the adjuvant treatment of ovarian cancer (104–106). The carboplatin combination was better tolerated and has subsequently become a standard first-line treatment (107).

When first introduced, paclitaxel-cisplatin was a more expensive therapy than the old standard of cyclophosphamide-cisplatin. A number of cost-effectiveness investigations were performed using data from GOG 111, which compared cisplatin plus paclitaxel to cisplatin plus cyclophosphamide. From the perspective of a US oncology practice, the total drug costs for cisplatin plus paclitaxel were 4 times higher than those for cisplatin plus cyclophosphamide (US \$9,918 vs. US \$2,527; year of costing not specified) (108). Compared with cisplatin plus cyclophosphamide, the incremental costs per year of life gained for cisplatin plus paclitaxel therapy were US \$19,820 for inpatient treatment and US \$21,222 for outpatient treatment. These incremental costs fall well within the generally accepted cost-effective range for new therapies.

Several cost-effectiveness analyses examined the addition of paclitaxel to first-line therapy from the perspective of health systems outside the US. From a Canadian health system perspective, cisplatin plus paclitaxel had an ICER of CaD \$32,213 (1993 costs for drug and hospital costs) per life-year gained compared to cyclophosphamide-cisplatin (109). The investigators originally

concluded that it may not be possible to adopt this therapy as first-line for all advanced-stage ovarian cancer patients because it would cost the province of Ontario an additional CaD \$9 million a year. Berger et al. investigated the cost-effectiveness of cisplatin plus paclitaxel from the perspective of various European countries' national health services. The incremental costs of cisplatin plus paclitaxel per life-year saved were evaluated for Germany (US \$9,362), Spain (US \$6,395), France (US \$6,642), Italy (US \$11,420), the Netherlands (US \$7,796), and the UK (US \$6,403) (110).

Carboplatin and paclitaxel are now both marketed as generics, and therefore these prior studies are less applicable than when originally published. Given the current low cost of paclitaxel, any clinically superior regimen using this drug is also likely to be found cost-effective. Chan et al. have recently performed an economic analysis based on results of a Phase III Japanese GOG trial (100), demonstrating that weekly dose-dense paclitaxel is cost-effective compared to a 3-week regimen in the setting of primary treatment (111).

Intraperitoneal chemotherapy The NCCN Guidelines for ovarian cancer recommend intraperitoneal (IP) chemotherapy as primary/adjuvant therapy for optimally debulked (<1cm) stage II or greater ovarian cancer treatment (112). Three Phase III clinical trials have identified advantages to the use of IP chemotherapy for adjuvant treatment of stage III ovarian cancer (97,113,114). The most recent of these studies demonstrated an overall survival advantage of 16 months in the IP arm at the expense of increased risk of adverse events and a significant reduction in quality of life.

Two analyses have evaluated the cost-effectiveness of IP chemotherapy for the primary treatment of stage III ovarian cancer. When comparing IP to intravenous (IV) chemotherapy, Bristow et al. reported that IP chemotherapy was potentially cost-effective compared to IV, with an ICER of \$37,454 per QALY (115). Havrilesky et al. reported an estimate of \$180,022 per QALY when using a 7-year time horizon, which was consistent with the current duration of survival results from GOG 172 (116). However, when the time horizon was extended to a lifetime under the assumption that any survival advantage realized with IP chemo would persist over that period, the ICER of IP chemotherapy dropped to \$32,053 per QALY. Also of note, under the assumption that IP chemotherapy is equally effective as an outpatient regimen, the ICER of IP compared to IV chemotherapy becomes even more attractive. While both studies informally incorporated quality of life based on the FACT surveys administered to patients enrolled on GOG trials of chemotherapy, neither performed a validated utility assessment. Conclusions that may be drawn from these studies are that IP chemotherapy is potentially cost-effective for women with stage III disease, but that more formal incorporation of quality of life, longer term follow-up of the results of the last Phase III study, and investigation of less costly outpatient IP regimens would strengthen this conclusion (115,116).

Bevacizumab Bevacizumab is an anti-vascular endothelial growth factor (VEGF) inhibitor of angiogenesis and is FDA-approved for treatments of renal cell carcinoma, colorectal cancer, glioblastoma, and non-small cell lung cancer. The ICON7 and GOG 218 Phase III clinical trials of newly diagnosed ovarian cancer independently reported a small 2- to 6-month PFS advantage to the addition of bevacizumab to primary combination carboplatin/paclitaxel, followed by 14 to 22 additional cycles of consolidation bevacizumab in the absence of progression (98,99). Even prior to the initial presentation of this data in ovarian cancer, questions were raised about the cost of universal bevacizumab. Cohn et al. performed a cost-effectiveness analysis examining the likely clinical benefit of bevacizumab and the cost of the drug as well as its associated adverse events. This analysis demonstrated that there was no reasonable scenario

under which bevacizumab could be considered cost-effective by existing measures (117).

A subset analysis of the ICON7 data revealed that the main benefit appears to be confined to women with high-risk disease such as those suboptimally cytoreduced and those with stage IV disease (99). While, ideally, treatment of a smaller subset of women with ovarian cancer who are most likely to benefit would make this drug more cost-effective, initial attempts at modeling this scenario did not demonstrate this to be a cost-effective alternative (118).

Consolidation therapy Consolidation regimens that have been studied for ovarian cancer are paclitaxel and bevacizumab; both have proven PFS benefits but neither has demonstrated an overall survival benefit. Lesnock et al. performed a cost-effectiveness analysis of consolidation therapy following carboplatin/paclitaxel, comparing 12 months additional paclitaxel to 17 cycles of additional bevacizumab. Clinical data were derived from the PFS results of GOG 178 and GOG 218. Consolidation therapy with paclitaxel was found to be cost-effective, with an ICER of \$13,402 compared to no consolidation therapy. Bevacizumab consolidation was dominated (less effective and more costly) by paclitaxel consolidation. This study was performed prior to mature overall survival results of GOG 218 and the authors noted that a significant overall survival improvement would potentially improve the value of bevacizumab consolidation (119).

Chemotherapy for recurrent ovarian cancer Most women with ovarian cancer will achieve clinical remission following surgery and primary adjuvant chemotherapy. Unfortunately, the majority of patients eventually develop recurrent disease which is rarely curable (120). Patients who experience recurrence more than 6 months after completing a first-line chemotherapy regimen are considered to have “platinum-sensitive” ovarian cancer and have an excellent response rate when re-treated with platinum agents (121,122).

The optimal treatment of recurrent ovarian cancer is subject to ongoing debate and is affected by considerations of survival, toxicity, and quality of life. Patients with platinum-sensitive disease have a good response rate to re-treatment with platinum-based regimens; two large RCTs have compared the use of single-agent therapy with combination regimens for platinum-sensitive ovarian cancer. These studies identified a PFS advantage for the combination regimens of gemcitabine plus carboplatin and paclitaxel plus platinum chemotherapy regimens (as well as an overall survival advantage for paclitaxel plus platinum) compared to platinum alone, and the authors suggested that the combination regimens should be considered standard of care (123,124).

On the basis of these 2 studies, Havrilesky et al. designed a Markov state transition model that evaluated the optimal treatment strategy for patients with recurrent platinum-sensitive ovarian cancer. Paclitaxel plus carboplatin had an ICER of \$15,564 per additional progression-free year compared to single-agent carboplatin, while gemcitabine plus carboplatin has a less attractive ICER of \$278,388 per additional progression-free year compared to paclitaxel plus carboplatin (125). Given that both carboplatin and paclitaxel are now available as generic drugs in the US, their cost advantage is not surprising. Neurologic and hematologic toxicities of the regimens were incorporated into a sensitivity analysis that varied the severity and costs associated with treatment. Over a reasonable range of utility scores, paclitaxel plus carboplatin was still cost-effective compared to carboplatin alone, and gemcitabine plus carboplatin remained non-cost-effective (125). These results must be interpreted on an individual basis with an individual's prior adverse event profile in mind; for example, it is unlikely that a patient with severe neurotoxicity due to prior taxane treatment would be re-treated with the same drug.

Recurrent ovarian cancer that occurs within 6 months of completing a first-line chemotherapy regimen has a poor prognosis, with cure being very unlikely. Rocconi et al. performed a cost-effectiveness analysis of treatment options for recurrent platinum-resistant ovarian cancer and concluded that only best supportive care (no chemotherapy) was clearly cost-effective, while second-line monotherapy was possibly marginally cost-effective (ICER \$64,104/YLS) as well (126). Even without incorporation of toxicity rates and costs, the authors found that combination chemotherapy regimens were never cost-effective for platinum-resistant disease due to unfavorable ICERs.

Cervical Cancer

Primary treatment The standard treatment of cervical cancer has been established for very early-stage and locally advanced-stage disease. However, there is continued debate over the appropriate treatment of Stage IB2 disease (127). Current options include primary surgery with radical hysterectomy and lymphadenectomy followed by tailored chemoradiation, primary chemoradiation, or neoadjuvant chemotherapy followed by radical hysterectomy and tailored chemoradiation. The choice of therapy depends on many factors including available resources, costs, patient characteristics, and physician preferences.

Two groups have developed health economic models to inform the treatment of stage IB2 cervical cancer. Rocconi et al. developed a decision model with a third-party payer perspective to compare 3 strategies: (a) radical hysterectomy followed by tailored therapy; (b) primary chemoradiation; and (c) neoadjuvant chemotherapy followed by simple hysterectomy. The metric used for comparison was a cost-effectiveness ratio in dollars per patient cured. Cure was defined as survival disease-free at 5 years. An ICER was not reported. Radical hysterectomy was the least costly strategy per survivor at \$41,212. Chemoradiation and neoadjuvant chemotherapy was followed by simple hysterectomy cost \$43,197 and \$72,613 per survivor, respectively (128). The authors concluded that radical hysterectomy is the most cost-effective treatment for stage IB2 cervical cancer.

In a second analysis, Jewell et al. used a modified Markov state transition decision model to compare primary chemoradiation (CR) to primary radical hysterectomy with tailored adjuvant therapy (RH+TA) for the treatment of stage IB2 cervical cancer. A third-party (payer) perspective was assumed. A small percentage of patients in the RH+TA group were assumed to have the radical hysterectomy abandoned due to advanced disease not detected by preoperative positron emission tomography (PET)/computed tomography (CT). Patients undergoing completed radical hysterectomy were divided into 3 risk groups based on surgical pathologic risk features. On the basis of literature review, it was assumed that 5% of patients would have high-risk features on final pathology, 85% would have intermediate-risk features, and 10% low-risk features. Patients with high-risk features were assumed to receive adjuvant chemoradiation (4500 cGy external beam radiotherapy with weekly sensitizing cisplatin followed by vaginal cuff high-dose rate [HDR] brachytherapy). Patients with intermediate-risk features would either receive no adjuvant treatment or external beam radiotherapy plus chemotherapy. Patients at low risk for recurrence would receive no adjuvant treatment. Adverse events included in the model were: anemia, neutropenia, deep vein thrombosis/pulmonary embolism, gastrointestinal fistula, genitourinary fistula, hydronephrosis, bladder dysfunction, small bowel obstruction, radiation proctitis, cystitis, severe infection, and vaginal dysfunction. The costs for individual primary treatment modalities were obtained using 2007 national Medicare reimbursement and fee schedules (<http://www.cms.hhs.gov>). The costs associated with treatment of each severe (CTCAE grades 3–5) nonhematologic adverse event were obtained from the national database of the

AHRQ's HCUP (www.hcup.ahrq.gov). The model predicted 5-year overall survival of 79.6% in the RH+TA arm and 78.9% in the CR arm. The mean cost of RH+TA was \$27,840 compared to \$21,403 for CR. The ICER comparing RH+TA to CR was \$63,689 per additional YLS (129).

Although this analysis did not find that radical hysterectomy was cost-saving, sensitivity analysis showed that radical hysterectomy was potentially cost-effective (i.e., the cost per life-year saved was within the range considered acceptable—approximately \$50,000–75,000/life-year) (129). While Rocconi et al. found radical hysterectomy with tailored adjuvant therapy to be the least expensive option, Jewell et al. found that RH+TA was the costlier treatment option in the base case. The difference in the outcomes may be related to Jewell's assumption that a higher proportion of women with stage IB2 cervical cancer who are treated with RH will receive adjuvant radiotherapy (47% vs. 40%), or their lower cost estimates for radiation treatments, possibly due to the use of Medicare reimbursement data to approximate costs and an institutional practice of using LDR, which appears to be less costly than HDR.

The differences in the outcomes in these models demonstrate the difficulty in economic analyses and show how the assumptions, inputs, and design of a model are critical to its results. These models were strictly cost-effectiveness models and neither incorporated quality-of-life measures. Cost-effectiveness models that lack consideration of quality of life may under- or over-estimate the value of a given treatment strategy.

Quality-of-life-related preferences for treatment Jewell et al. elicited preferences for calculation of utility scores from cervical cancer survivors and the general public for the treatment of early-stage cervical cancer. The authors created descriptions of health states that included detailed information about available treatments for early-stage cervical cancer. Surgical scenarios ranged from minimally invasive radical hysterectomy with low-risk pathology requiring no additional treatment to aborted radical hysterectomy due to locally advanced disease followed by primary chemoradiation and brachytherapy. Primary chemoradiation (including teletherapy and brachytherapy) was also evaluated. Physical and emotional aspects of each treatment were outlined and, where appropriate, details about initial postoperative recovery, outpatient whole pelvic radiation, outpatient chemotherapy, and inpatient brachytherapy were described in each health state scenario. Common side effects were incorporated into each description. The TTO method was used. Health states describing chemoradiation were less preferred than health states describing surgery, regardless of whether adjuvant chemoradiation was given (Table 18.2). Even in health scenarios with similar 5-year survival, subjects ranked surgery followed by tailored adjuvant treatment as equivalent or slightly preferred over primary chemoradiation. The subject ranked a minimally invasive approach as most preferred, suggesting that an overnight hospitalization, smaller incision sites, and faster return to activities of daily living are preferred (130).

Use of radiation therapy in cervical cancer Intracavitary radiation treatment is recognized to play a significant and important role in the standard radical radiotherapy treatment of cervical carcinoma. The majority of centers worldwide use either low-dose rate (LDR) or high-dose rate (HDR) methods. Randomized trials have confirmed the apparent equivalence of HDR and LDR in terms of the incidence of adverse effects, tumor control, and survival (131). HDR is becoming more prevalent, possibly based on its outpatient nature, the ability to treat a greater number of patients, the ability to treat tumors at different sites, and the perceived cost savings to the health care system mainly due to the outpatient setting of the treatment. However, HDR treatment costs per insertion are frequently greater than

Table 18.2 Utility Scores Elicited from Members of the Public and Cervical Cancer Survivors for Health States Related to the Treatment of Newly Diagnosed Cervical Cancer

Rank	Treatment	Mean	95% Confidence Intervals
1	Minimally invasive radical hysterectomy No adjuvant treatment	0.94	0.89–0.99
2	Radical hysterectomy Low-risk features No adjuvant treatment	0.89	0.82–0.97
3	Radical hysterectomy Intermediate-risk features No adjuvant treatment	0.89	0.82–0.96
4	Radical hysterectomy Intermediate-risk features Adjuvant chemoradiation	0.80	0.72–0.89
5	Radical hysterectomy High-risk features Adjuvant chemoradiation High-dose rate brachytherapy	0.78	0.69–0.87
6	Primary chemoradiation	0.76	0.66–0.85
7	Aborted radical hysterectomy due to extent of disease Primary chemoradiation	0.68	0.57–0.79

Reprinted from Jewell EL, Smrtka M, Broadwater G, et al. Utility scores and treatment preferences for clinical early-stage cervical cancer. *Value Health*. 2011;14(4):582–586, with permission. (130)

LDR and increasing attention is now being paid to thorough health economic analysis by health care professionals in an attempt to reduce the escalating health care costs.

Jones et al. undertook a formal analysis of LDR versus HDR brachytherapy from a Canadian hospital perspective (132). The cost model incorporated fixed and direct costs arising from equipment purchases, equipment maintenance fees, costs of patient care, and operating costs (staff and operating room costs). The cost to a hospital of an HDR administration unit is greater than the costs of each type of LDR unit. On the basis of this cost difference and the practical limitations on the number of patients who can be accommodated by each machine per year, this study demonstrated that the LDR technique is less expensive when treating up to 80 patients per year. However, the ability to treat a significantly greater number of patients and the potential to treat other sites made the use of an HDR unit a more reasonable choice for centers where over 80 cervical cancer patients are treated annually. Therefore, purchase of an HDR unit is a cost-saving strategy for centers with a greater caseload.

Endometrial Cancer

Endometrial cancer is a disease in which outcomes research can be challenging; despite the high incidence of disease, the event

rate (recurrence or death) is low. The result of these characteristics is that any intervention must be extremely powerful to demonstrate a statistically significant improvement in cancer specific outcomes. As such, randomized clinical trials for cases that are at low- or intermediate-risk for recurrence may take a long time to accrue and demonstration of significance may be challenging. The CER approaches, therefore, may be quite relevant in endometrial cancer. CER in endometrial cancer spans the aspects of surgical management, the use of adjuvant radiation and chemotherapy, surveillance for disease recurrence, and the evaluation and management of individuals at risk for or diagnosed with Lynch syndrome-associated cancers.

Perioperative Setting

CER techniques have been most commonly utilized in the evaluation of surgical management of endometrial cancer, and most commonly are related to the cost-effectiveness of various interventions. Given the current controversies regarding the role and expense of preoperative testing, minimally invasive surgery, and the performance of a lymphadenectomy, significant opportunities exist to utilize CER to address these perioperative issues in endometrial cancer.

Preoperative Testing

The use of preoperative imaging in patients with clinical stage I endometrial cancer has, in certain circumstances, been demonstrated to identify disease that might not be amenable to resection. While certain authors supported the strategy of preoperative CT in patients planned to undergo surgery for endometrial cancer, others questioned the effectiveness and cost of this intervention. Bansal et al. performed a study evaluating patients with endometrial cancer who underwent a preoperative CT of the abdomen and pelvis (133). In 7/250 (3%) patients over a 16-year period, the CT results led to an alteration of the surgical plan. In patients with high-risk histology (serous, clear cell, and sarcoma), the plan was changed in up to 13% of cases. When the cost of imaging was incorporated into their model, the authors estimated that more than \$17,000 was expended to alter the management of 1 patient. As such, the authors argued that routine preoperative CT in patients with clinical stage I endometrial cancer was not cost-effective.

Surgical Approaches to Endometrial Cancer Staging

Laparotomy versus minimally invasive surgery. Over the last few decades, minimally invasive surgery has been incorporated into the management of many malignancies, including endometrial cancer. Initial reports of this surgical approach demonstrated the feasibility and acceptable toxicity of laparoscopic staging for endometrial cancer. Subsequently, randomized trials of laparotomy versus laparoscopy were reported, including studies from the Netherlands (134), Australia (135), and the U.S. (136), all demonstrating similar oncologic outcomes between groups. Furthermore, these trials demonstrated that laparoscopy was associated with a modest improvement in quality of life compared to laparotomy (137,138). Recently, the investigators from the Netherlands evaluated the cost of treatment relative to the survival and quality of life in subjects undergoing laparotomy or laparoscopic staging of their endometrial cancer (139). These investigators suggested that despite a slightly increased cost for minimally invasive surgery (higher operative costs but lower hospital stay costs), total laparoscopic hysterectomy remains cost-effective because of the low rate of complications seen in the minimally invasive arm compared with laparotomy. While the absolute costs seen in this population may not be identical to that in other geographic regions, it is likely that trends favoring the cost-effectiveness of minimally invasive surgical staging for endometrial cancer would be similar to those in other parts

of the world. This group also performed a meta-analysis of 12 trials of laparoscopic endometrial cancer surgery and reached the conclusion that laparoscopy was cost-effective compared to laparotomy (10), acknowledging that the lack of quality-of-life data precluded a definitive statement regarding the utility of this procedure from a societal perspective.

Laparoscopy versus robotic surgery. In 2006, the FDA cleared the first computer-aided (robotic) surgical system for hysterectomy. There has subsequently been a rapid incorporation of robotic surgery into gynecologic cancer practices, mainly for the treatment of endometrial cancer. Initial reports of this surgical approach demonstrated feasibility and acceptable toxicity. However, the initial purchase price of the robot (>\$1 million), yearly maintenance contract (>\$100,000 annually), and limited use disposable instruments add a fixed cost to this procedure over laparoscopy or laparotomy. Given the expense of robotic surgery, analyses of the cost of robotic surgery have been published, often with differing conclusions. Initially, Bell et al. described a series of patients who underwent abdominal, laparoscopic, or robotic staging for endometrial cancer, with the robotic approach being found less costly compared with laparotomy, but not significantly more expensive than laparoscopy (9). Subsequent to this report, other CER approaches have been utilized to assess the cost-effectiveness and comparative effectiveness of robotic surgery compared to other surgical approaches. Barnett et al. utilized decision modeling from the perspectives of both society and the hospital (with and without the cost of the purchase of the robot incorporated) to assess the impact of surgical approach (laparotomy, laparoscopy, and robotic) for staging of endometrial cancer (7). These authors concluded that while laparoscopy is the least expensive approach, the decreased societal cost associated with an early return to normal function makes robotic surgery less expensive than laparotomy. In sensitivity analysis, when the costs of disposable instruments and equipment are minimized to less than one-half their current cost, robotic surgery becomes the least costly approach. The modeling approach with sensitivity analyses is critically important in helping to understand the factors which drive cost in endometrial cancer surgery, and to acknowledge that the perspective from which the analysis is taken significantly impacts the conclusions that can be drawn. Additionally, a population-based CER analysis was undertaken by Wright et al. describing more than 2,400 women who underwent minimally invasive surgery for endometrial cancer, 58% robotically and 42% laparoscopically (140). These authors found similar rates of complications and an increased cost with robotic surgery, and concluded that longer term outcome data regarding robotic surgery are necessary before this approach is considered standard for the management of endometrial cancer. Collectively, the CER data regarding robotic endometrial cancer surgery suggest an increased cost, decreased morbidity compared with laparotomy, and cost-effectiveness that varies based on the perspective from which the data are interpreted.

Lymphadenectomy for surgical staging. Following two randomized trials suggesting that lymphadenectomy for endometrial cancer does not improve outcomes (141,142), the role of this procedure in the routine management of endometrial cancer has undergone increased scrutiny. Various strategies have been suggested to identify patients who are at highest risk for metastasis to the lymph nodes, and generally incorporate tumor grade, depth of myometrial invasion, histology and tumor size. Various authors have evaluated the cost-effectiveness of the strategies of routine lymphadenectomy versus a selective staging strategy. Kwon et al. suggested that as tumor grade increases, lymphadenectomy is more cost-effective than its omission, mainly due to the reduced rate of radiation in node-negative patients (143). Cohn et al. modeled grade 1 cancers and demonstrated that even in this group of patients at low risk for

lymph node metastasis, routine lymphadenectomy was more cost-effective than a strategy wherein lymphadenectomy is performed selectively, assuming a lower rate of adjuvant radiation in the staged patients (144). Importantly, these authors did not include an analysis of complications or quality of life in their models. Another approach to address the role of surgical staging would be to develop a test that could predict, prior to surgery, which patients are at highest risk for the presence of lymph node metastasis. Havrilesky et al. modeled such a hypothetical test and determined that a test that could reliably predict lymph node metastasis could be cost-effective as long as it was fairly inexpensive (145). Importantly, the cost-effectiveness of such a strategy is independent of the cost of adjuvant therapy in their model.

Adjuvant radiation therapy. A number of studies have been performed analyzing the comparative cost and cost-effectiveness of adjuvant radiation in patients with endometrial cancer. Lachance et al. reported a model that included patients with stage I endometrial cancer, and evaluated strategies of observation, vaginal brachytherapy, and pelvic teletherapy (146). The authors estimated that vaginal brachytherapy would significantly reduce recurrences at an expense of almost \$66,000 per survivor. While teletherapy could reduce recurrences as well, its use was associated with greater expense without an increase in survival beyond that of vaginal brachytherapy. In another study in patients with early-stage disease at intermediate risk for recurrence, Rankins et al. created a decision model demonstrating that the cost-effectiveness of adjuvant pelvic teletherapy was dependent on the risk of recurrence and the efficacy of adjuvant therapy; in the population enriched for a high risk for recurrence, radiation was cost-effective (147). These data suggest that routine adjuvant radiation for early-stage endometrial cancer is not cost-effective. However, in patients at a high risk for recurrence, this balance shifts, with adjuvant therapy becoming adequately cost-effective to recommend its use. Again, these studies are plagued by their lack of information on quality of life, specifically given the increasing data suggesting a deterioration of the quality of life domains of sexuality, urinary, and intestinal functions in patients receiving certain forms of radiation for endometrial cancer (148).

Surveillance for endometrial cancer recurrence. Given that the survival of women with endometrial cancer is approximately 85% overall, investigators have challenged the notion that routine intermittent surveillance for pelvic examination and vaginal cytology (with or without chest imaging) is cost-effective or even necessary for most women with endometrial cancer. In support of the trend toward decreased intensity of surveillance, it has been estimated that the cost of routine vaginal cytology to identify a single asymptomatic recurrence is more than \$44,000 (149). Whether the identification of this asymptomatic individual leads to improved outcomes is even less certain (150).

Lynch syndrome. From clinic-based studies, it is estimated that 2.3% of patients with endometrial cancer have Lynch syndrome as the cause of their disease (151). Given the relatively low prevalence of the disease, the ability to distinguish these patients from all those with sporadic disease would be enormously beneficial, as the probands and their families could be introduced to prevention and screening interventions that might decrease the risk of dying from Lynch-related malignancies. However, the clinical Amsterdam criteria are relatively insensitive and non-specific in identifying Lynch syndrome. Thus, many institutions

have begun utilizing immunohistochemistry (IHC) for the DNA mismatch repair genes as an initial screen for Lynch syndrome. Health economic studies of this strategy have demonstrated that utilizing IHC in patients with a first-degree relative with a Lynch-associated cancer is cost-effective (152). Other investigators, while acknowledging that clinical judgment is key to the interpretation of their model, have shown that the routine use of IHC, with a subsequent triage to genetic testing if IHC is abnormal, is potentially cost-effective when compared to other screening strategies (153).

Additionally, the cost-effectiveness of strategies to prevent the disease in probands with known Lynch syndrome has been evaluated. Kwon et al. demonstrated that in this population, annual surveillance with endometrial biopsy, pelvic ultrasound, and CA-125 at 30 years plus risk-reducing hysterectomy and oophorectomy at 40 years is the most effective strategy, though substantially more expensive than preventative surgery alone or screening alone, with an additional \$194,000 spent per increase in year of survival compared to the next best strategy (93). The cost-effectiveness of risk-reducing surgery has also been confirmed by Yang et al., who demonstrated that this intervention is more cost-effective than either yearly examination or yearly invasive screening for malignancy (154).

Summary

Gynecologic oncology provides a rich opportunity to investigate the comparative effectiveness of various diagnostic, therapeutic, screening, and preventative strategies. While the field is still relatively young, substantial knowledge about these strategies has been gained through CER techniques and modeling. Continued investigation with refinement of CER tools for the investigation of gynecologic cancer is needed to advance the state of knowledge.

KEY POINTS

1. Comparative effectiveness research (CER) provides the framework for studies that compare the potential harms and benefits of strategies to prevent, diagnose, or treat gynecologic malignancy.
2. Health economic studies, including cost-effectiveness and cost-utility analyses, are a subset of CER in which medical interventions are compared on the basis of their relative costs, as well as their potential harms and benefits.
3. A key factor in the development of a cost-utility model is the incorporation of quality of life, which requires a preference-based utility. The utility may be derived using a variety of quality-of-life-related instruments. Use of the utility allows the results of a model to be expressed in QALYs, which is a standard effectiveness outcome.
4. The results of health economic decision models are highly dependent on their perspective and the assumptions made in their construction.
5. Uncertainty in health economic models is best described using multiple sensitivity analyses.
6. There is a growing body of CER evidence to guide clinical and resource allocation decisions in gynecologic oncology.

REFERENCES

- Iglehart JK. Prioritizing comparative-effectiveness research—IOM recommendations. *N Engl J Med*. 2009;361(4):325–328.
- Mant D. Can randomised trials inform clinical decisions about individual patients? *Lancet*. 1999;353(9154):743–746.
- Berger ML, Dreyer N, Anderson F, et al. Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. *Value Health*. 2012;15(2):217–230.
- Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. Oxford; New York: Oxford University Press; 2005.
- Excellence NfHaC. Guide to the methods of technology appraisal. 2008. <http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdated-June2008.pdf>.
- Gold M, Siegel J, Russell L, et al. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
- Barnett JC, Judd JP, Wu JM, et al. Cost comparison among robotic, laparoscopic, and open hysterectomy for endometrial cancer. *Obstet Gynecol*. 2010;116(3):685–693.
- Williams A. Priority setting in public and private health care. A guide through the ideological jungle. *J Health Econ*. 1988;7(2):173–183.
- Bell MC, Torgerson J, Seshadri-Kreaden U, et al. Comparison of outcomes and cost for endometrial cancer staging via traditional laparotomy, standard laparoscopy and robotic techniques. *Gynecol Oncol*. 2008;111(3):407–411.
- Bijen CB, Vermeulen KM, Mourits MJ, et al. Costs and effects of abdominal versus laparoscopic hysterectomy: systematic review of controlled trials. *PLoS One*. 2009;4(10):e7340.
- Petitti DB. *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. 2nd ed. New York, NY: Oxford University Press; 2000.
- Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med*. 1990;113(2):147–154.
- Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst*. 2008;100(9):630–641.
- Drummond MF, O'Brien B, Stoddart GL, et al. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd ed. New York, NY: Oxford University Press; 1997.
- Doubilet P, Begg CB, Weinstein MC, et al. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making*. 1985;5(2):157–177.
- Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value Health*. 2005;8(5):521–533.
- Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis*. 1987;40(6):593–603.
- Froberg DG, Kane RL. Methodology for measuring health-state preferences—II: Scaling methods. *J Clin Epidemiol*. 1989;42(5):459–471.
- Torrance GW. Measurement of health state utilities for economic appraisal. *J Health Econ*. 1986;5(1):1–30.
- Ware JE Jr. Standards for validating health measures: definition and content. *J Chronic Dis*. 1987;40(6):473–480.
- Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res*. 1972;7(2):118–133.
- Llewellyn-Thomas H, Sutherland HJ, Tibshirani R, et al. The measurement of patients' values in medicine. *Med Decis Making*. 1982;2(4):449–462.
- Brazier J. Valuing health States for use in cost-effectiveness analysis. *Pharmacoeconomics*. 2008;26(9):769–779.
- Feeny D, Furlong W, Boyle M, et al. Multi-attribute health status classification systems. Health Utilities Index. *Pharmacoeconomics*. 1995;7(6):490–502.
- Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol-questionnaire. *Health Econ*. 1993;2(3):237–246.
- Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53–72.
- Dolan P, Gudex C, Kind P, et al. The time trade-off method: results from a general population study. *Health Econ*. 1996;5(2):141–154.
- Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21(2):271–292.
- Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care*. 2004;42(9):851–859.
- Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570–579.
- Dobrez D, Cella D, Pickard AS, et al. Estimation of patient preference-based utility weights from the functional assessment of cancer therapy – general. *Value Health*. 2007;10(4):266–272.
- Cheung YB, Thumboo J, Gao F, et al. Mapping the English and Chinese versions of the Functional Assessment of Cancer Therapy-General to the EQ-5D utility index. *Value Health*. 2009;12(2):371–376.
- Ubel PA, Loewenstein G, Jepson C. Whose quality of life? A commentary exploring discrepancies between health state evaluations of patients and the general public. *Qual Life Res*. 2003;12(6):599–607.
- Arnold D, Gilling A, Stevens A, et al. Comparison of direct and indirect methods of estimating health state utilities for resource allocation: review and empirical analysis. *BMJ*. 2009;339:b2688.
- Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13(4):322–338.
- Havrilesky LJ, Sanders GD, Kulasingam S, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity: implications for potential mortality reduction. *Cancer*. 2011;117(3):545–553.
- Taylor DC, Pawar V, Kruzikas D, et al. Methods of model calibration: observations from a mathematical model of cervical cancer. *Pharmacoeconomics*. 2010;28(11):995–1000.
- Kulasingam SL, Rajan R, St Pierre Y, et al. Human papillomavirus testing with Pap triage for cervical cancer prevention in Canada: a cost-effectiveness analysis. *BMC Med*. 2009;7:69.
- Choi YH, Jit M, Gay N, et al. Transmission dynamic modelling of the impact of human papillomavirus vaccination in the United Kingdom. *Vaccine*. 2010;28(24):4091–4102.
- Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, et al. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U. S. Preventive Services Task Force. *Ann Intern Med*. 2008;149(9):659–669.
- Mandelblatt JS, Cronin KA, Bailey S, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med*. 2009;151(10):738–747.
- Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA*. 2003;290(6):781–789.
- Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis*. 2004;10(11):1915–1923.
- Barnabas RV, Laukkanen P, Koskela P, et al. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. *PLoS Med*. 2006;3(5):e138.
- Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology*. 2002;13(6):631–639.
- Van de Velde N, Brisson M, Boily MC. Modeling human papillomavirus vaccine effectiveness: quantifying the impact of parameter uncertainty. *Am J Epidemiol*. 2007;165(7):762–775.
- French KM, Barnabas RV, Lehtinen M, et al. Strategies for the introduction of human papillomavirus vaccination: modelling the optimum age- and sex-specific pattern of vaccination in Finland. *Br J Cancer*. 2007;96(3):514–518.
- Goldie SJ, Grima D, Kohli M, et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *Int J Cancer*. 2003;106(6):896–904.
- Kohli M, Ferko N, Martin A, et al. Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK. *Br J Cancer*. 2007;96(1):143–150.
- Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis*. 2007;13(1):28–41.
- Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *J Natl Cancer Inst Monogr*. 2003;(31):14–19.
- Whitlock EP, Vesco KK, Eder M, et al. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the U. S. Preventive Services Task Force. *Ann Intern Med*. 2011;155(10):687–697.
- Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer*. 2007;121(3):621–632.
- Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis*. 2003;9(1):37–48.
- Goldie SJ, Kohli M, Grima D, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst*. 2004;96(8):604–615.
- Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. *N Engl J Med*. 2008;359(8):821–832.
- Brisson M, van de Velde N, Franco EL, et al. Incremental impact of adding boys to current human papillomavirus vaccination programs: role of herd immunity. *J Infect Dis*. 2011;204(3):372–376.
- Eddy DM. The frequency of cervical cancer screening. Comparison of a mathematical model with empirical data. *Cancer*. 1987;60(5):1117–1122.
- ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin no. 109: Cervical cytology screening. *Obstet Gynecol*. 2009;114(6):1409–1420.

60. Smith RA, Cokkinides V, Brooks D, et al. Cancer screening in the United States, 2010: a review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin.* 2010;60(2):99–119.
61. Canfell K, Barnabas R, Patnick J, et al. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. *Br J Cancer.* 2004;91(3):530–536.
62. Kulasingam SL, Havrilesky L, Ghebre R, et al. *Screening for cervical cancer: a decision analysis for the U.S. Preventive Services Task Force.* AHRQ Publication No. 11-05157-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
63. Mandelblatt JS, Lawrence WF, Womack SM, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA.* 2002;287(18):2372–2381.
64. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA.* 2002;287(18):2382–2390.
65. Muhlberger N, Sroczynski G, Esteban E, et al. Cost-effectiveness of primarily human papillomavirus-based cervical cancer screening in settings with currently established Pap screening: a systematic review commissioned by the German Federal Ministry of Health. *Int J Technol Assess Health Care.* 2008;24(2):184–192.
66. Goldhaber-Fiebert JD, Stout NK, Salomon JA, et al. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination. *J Natl Cancer Inst.* 2008;100(5):308–320.
67. Berkhof J, Coupe VM, Bogaards JA, et al. The health and economic effects of HPV DNA screening in The Netherlands. *Int J Cancer.* 2010;127(9):2147–2158.
68. Ogilvie GS, Kraiden M, van Niekerk DJ, et al. Primary cervical cancer screening with HPV testing compared with liquid-based cytology: results of round 1 of a randomised controlled trial - the HPV FOCAL Study. *Br J Cancer.* 2012;107(12):1917–1924.
69. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiol Rev.* 2006;28:88–100.
70. Garnett GP, Kim JJ, French K, et al. Chapter 21: Modelling the impact of HPV vaccines on cervical cancer and screening programmes. *Vaccine.* 2006;24(suppl. 3):S3/178–S3/186.
71. Jit M, Demartean N, Elbasha E, et al. Human papillomavirus vaccine introduction in low-income and middle-income countries: guidance on the use of cost-effectiveness models. *BMC Med.* 2011;9:54.
72. Goldie SJ, O'Shea M, Campos NG, et al. Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries. *Vaccine.* 2008;26(32):4080–4093.
73. Kim JJ, Goldie SJ. Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States. *BMJ.* 2009;339:b3884.
74. Jit M, Chapman R, Hughes O, et al. Comparing bivalent and quadrivalent human papillomavirus vaccines: economic evaluation based on transmission model. *BMJ.* 2011;343:d5775.
75. Tully SP, Anonychuk AM, Sanchez DM, et al. Time for change? An economic evaluation of integrated cervical screening and HPV immunization programs in Canada. *Vaccine.* 2012;30(2):425–435.
76. Coupe VM, Bogaards JA, Meijer CJ, et al. Impact of vaccine protection against multiple HPV types on the cost-effectiveness of cervical screening. *Vaccine.* 2012;30(10):1813–1822.
77. Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2006;102(3):432–439.
78. Buys SS, Partridge E, Greene MH, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. *Am J Obstet Gynecol.* 2005;193(5):1630–1639.
79. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA.* 2011;305(22):2295–2303.
80. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol.* 2009;10(4):327–340.
81. Skates SJ, Singer DE. Quantifying the potential benefit of CA 125 screening for ovarian cancer. *J Clin Epidemiol.* 1991;44(4–5):365–380.
82. Urban N, Drescher C, Etzioni R, et al. Use of a stochastic simulation model to identify an efficient protocol for ovarian cancer screening. *Control Clin Trials.* 1997;18(3):251–270.
83. Havrilesky LJ, Sanders GD, Kulasingam S, et al. Reducing ovarian cancer mortality through screening: Is it possible, and can we afford it? *Gynecol Oncol.* 2008;111(2):179–187.
84. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003;72(5):1117–1130.
85. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA.* 2011;305(22):2304–2310.
86. Olivier RI, Lubsen-Brandsma MA, Verhoef S, et al. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. *Gynecol Oncol.* 2006;100(1):20–26.
87. Stirling D, Evans DG, Pichert G, et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. *J Clin Oncol.* 2005;23(24):5588–5596.
88. Hogg R, Friedlander M. Biology of epithelial ovarian cancer: implications for screening women at high genetic risk. *J Clin Oncol.* 2004;22(7):1315–1327.
89. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst.* 2009;101(2):80–87.
90. Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. *J Clin Oncol.* 2010;28(2):222–231.
91. Anderson K, Jacobson JS, Heitjan DF, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. *Ann Intern Med.* 2006;144(6):397–406.
92. Grann VR, Patel PR, Jacobson JS, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. *Breast Cancer Res Treat.* 2011;125(3):837–847.
93. Kwon JS, Sun CC, Peterson SK, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. *Cancer.* 2008;113(2):326–335.
94. Shuster LT, Gostout BS, Grossardt BR, et al. Prophylactic oophorectomy in premenopausal women and long-term health. *Menopause Int.* 2008;14(3):111–116.
95. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol.* 2009;113(5):1027–1037.
96. Greene MH, Piedmonte M, Alberts D, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev.* 2008;17(3):594–604.
97. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;354(1):34–43.
98. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473–2483.
99. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011;365(26):2484–2496.
100. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet.* 2009;374(9698):1331–1338.
101. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996;334(1):1–6.
102. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst.* 2000;92(9):699–708.
103. Piccart MJ, Bertelsen K, Stuart G, et al. Long-term follow-up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide-cisplatin combination in advanced ovarian cancer. *Int J Gynecol Cancer.* 2003;13(suppl. 2):S144–S148.
104. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003;21(17):3194–3200.
105. Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol.* 2000;18(17):3084–3092.
106. du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst.* 2003;95(17):1320–1329.
107. Ozols RF. Update on the management of ovarian cancer. *Cancer J.* 2002;8(suppl. 1):S22–S30.
108. McGuire W, Neugut AI, Arikan S, et al. Analysis of the cost-effectiveness of paclitaxel as alternative combination therapy for advanced ovarian cancer. *J Clin Oncol.* 1997;15(2):640–645.
109. Elit LM, Gafni A, Levine MN. Economic and policy implications of adopting paclitaxel as first-line therapy for advanced ovarian cancer: an Ontario perspective. *J Clin Oncol.* 1997;15(2):632–639.

110. Berger K, Fischer T, Szucs TD. Cost-effectiveness analysis of paclitaxel and cisplatin versus cyclophosphamide and cisplatin as first-line therapy in advanced ovarian cancer. A European perspective. *Eur J Cancer*. 1998;34(12):1894–1901.
111. Dalton HJ, Yu X, Hu L, et al. An economic analysis of dose dense weekly paclitaxel plus carboplatin versus every-3-week paclitaxel plus carboplatin in the treatment of advanced ovarian cancer. *Gynecol Oncol*. 2012;124(2):199–204.
112. Morgan RJ Jr, Alvarez RD, Armstrong DK, et al. NCCN Clinical Practice Guidelines in Oncology: epithelial ovarian cancer. *J Natl Compr Canc Netw*. 2011;9(1):82–113.
113. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335(26):1950–1955.
114. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol*. 2001;19(4):1001–1007.
115. Bristow RE, Santillan A, Salani R, et al. Intraperitoneal cisplatin and paclitaxel versus intravenous carboplatin and paclitaxel chemotherapy for stage III ovarian cancer: a cost-effectiveness analysis. *Gynecol Oncol*. 2007;106(3):476–481.
116. Havrilesky LJ, Alvarez Secord A, Darcy KM, et al. Cost effectiveness of intraperitoneal compared with intravenous chemotherapy for women with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2008;26(25):4144–4150.
117. Cohn DE, Kim KH, Resnick KE, et al. At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. *J Clin Oncol*. 2011;29(10):1247–1251.
118. Barnett JC, Alvarez-Secord A, Cohn D, et al. Cost-effectiveness of a predictive biomarker for bevacizumab responsiveness in the primary treatment of ovarian cancer. *Gynecol Oncol*. 2012;125(suppl. 1):S66.
119. Lesnock JL, Farris C, Krivak TC, et al. Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer. *Gynecol Oncol*. 2011;122(3):473–478.
120. Hensley ML. Epithelial ovarian cancer. *Curr Treat Options Oncol*. 2002;3(2):131–141.
121. Rose PG, Fusco N, Fluellen L, et al. Second-line therapy with paclitaxel and carboplatin for recurrent disease following first-line therapy with paclitaxel and platinum in ovarian or peritoneal carcinoma. *J Clin Oncol*. 1998;16(4):1494–1497.
122. Dizon DS, Hensley ML, Poyner EA, et al. Retrospective analysis of carboplatin and paclitaxel as initial second-line therapy for recurrent epithelial ovarian carcinoma: application toward a dynamic disease state model of ovarian cancer. *J Clin Oncol*. 2002;20(5):1238–1247.
123. Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet*. 2003;361(9375):2099–2106.
124. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol*. 2006;24(29):4699–4707.
125. Havrilesky LJ, Secord AA, Kulusingam S, et al. Management of platinum-sensitive recurrent ovarian cancer: a cost-effectiveness analysis. *Gynecol Oncol*. 2007;107(2):211–218.
126. Rocconi RP, Case AS, Straughn JM Jr, et al. Role of chemotherapy for patients with recurrent platinum-resistant advanced epithelial ovarian cancer: a cost-effectiveness analysis. *Cancer*. 2006;107(3):536–543.
127. Grigsby PW. Primary radiotherapy for stage IB or IIA cervical cancer. *J Natl Cancer Inst Monogr*. 1996;21:61–64.
128. Rocconi RP, Estes JM, Leath CA 3rd, et al. Management strategies for stage IB2 cervical cancer: a cost-effectiveness analysis. *Gynecol Oncol*. 2005;97(2):387–394.
129. Jewell EL, Kulusingam S, Myers ER, et al. Primary surgery versus chemoradiation in the treatment of IB2 cervical carcinoma: a cost effectiveness analysis. *Gynecol Oncol*. 2007;107(3):532–540.
130. Jewell EL, Smrka M, Broadwater G, et al. Utility scores and treatment preferences for clinical early-stage cervical cancer. *Value Health*. 2011;14(4):582–586.
131. Shigematsu Y, Nishiyama K, Masaki N, et al. Treatment of carcinoma of the uterine cervix by remotely controlled afterloading intracavitary radiotherapy with high-dose rate: a comparative study with a low-dose rate system. *Int J Radiat Oncol Biol Phys*. 1983;9(3):351–356.
132. Jones G, Lukka H, O'Brien B. High dose rate versus low dose rate brachytherapy for squamous cell carcinoma of the cervix: an economic analysis. *Br J Radiol*. 1994;67(803):1113–1120.
133. Bansal N, Herzog TJ, Brunner-Brown A, et al. The utility and cost effectiveness of preoperative computed tomography for patients with uterine malignancies. *Gynecol Oncol*. 2008;111(2):208–212.
134. Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. *Lancet Oncol*. 2010;11(8):763–771.
135. Kondalsamy-Chennakesavan S, Janda M, Gebiski V, et al. Risk factors to predict the incidence of surgical adverse events following open or laparoscopic surgery for apparent early stage endometrial cancer: results from a randomised controlled trial. *Eur J Cancer*. 2012;48(14):2155–2162.
136. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. *J Clin Oncol*. 2012;30(7):695–700.
137. Janda M, Gebiski V, Brand A, et al. Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial. *Lancet Oncol*. 2010;11(8):772–780.
138. Kornblith AB, Huang HQ, Walker JL, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009;27(32):5337–5342.
139. Bijen CB, Vermeulen KM, Mourits MJ, et al. Cost effectiveness of laparoscopy versus laparotomy in early stage endometrial cancer: a randomised trial. *Gynecol Oncol*. 2011;121(1):76–82.
140. Wright JD, Burke WM, Wilde ET, et al. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. *J Clin Oncol*. 2012;30(8):783–791.
141. Panici PB, Maggioni A, Hacker N, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. *J Natl Cancer Inst*. 2005;97(8):560–566.
142. Kitchener H, Swart AM, Qian Q, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*. 2009;373(9658):125–136.
143. Kwon JS, Carey MS, Goldie SJ, et al. Cost-effectiveness analysis of treatment strategies for Stage I and II endometrial cancer. *J Obstet Gynaecol Can*. 2007;29(2):131–139.
144. Cohn DE, Huh WK, Fowler JM, et al. Cost-effectiveness analysis of strategies for the surgical management of grade 1 endometrial adenocarcinoma. *Obstet Gynecol*. 2007;109(6):1388–1395.
145. Havrilesky LJ, Maxwell GL, Chan JK, et al. Cost effectiveness of a test to detect metastases for endometrial cancer. *Gynecol Oncol*. 2009;112(3):526–530.
146. Lachance JA, Stukenborg GJ, Schneider BF, et al. A cost-effective analysis of adjuvant therapies for the treatment of stage I endometrial adenocarcinoma. *Gynecol Oncol*. 2008;108(1):77–83.
147. Rankins NC, Secord AA, Jewell E, et al. Cost-effectiveness of adjuvant radiotherapy in intermediate risk endometrial cancer. *Gynecol Oncol*. 2007;106(2):388–393.
148. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. *Eur J Cancer*. 2012;48(11):1638–1648.
149. Bristow RE, Purinton SC, Santillan A, et al. Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance. *Gynecol Oncol*. 2006;103(2):709–713.
150. Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol*. 2011;204(6):466–478.
151. Hampel H, Panescu J, Lockman J, et al. Comment on: screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. *Cancer Res*. 2007;67(19):9603.
152. Kwon JS, Scott JL, Gilks CB, et al. Testing women with endometrial cancer to detect Lynch syndrome. *J Clin Oncol*. 2011;29(16):2247–2252.
153. Resnick K, Straughn JM Jr, Backes F, et al. Lynch syndrome screening strategies among newly diagnosed endometrial cancer patients. *Obstet Gynecol*. 2009;114(3):530–536.
154. Yang KY, Caughey AB, Little SE, et al. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) families. *Fam Cancer*. 2011;10(3):535–543.

SECTION III

DISEASE SITES

CHAPTER

19

Vulva

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INTRODUCTION

Malignant tumors of the vulva are rare and account for less than 5% of all cancers of the female genital tract. In 2012, there will be an estimated 4,490 new cases of, and 950 deaths from, invasive vulvar carcinoma in the United States (1). Because of its low incidence, most primary care providers will never encounter a patient with vulvar cancer. Although a rare patient with vulvar cancer will present without symptoms, the vast majority of women with vulvar cancer initially present with complaints such as vulvar irritation, pruritis, pain, or a mass that does not resolve. The interval between the onset of symptoms and the diagnosis of cancer can be protracted when a woman who is embarrassed by new vulvar symptoms delays seeking care, or a physician prescribes empiric topical therapies without a proper physical examination or tissue biopsy confirmation. Jones and Joura evaluated the clinical events preceding the diagnosis of squamous cell carcinoma of the vulva and found that 88% of patients had experienced symptoms for more than 6 months, 31% of women had 3 or more medical consultations prior to the diagnosis of vulvar carcinoma, and 27% had applied topical estrogen or corticosteroids to the vulva (2).

The vulva is covered by keratinized squamous epithelium; accordingly, the majority of malignant vulvar tumors are squamous cell carcinomas. Consequently, our current understanding of the epidemiology, spread patterns, prognostic factors, and survival data for vulvar cancer is largely derived from experience with squamous cell carcinomas. Malignant melanoma is the second most common cancer of the vulva. Although there is some consensus regarding the behavior and treatment of vulvar melanoma, its rarity has thus far precluded the conduct of robust, prospective clinical trials. A number of other malignant tumors, both epithelial and stromal in origin, arise from normal vulvar tissue and are discussed in detail later in this chapter. Finally, the vulva may be secondarily involved with malignant disease originating in the cervix, bladder, anorectum, colon, breast, or other organs.

The traditional therapeutic approach to vulvar cancer has been radical surgical excision of the primary tumor and

inguinofemoral lymphadenectomy. Experience has shown that survival is improved with the administration of postoperative radiation therapy to selected patients deemed to be at high risk for locoregional failure. More recently, the use of neo-adjuvant radiotherapy with concomitant radio-sensitizing chemotherapy has proven to be effective in treating vulvar cancer patients for whom radical surgery would be either too morbid or technically not feasible. New surgical techniques, including sentinel lymph node biopsy, hold the promise of better outcomes for patients with early disease. An individualized approach to vulvar cancer management, often employing multiple modalities in an effort to achieve disease control with better cosmetic results and sexual function, is now the norm. These and other topics pertinent to the principles of management of women with vulvar cancer are the subjects of this chapter.

ANATOMY

The vulva consists of the external genital organs—including the mons pubis, labia minora and majora, clitoris, vaginal vestibule, and perineal body—and their supporting subcutaneous tissues. The vulva is bordered superiorly by the anterior abdominal wall, laterally by the labiocrural fold at the medial thigh, and inferiorly by the anus. The vagina and urethra open onto the vulva. The mons pubis is a prominent mound of hair-bearing skin and subcutaneous adipose and connective tissue that is located anterior to the pubic symphysis. The labia majora are two elongated skin folds that course posterior from the mons pubis and blend into the perineal body. The labia minora are a smaller pair of skin folds medial and parallel to the labia majora that extend inferiorly to form the margin of the vaginal vestibule. Superiorly, the labia minora separate into 2 components that course above and below the clitoris, fusing with those of the opposite side to form the prepuce and frenulum, respectively. The skin of the labia minora contains sebaceous glands near its junction with the labia majora, but it is not hair-bearing and it has little or no underlying adipose tissue. The clitoris is supported externally

David H. Moore, Wui-Jin Koh, and William P. McGuire contributed to prior editions of this chapter

by the fusion of the labia minora (prepuce and frenulum) and is approximately 2 to 3 cm anterior to the urethral meatus. It is composed of erectile tissue organized into the glans, body, and two crura. Two loosely fused corpora cavernosa form the body of the clitoris and extend superiorly from the glans, ultimately dividing into the two crura. The crura course laterally beneath the ischiocavernosus muscles and attach to the ischial rami.

The vaginal vestibule is situated in the center of the vulva and is homologous to the male distal urethra. It has squamous mucosal epithelium that is demarcated bilaterally and posteriorly by the junction with the keratinized epithelium at Hart's line, located on the medial labia minora and inferiorly on the perineal body. The vagina, urethra, periurethral glands, minor vestibular glands, and the Bartholin's glands open onto the vestibule. Anteriorly, the minor small vestibular glands are located beneath the vestibular mucosa and open onto its surface predominantly on the more anterior vestibule. The vestibular bulbs, a loose collection of bilateral erectile tissue covered superficially by the bulbocavernosus muscle, are located laterally. The Bartholin's glands, two small, mucus-secreting glands situated within the subcutaneous tissue of the posterior labia majora, have ducts opening onto the posterolateral portion of the vestibule. The perineal body is a 3 to 4 cm band of skin and subcutaneous tissue located between the posterior extensions of the labia majora. It separates the vaginal vestibule from the anus and forms the posterior margin of the vulva.

Vascular Anatomy and Neurologic Innervation

The vulva has a rich blood supply derived primarily from the internal pudendal artery, which arises from the anterior division of the internal iliac (hypogastric) artery, and the superficial and deep external pudendal arteries, which arise from the femoral artery. The internal pudendal artery exits the pelvis and passes behind the ischial spine to reach the posterolateral vulva, where it divides into several small branches to the ischiocavernosus and bulbocavernosus muscles, the perineal artery, artery of the bulb, urethral artery, and dorsal and deep arteries of the clitoris. Both external pudendal arteries travel medially to supply the labia majora and their deep structures. These vessels anastomose freely with branches from the internal pudendal artery. Innervation of the vulva is derived from multiple sources and spinal cord levels. The mons pubis and upper labia majora are innervated by the ilioinguinal nerve (L1) and the genital branch of the genitofemoral nerve (L1–2). Either of these nerves may be easily injured during pelvic lymph node dissection, with resulting paresthesias. The pudendal nerve (S2–4) enters the vulva in parallel with the internal pudendal artery and gives rise to several branches that innervate the lower vagina, labia, clitoris, perineal body, and their supporting structures.

Groin Anatomy and Lymphatic Drainage

Vulvar lymphatics run anteriorly through the labia majora, turn laterally at the mons pubis, and drain primarily into the superficial inguinal lymph nodes. Dye studies by Parry-Jones demonstrated that vulvar lymphatic channels do not extend laterally to the labiocrural folds and do not cross the midline, unless the site of dye injection is at the clitoris or perineal body (3).

The vulvar lymphatics drain to the superficial inguinal lymph nodes located within the femoral triangle formed by the inguinal ligament superiorly, the border of the sartorius muscle laterally, and the border of the adductor longus muscle medially. There are 8 to 10 inguinal lymph nodes lying along the saphenous vein and its branches between Camper's fascia and fascia overlying the femoral vessels (Fig. 19.1A–C) (4). The first draining lymph node is termed the sentinel lymph node (SLN) and can

be identified only by the use of various lymphatic mapping techniques. The SLN is frequently found medial to the femoral vein just above the adductor muscle. Second echelon lymph nodes may be in the groin or pelvis. Cloquet's node, or the most superior inguinal lymph node, is located under the inguinal ligament. Lymphatic drainage from the SLN is sequentially to the external iliac, common iliac, and aortic lymph nodes (Fig. 19.1A–C).

The fossa ovalis is a crescent-shaped terminus of the fascia lata and the site where vascular and lymphatic structures meet with the femoral vessels. The cribriform fascia is a term widely used in the literature describing the anatomy of the groin and is said to cover the fossa ovalis. The cribriform fascia is hard to identify and is more of a "lamina" than an actual fascia. SLN biopsy with lymphatic mapping deemphasizes the need to identify the cribriform structure and focuses the surgeon's attention on functional *in vivo* surgical anatomy rather than textbook descriptions of lymph node locations.

EPIDEMIOLOGY

An estimated 4,490 women were diagnosed with vulvar cancer in the United States in 2012, and approximately 950 will die of the disease (1). Vulvar squamous cell carcinoma accounts for approximately 3% to 5% of all gynecologic malignancies and 1% of all carcinomas in women, with an incidence rate of 1 to 2 per 100,000 women (1). Most vulvar cancers occur in postmenopausal women in the seventh decade, although more recent reports have identified a trend toward younger age at diagnosis (5,6). Earlier observational studies suggested associations between hypertension, diabetes mellitus, and obesity and vulvar carcinoma; however, subsequent analyses have not confirmed the prognostic significance of these diagnoses (7).

Several infectious agents have been proposed as possible etiologic agents in vulvar carcinoma, including granulomatous infections, herpes simplex virus, and, most notably, human papillomavirus (HPV). HPV infection is present in virtually 100% of women with cervical cancer. The relationship between HPV infection and vulvar cancer is much less straightforward. This is likely due to the different etiologic pathways that are believed to be responsible for vulvar cancer. These different etiologic pathways are discussed in detail in the chapter on preinvasive disease; however, because of subject matter overlap, some of the data related to HPV and invasive squamous cell carcinoma of the vulva are discussed here.

Vulvar condylomas have a well-described relationship to HPV, and strong associations between vulvar condylomas and the later development of vulvar cancer have been identified (8). The role of HPV in the development of premalignant and malignant lesions of the vulva has become clearer as molecular techniques for HPV detection and mutational analyses have improved (9). Earlier studies identified HPV DNA in both invasive and carcinoma *in situ* lesions via immunohistochemistry. More recent studies have used DNA detection methods such as polymerase chain reaction (PCR) and *in situ* hybridization to detect high-risk serotypes (9). Among HPV serotypes, 16 is the most common; however, many other serotypes, including 18, 31, 33, and others, have been implicated (9). HPV DNA can be identified in approximately 85% of intraepithelial lesions (range, 42% to 100%), but is seen in only 10% to 50% of invasive lesions (9). The reason such a wide range of associated HPV is seen associated with vulvar intraepithelial neoplasia (VIN) and vulvar cancer has to do with differences between studies regarding which VIN subtypes (usual or differentiated) are being studied, different DNA detection methods with different sensitivity, and differences between studies regarding which HPV serotypes are being assayed.

Although HPV DNA is associated with the vast majority of intraepithelial lesions (~85%), it is much less commonly seen in association with invasive lesions (~40%) (9). Marked differences

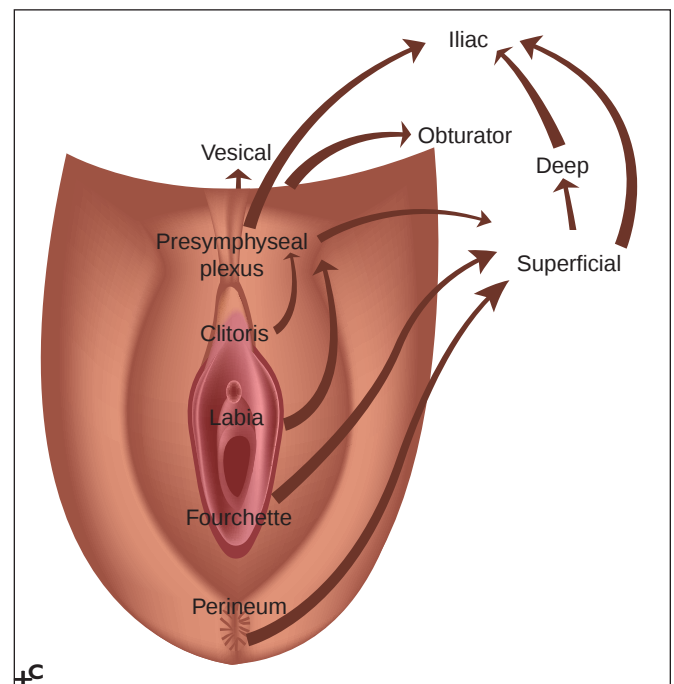
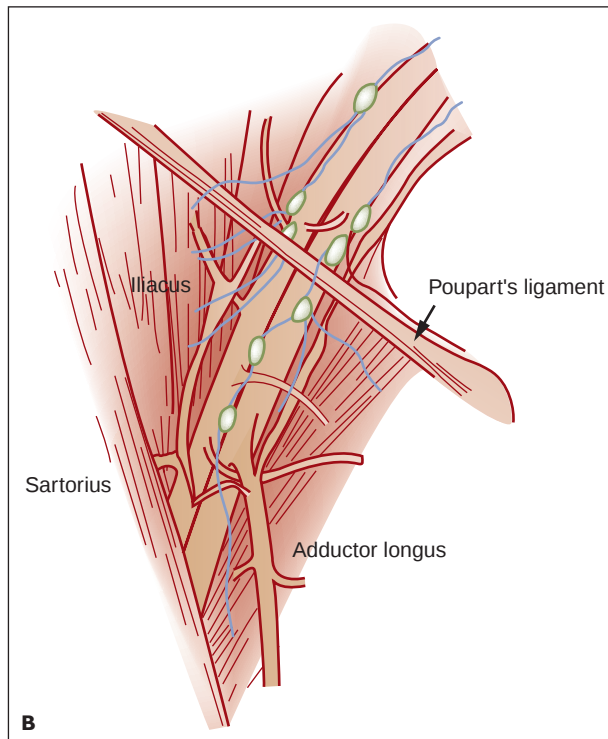
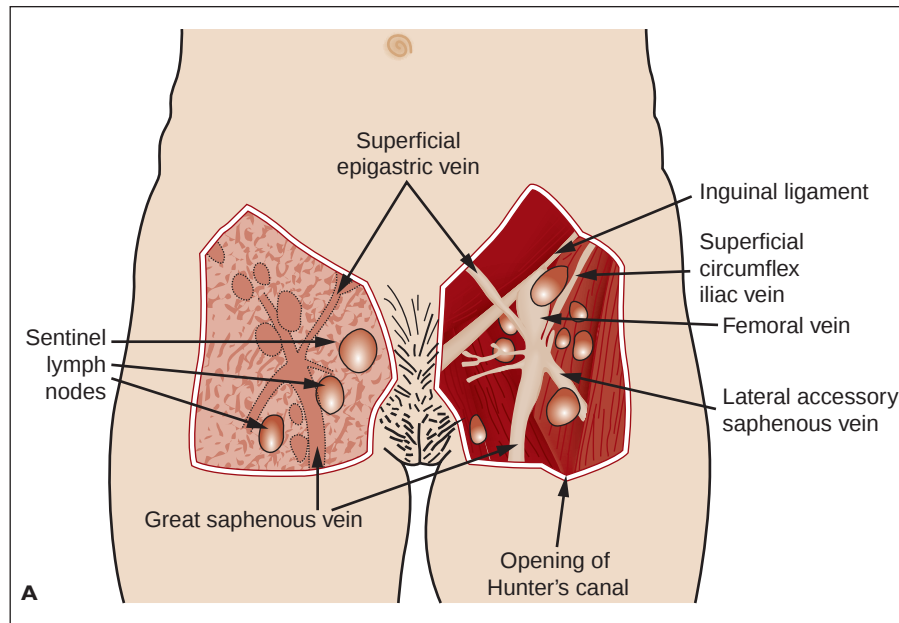


FIGURE 19.1. These historic figures illustrate some of the problems depicting the lymphatic anatomy of the groin. **A** and **B** illustrate vessels, muscles, and nerves accurately. **A** refers to sentinel nodes; however, this is based on location rather than a mapping procedure, which is misleading. **B** shows nodes between the femoral artery and vein. Lymph nodes between the vessels are common in the pelvis but not in the groin. **C**: shows direct drainage from the clitoral area of the vulva to pelvic lymph nodes. This drainage pattern is not observed with preoperative or intraoperative lymphatic mapping studies.

between HPV positivity in VIN and vulvar cancers are also seen with respect to age. Basta et al. conducted a retrospective case control study examining the coexistence of HPV and the incidence of both VIN and stage I vulvar cancer. HPV infection was present in 61.5% of cases of VIN and vulvar cancer in women aged less than or equal to 45 years, and in 17.5% of women older than 45 years (10).

Chronic immunosuppression and tobacco smoking have also been linked as cofactors for the development of invasive vulvar cancer (11,12). Vulvar cancer incidence is increased in female renal transplant patients as well as women with HIV and AIDS

(11,13). Smoking is an independent risk factor for the development of squamous cell carcinoma of the vulva, although the reason for this is unclear. One hypothesis is that genetic variations in T-cell-mediated IL-2 responses among smokers may explain differential susceptibility to the development of squamous vulvar carcinomas (12). Significant correlations between smoking status, historical number of sexual partners, history of genital warts, and a history of an abnormal Pap smear have been detailed by Brinton et al. (Table 19.1) (7).

Chronic vulvar inflammatory lesions, such as vulvar dys- trophies, including lichen sclerosus (LS), lichen planus, lichen

Table 19.1 Relative Risks of *In Situ* and Invasive Vulvar Cancers by Selected Risk Factors

	In situ Series			Invasive Series		
	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI
No. of Sexual Partners						
0–1	17	1.00		48	1.00	
2	11	2.78	0.9–8.3	17	1.22	0.6–2.5
3–4	23	2.33	0.9–6.0	28	3.32	1.6–7.1
5–9	23	5.08	1.7–14.8	11	1.50	0.6–3.9
≥10	22	2.74	0.9–7.9	8	0.83	0.3–2.5
Trend test	<i>p</i> = 0.03			<i>p</i> = 0.24		
Ever Had an Abnormal Pap Smear						
No	64	1.00		90	1.00	
Yes	30	1.92	0.9–3.9	11	1.41	0.5–3.6
No previous Pap smear	2	0.37	0.1–1.9	10	2.46	0.9–6.7
Ever Had Genital Warts						
No	73	1.00		105	1.00	
Yes	23	18.50	5.5–62.5	8	14.55	1.71–25.6
Current Smoking Status						
Nonsmoker	22	1.00		46	1.00	
Current smoker	55	4.65	2.2–10.0	48	1.19	0.6–2.2
Ex-smoker	19	1.78	0.7–4.4	19	0.40	0.2–0.8

CI, confidence interval; RR, relative risk.

Source: Reprinted with permission from Brinton LA, Nasca PC, Mallin K, et al. Case-control study of cancer of the vulva. *Obstet Gynecol.* 1990;75:864.

simplex chronicus, squamous cell hyperplasia, and vulvar intraepithelial neoplasia II/III (usual as well as differentiated types), particularly differentiated VIN (dVIN), have been suggested as precursors of invasive squamous cancers (14,15). Carli et al. suggested a possible role of LS as a precursor to vulvar cancer based on their observation that 32% of vulvar cancer cases not related to HPV were associated with LS (16). More recently, in a pathologic reevaluation of patients with a diagnosis of LS who were followed clinically for a minimum of 10 years, van de Nieuwenhof and colleagues identified concordant diagnoses of LS in 58/61 patients who did not progress to cancer, and concordant diagnoses of LS in only 29/60 patients who were identified with a subsequent diagnosis of vulvar cancer. The majority of patients reclassified as having something other than LS were considered to have dVIN (25/31 patients). This study highlights dVIN as a uniquely at-risk histology that deserves prompt treatment and close follow-up. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as LS, that have progressed to vulvar squamous cell carcinoma (15).

In an observational study of women with carcinoma *in situ*, 7 of 8 untreated cases progressed to invasive carcinoma within 8 years, and 4 of 105 treated women presented with invasive tumors from 7 to 18 years later (17). In a subsequent study of 405 cases of VIN 2 to 3, Jones et al. found that 3.8% of patients had developed invasive cancer despite therapy, and 10 untreated patients had developed invasive cancer in 1.1 to 7.3 years (mean, 3.9 years) (18). Although some intraepithelial lesions regress spontaneously, it appears that a significant number persist or progress to invasive cancer.

Trimble et al. postulated that squamous carcinoma of the vulva may represent a final common endpoint of heterogeneous

etiologic pathways (19). According to their studies, two histologic subtypes, those with basaloid or warty features, are associated with HPV, whereas keratinizing squamous carcinomas are not. Furthermore, basaloid or warty carcinomas are associated with classic risk factors for cervical carcinoma, including age at first intercourse, lifetime number of sexual partners, prior abnormal Pap smears, smoking, and lower socioeconomic status. Keratinizing squamous carcinomas are weakly linked to these factors, and in some cases not at all.

Mitchell et al. evaluated 169 women with invasive vulvar cancers and noted that second genital squamous neoplasms occurred in 13% of cases (20). The risk of a second primary tumor was significantly increased in cancer cases with HPV DNA, intraepithelioid growth pattern, or adjacent dysplasia. These observations support the concept that some squamous lesions may be initiated by sexually transmitted viruses capable of producing neoplastic change within the entire field of the lower genital tract. The obvious clinical implication of this observation is that a patient with an established squamous lesion of the vulva, vagina, or cervix needs to be evaluated and monitored for new or coexistent lesions at other sites.

NATURAL HISTORY (PATTERNS OF SPREAD)

Vulvar cancers metastasize in 3 ways: (a) local growth and extension into adjacent organs, (b) lymphatic embolization to regional lymph nodes in the groin, and (c) hematogenous dissemination to distant sites.

Inguinal node metastasis can be predicted by the presence of multiple risk factors, including tumor diameter, higher histologic grade (degree of differentiation), depth of stromal invasion, and lymphovascular space invasion (21,22). Clinically important observations regarding nodal metastases include the following: (a) inguinal nodes are the most frequent site of lymphatic metastasis; (b) in-transit metastases within vulvar epithelium and deep tissues are exceedingly rare, suggesting that most initial lymphatic metastases represent embolic phenomena; (c) Metastasis to the contralateral groin or deep pelvic nodes are unusual in the absence of ipsilateral groin metastases; and (d) nodal involvement generally proceeds in a stepwise fashion from the superficial inguinal to the deep inguinal and then to the pelvic nodes (21,22).

Spread beyond the inguinal lymph nodes is considered distant metastasis (stage IVB). Such metastases occur either due to sequential lymphatic spread to secondary and tertiary nodal groups or as a result of hematogenous dissemination to more distant sites, such as bone, lung, or liver. Distant metastases are uncommon at initial presentation and are usually seen in the setting of recurrent disease.

CLINICAL PRESENTATION

Most women with vulvar cancer present with pruritus and a recognizable lesion. Selecting the most appropriate site for biopsy in women with condyloma, chronic vulvar LS, multifocal high-grade squamous intraepithelial lesions (VIN 3), or Paget's disease can be difficult, and multiple biopsies may be required. Optimal management for any patient presenting with a suspicious lesion is to proceed directly to biopsy under local analgesia. Tissue biopsies should include the cutaneous lesion in question and representative contiguous underlying stroma, so that the presence and depth of invasion (DOI) can be accurately assessed. Because DOI is a central issue in the management of vulvar cancer, punch biopsies are encouraged and shave biopsies are discouraged in the diagnosis of vulvar lesions. If invasion is suspected and a punch biopsy fails to confirm the clinical suspicion, then an incisional or excisional biopsy should be performed. Primary care physicians should be encouraged not to excise a lesion if avoidable, to facilitate the sentinel node procedure by a gynecologic oncologist. Figure 19.2 illustrates a relatively early-stage vulvar cancer.

DIAGNOSTIC EVALUATION

The evaluation of a patient with vulvar cancer must take into consideration the clinical extent of disease and the presence of



FIGURE 19.2. Early-stage vulvar cancer.

coexisting medical illnesses. Initial evaluation should include a detailed physical examination with measurements of the primary tumor, assessment for extension to adjacent mucosal or bony structures, and clinical evaluation of the inguinal lymph nodes. It is helpful to record the distance from vital structures such as the clitoris, urethral meatus, and anus, since these structures are a limiting factor for obtaining adequate surgical margins. Diagnostic imaging is not required in women with small primary lesions and normal body habitus. In obese women, the inguinal nodes are difficult to palpate and imaging may be helpful in identifying the presence of lymphadenopathy. Patients with large or fixed tumors, and those who are difficult to examine in the clinic, may benefit from an exam under anesthesia with cystourethroscopy and proctosigmoidoscopy. Figure 19.3 illustrates an advanced tumor, for which such an approach can help determine resectability.

Radiographic studies that have been described as beneficial are computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound, and single photon emission CT (SPECT) (23–26). While newer imaging modalities can be of benefit in treatment planning, it is also important to note that published series are small, and no individual modality has been shown to be superior to others in terms of detecting metastatic or recurrent disease. The best modality might differ depending on the practice situation and skills of the diagnostic imaging consultants. Suspicious lymph nodes should be biopsied if the findings would alter the surgical plan. Because neoplasia of the female genital tract is often multifocal, evaluation of the vagina and cervix, including cervical cytologic screening, should always be performed in women with vulvar



FIGURE 19.3. Advanced vulvar cancer.

neoplasms (27). Lymphoscintigraphy will be discussed later in this chapter.

STAGING

The International Federation of Gynecology and Obstetrics (FIGO) adopted a modified surgical staging system for vulvar cancer in 1989. This staging system was revised in 1995 and

more recently in 2009 (Table 19.2) (28,29). The 2009 revision was performed to address issues with the 1995 version, namely, the lack of a useful prognostic spread among stages, as well as significant prognostic heterogeneity among stage III patients. Since the 1995 revision, much has been learned about the significance of the number of involved nodes, the size of inguinal metastases, and nodal morphology.

The technique recommended by the International Society for the Study of Vulvar Disease, the International Society of Gynecologic Pathologists, the College of American Pathologists, and

Table 19.2 Integrated 2009 FIGO and AJCC Staging System for Squamous Cell Carcinoma of the Vulva

FIGO		AJCC		
		T	N	M
		Tis: No invasion past basement membrane (not in FIGO system)		
I: Tumor confined to the vulva				
1A	Lesions ≤ 2 cm in size, confined to vulva or perineum and with stromal invasion ≤ 1.0 mm, no nodal metastasis	T1a	N0	M0
1B	Lesions > 2 cm in size or with stromal invasion > 1.0 mm, confined to the vulva or perineum, with negative nodes	T1b	N0	M0
II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus), with negative nodes	T2	N0	M0
III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus), with positive inguinofemoral lymph nodes	T1 or T2	N1-N3	M0
IIIA	(i) 1–2 lymph node metastasis(es) (< 5 mm), or (ii) 1 lymph node metastasis (≥ 5 mm)	T1 or T2	N1a = (i) N1b = (ii)	M0
IIIB	(i) 3 or more lymph node metastases (< 5 mm) or (ii) 2 or more lymph node metastases (≥ 5 mm)	T1 or T2	N2a = (i) N2b = (ii)	M0
IIIC	Positive nodes with extracapsular spread	T1 or T2	N2c N3 = inguinal skin ulceration or fixed nodes	M0
IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures	T3 = any size, involves upper urethra, bladder, rectum, bone		
IVA	Tumor invades: (i) upper urethral and / or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguinofemoral lymph nodes	T3		M0
IVB	Distant metastasis: includes pelvic nodes	T1, T2 or T3		M1
		AJCC stage groupings		
		Stage	T, N, M combination	
		0	Tis, N0, M0	
		IA	T1a, N0, M0	
		IB	T1b, N0, M0	
		II	T2, N0, M0	
		IIIA	T1 or T2, N1a or N1b, M0	
		IIIB	T1 or T2, N2a or N2b, M0	
		IIIC	T1 or T2, N2c, M0	
		IVA	Either T1 or T2, N3, M0 or T2, any N, M0	
		IVB	any T, any N, M1	

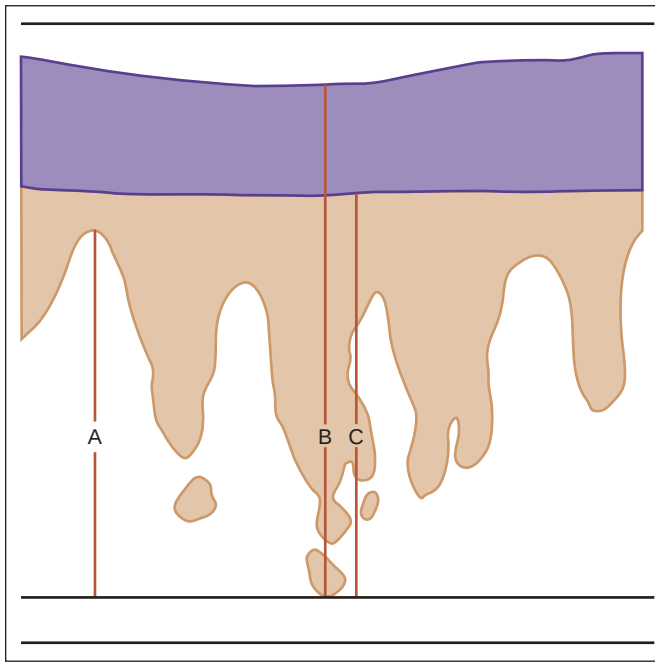


FIGURE 19.4. Methods for measurement for vulvar superficially invasive carcinomas. Depth of invasion (**A**): the measurement from the epithelial stromal junction of the most superficial dermal papillae to the deepest point of invasion. This measurement is defined as the depth of invasion and is used to define stage IA vulvar carcinoma. The measurement (**B**) is the thickness of the tumor: from the surface of the lesion to the deepest point of invasion. Measurement (**C**) is from the bottom of the granular layer to the deepest point of invasion. This is also defined as thickness of the tumor in cases where there is a keratinized surface. The International Society of Gynecological Pathologists and the World Health Organization recommend that both the depth of invasion and the thickness of tumor, as well as the method of measurement, be defined in the pathology reports.

Source: Reprinted with permission from Wilkinson EJ. Superficial invasive carcinoma of the vulva. *Clin Obstet Gynecol.* 1985;28:188–192.

the World Health Organization to assess depth of stromal invasion is to measure from the base of the epithelium (epithelial-stromal junction) at the nearest superficial dermal papillae to the deepest point of tumor penetration (30). These definitions and methods of measurement are supported by the recent CAP-ASCCP LAST terminology project (Fig. 19.4) (31).

Among squamous cell carcinomas limited to the vulva, those with a DOI less than or equal to 1 mm are associated with a <1% risk for lymph node metastasis. Tumors with a DOI of 1.1 to 3.0 mm are associated with lymph node metastases in 6% to 12% of patients, and approximately 15% to 20% of tumors with a DOI of 3.1 to 5.0 mm are associated with positive lymph nodes (32).

In the 2009 revision, all stage I and stage II patients have uninvolved lymph nodes. There is no clear definition of how many lymph nodes constitutes an adequate evaluation. SLN biopsy is not mentioned as a requirement; however, the emphasis on the size of micrometastases in stage III implies that an SLN biopsy is performed either alone or as part of a lymphadenectomy.

The new staging system adds 3 pathologic groupings within stage III (a, b, and c), each of which contains prognostic significance. These 3 groups are number of positive nodes, size of the largest inguinal node metastasis, and the presence or absence of extracapsular extension. These pathologic features have been shown in multiple studies to be the strongest predictors of mortality related to vulvar cancer (28).

The other notable difference in the new schema is the absence of stage difference based on unilaterality versus bilaterality of groin involvement; any groin metastasis is considered stage III

disease. As in 1995, the 2009 FIGO staging guidelines for vulvar cancer were devised with correlation for the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification scheme (Table 19.2) (33). Tumor assessment is based on physical examination, with endoscopy in cases of bulky disease. Nodal status is determined by the surgical evaluation of the groins. The presence or absence of distant metastases should be based on an individualized diagnostic workup based on the patient's clinical presentation (28).

Because of the infrequent incidence of vulvar melanoma there has historically been a paucity of data to guide staging algorithms for patients with this disease. Recent data though support an assertion that AJCC staging guidelines (updated in 2010) for cutaneous melanoma should be applied to vulvar melanoma. Moxley et al. (34) examined 77 cases of vulvar melanoma from 5 academic medical centers, applying the 2002 modifications of the AJCC staging system for cutaneous melanoma, Breslow thickness and Clark level to all patients. Breslow's thickness was associated with recurrence ($p = 0.002$) but not survival; however, the AJCC-2002 staging system was predictive of overall survival ($p = 0.006$) in patients with vulvar melanoma (34). It is important to emphasize that primary tumor thickness (using Breslow's method) and nodal status are the primary determinants of survival in this disease. Also important, however, are the presence or absence of ulceration and mitotic rate; these descriptors also factor prominently in the staging of cutaneous melanoma (Table 19.3).

PATHOLOGY

Most vulvar malignancies arise within squamous epithelium. Although the vulva does not have an identifiable transformation zone, as the cervix does, squamous neoplasms arise most commonly on the labia minora, clitoris, posterior fourchette, perineal body, or medial aspects of the labia majora. Within the vulvar vestibule and fourchette, squamous neoplasia may arise where keratinized stratified squamous epithelium transitions to the nonkeratinized squamous mucosa of the vestibule, also known as Hart's line (35).

Most vulvar squamous carcinomas arise within areas of epithelium associated with a recognizable epithelial cell abnormality. Approximately 60% of cases have adjacent HSIL (VIN 3). In cases of superficially invasive squamous carcinoma of the vulva, the frequency of adjacent HSIL (VIN 3) approaches 85% (36). Lichen sclerosis, usually with associated hyperplastic features, and/or HSIL (VIN 3), can be found adjacent to vulvar squamous cell carcinoma in 15% to 40% of the cases (37,38). Granulomatous disease is also associated with vulvar squamous cell carcinoma; however, this is not a commonly associated finding in the United States. Thus, vulvar squamous cell carcinoma precursors can be considered in distinct groups: those associated with HPV, "usual" VIN, and those that are not (e.g., those associated with LS, chronic granulomatous disease) (see Epidemiology section).

Epithelial Carcinomas

Squamous Cell Carcinomas

The term microinvasive carcinoma is not recognized as meaningful in reference to vulvar cancer because there are no commonly agreed on pathologic criteria established for this term. The recent CAP-ASCCP terminology committee on Lower Anogenital tract terminology (the LAST committee) stated that the descriptor "superficially invasive squamous cell carcinoma" be defined as stage IA carcinoma, and that the term "microinvasive

Table 19.3A TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness	Ulceration Status/Mitoses
Tis	NA	
T1	≤ 1.00	a: Without ulceration and mitoses < 1/mm ² b: With ulceration or mitoses ≥ 1/mm ²
T2	1.01–2.00	a: Without ulceration b: With ulceration
T3	2.01–4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis ^a b: Macrometastasis ^b
N2	2-3	a: Micrometastasis ^a b: Macrometastasis ^b c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

LDH, lactate dehydrogenase; NA, not applicable.

^aMicrometastases are diagnosed after sentinel lymph node biopsy.^bMicrometastases are defined as clinically detectable nodal metastases confirmed pathologically.**Table 19.3B**

Clinical Staging				Pathologic Staging			
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	>N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0

(continued)

Table 19.3B Continued

Clinical Staging				Pathologic Staging			
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

Source: Reprinted with permission from Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. New York, NY: Springer; 2009.

carcinoma” not be used in reference to vulvar squamous cell carcinoma (31). The DOI is defined as the measurement from the epithelial dermal junction of the most superficial adjacent dermal papillae to the deepest point of invasion (31). In comparison, tumor thickness is measured from the overlying surface epithelium or from the bottom of the granular layer if the surface is keratinized, to the deepest point of invasion, as specified by the International Society of Gynecologic Pathologists (ISGYP), the World Health Organization, and FIGO (Fig. 19.4).

Stage I squamous carcinomas of the vulva with a DOI of 3 mm have a lymph node metastasis rate averaging 12%. Tumors with a DOI of 5 mm or more have a lymph node metastasis rate of at least 15%. Tumors with a DOI of 1 mm or less carry little risk of lymph node metastasis (30).

DOI and tumor thickness are separately defined and measured because considerable variations can exist among measurements from various superficial points in tumors of approximately 1 mm (Fig. 19.4) (39). There are significant differences between tumor DOI and thickness when superficially invasive tumors are measured. Tumors with invasion deeper than 1 mm can be readily measured by determining thickness, but tumors with surface ulceration may have a thickness, as measured from the surface, significantly less than the DOI. With large tumors, thickness may be the only reliable measurement because of the lack of identifiable adjacent dermal papillae.

In addition to tumor stage and depth or thickness, other pathologic features include vascular space invasion, growth pattern of the tumor, grade of the tumor, and tumor type. Vascular space involvement can be defined as tumor within an endothelial lined vascular space. Strict pathologic criteria require that the tumor be attached to the wall of the vessel, but this is not observed in all cases. Vascular space involvement by squamous cell carcinoma of the vulva is associated with a higher frequency of lymph node metastasis and a lower overall 5-year survival rate. No reliable methods unambiguously predict lymph node metastasis by quantitation of vascular space involvement by tumor.

Tumor growth pattern influences the rate of lymph node metastasis and survival in tumors exceeding 1 mm in DOI. In stage IA vulvar carcinomas, tumor growth pattern does not influence the risk of node involvement (32). Three factors describe tumor growth patterns: confluent; compact (pushing pattern); and finger-like (or spray or diffuse), a pattern also described as poorly differentiated (32). Confluent growth is defined as a tumor mass composed of interconnected tumor exceeding 1 mm in

dimension (Fig. 19.5). Tumors with confluent growth, by definition, have a DOI exceeding 1 mm. Confluent growth is characteristic of deeply invasive squamous cell carcinomas that are associated with stromal desmoplasia, resulting in fibrovascular stromal changes adjacent to the interconnected cords of tumor.

Compact (pushing; well-differentiated) growth is squamous tumor growth that maintains continuity with the overlying epithelium and infiltrates as a well-defined and well-circumscribed tumor mass, without islands of infiltrating tumor remote from the tumor mass. Tumors with compact growth typically have thickness of 5 mm or less and rarely invade vascular space. They are characteristically well-differentiated, with the tumor cells resembling the squamous cells of the adjacent and overlying epithelium. There is usually minimal stromal desmoplasia, although there may be a lymphocytic inflammatory cell infiltrate.

Finger-like (spray or diffuse; poorly differentiated) growth is characterized by a trabecular appearance with small islands of poorly differentiated tumor cells found within the dermis or

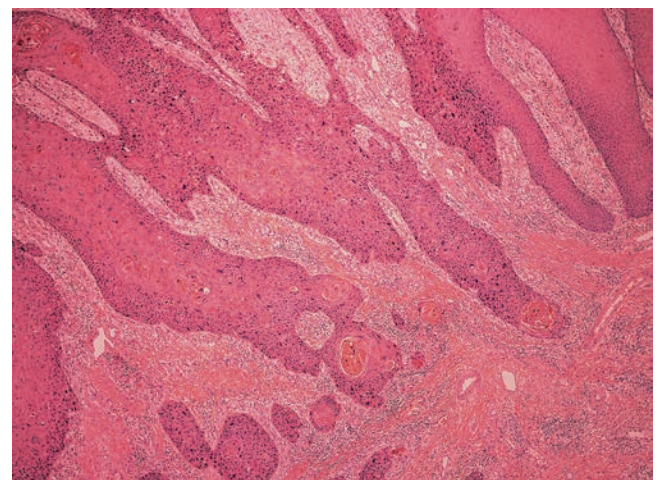


FIGURE 19.5. Confluent pattern of invasion. The tumor has a compact, pushing growth pattern with a well-defined tumor-dermal interface. The tumor diameter exceeds 1 cm, and has finger-like growth pattern, with small, variable-sized tumor nests within the adjacent dermis. The adjacent dermis has a desmoplastic, fibrotic appearance.

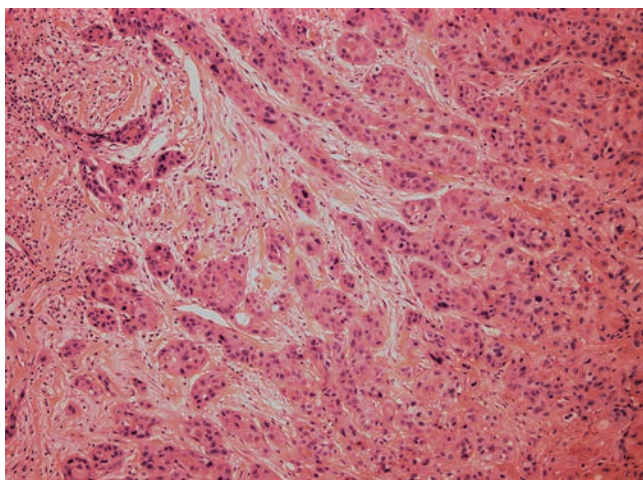


FIGURE 19.6. Finger-like growth. The tumor forms small nests surrounded by a desmoplastic stroma.

submucosa deeper than the bulk of the tumor mass. Tumors with this growth pattern are typically associated with a desmoplastic stromal response (Fig. 19.6) and a lymphocytic inflammatory cell infiltrate. In tumors with a DOI less than 5 mm, the finger-like pattern of growth is associated with a higher frequency of inguinofemoral lymph node metastasis.

In some cases, a single tumor may have both compact and finger-like growth patterns. Mixed patterns, in our experience, are more commonly encountered in frankly invasive vulvar carcinomas and are rarely seen in superficially invasive tumors. The GOG has referred to tumors with a compact pattern of growth as well-differentiated, and to tumors with the finger-like pattern of growth as poorly differentiated. Using this terminology, the GOG proposed the following grading system for vulvar squamous cell carcinoma:

- Grade 1 tumors are composed of well-differentiated tumor and contain no poorly differentiated element.
- Grade 2 tumors contain both patterns, with the poorly differentiated portions making up one-third or less of the tumor.
- Grade 3 tumors also contain both components, with the poorly differentiated portion composing more than one-third but less than one-half of the tumor.
- Grade 4 tumors have one-half or more of the tumor composed of the poorly differentiated elements.

The ISGYP Committee of Terminology for Nonneoplastic Epithelial Disorders and Tumors recommended that the following information be included in the pathology report of all excised vulvar squamous cell carcinomas, information also supported by the College of American Pathologists, and often used by tumor registries (40):

1. Depth of tumor invasion in millimeters
2. Thickness of the tumor in millimeters
3. Method of measurement of the DOI and thickness
4. Presence or absence of vascular space (lymphatic) involvement by tumor
5. Diameter of the tumor, measured from the specimen in the fresh or fixed state
6. Clinical measurement of the tumor diameter, if available

In a multivariable retrospective analysis of 39 cases of vulvar squamous carcinoma, in addition to clinical stage and when corrected for treatment modality, pattern of tumor invasion, depth of tumor invasion, and lymph node status were all found to be significant prognostic factors. In addition, dermal desmoplasia associated with tumor invasion also

had a suggestive association. Findings that did not correlate with survival were squamous cell carcinoma type, vascular space involvement by tumor, adjacent HSIL VIN, tumor nuclear grade, or associated degree of inflammatory response. DNA ploidy analysis (i.e., diploid versus aneuploid) of vulvar carcinoma does not appear to have significance in regard to survival (41).

Several histopathologic types of vulvar squamous cell carcinoma are recognized. The usual types include squamous cell carcinoma, keratinizing type; squamous cell carcinoma, non-keratinizing type; basaloid carcinoma; and warty (condylomatous) carcinoma (42). Less common types include acantholytic squamous cell carcinoma, squamous cell carcinoma with tumor giant cells and spindle cell squamous carcinoma, squamous cell carcinoma with sarcoma-like stroma, sebaceous carcinoma, verrucous carcinoma, and other rarer types (38,42).

Vulvar squamous cell carcinomas of the basaloid and warty types, as well as HSIL (VIN 2/3) of all but the differentiated type, are recognized to be associated with human papillomavirus, primarily HPV 16. The HPV can be detected within the tumor cells by a variety of techniques, including polymerase chain reaction (PCR), hybrid capture, and *in situ* hybridization. In addition, it is now recognized that approximately one-quarter ($27\% \pm 9\%$) of the women with vulvar squamous carcinoma have anti-HPV 16 antibodies expressed serologically as IgG antibodies to HPV 16 virus-like particles as measured by enzyme-linked immunosorbent assay (ELISA) (43).

Adenoid squamous carcinoma (pseudoangiosarcomatous carcinoma, acantholytic squamous cell carcinoma, pseudoglandular squamous cell carcinoma) refers to squamous cell carcinomas with pseudoglandular features. These tumors are characterized by small gland-like spaces within a tumor that otherwise appears to be a poorly differentiated squamous cell carcinoma. It is considered a highly aggressive variant of vulvar squamous cell carcinoma (44). This tumor should be differentiated from adenosquamous carcinomas that contain an obvious adenocarcinoma component (37). Adenoid squamous carcinoma does not contain sialomucin, but adenosquamous carcinoma typically does contain mucin within the adenocarcinoma component. *Squamous cell carcinoma with tumor giant cells* has multinucleated tumor giant cells intermixed within the squamous carcinoma (45). This tumor may resemble amelanotic melanoma. Squamous cell carcinoma with tumor giant cells, unlike melanoma, does not express S100 antigen, HMB45, or Melan-A on immunoperoxidase studies. This tumor does express low-molecular-weight keratin, similar to other squamous carcinomas.

Sebaceous carcinoma of the vulva. These tumors, which arise from the sebaceous glands of the vulvar skin, may be associated with VIN. This rare tumor is aggressive. The tumor cells are relatively large with large nuclei and prominent nucleoli with prominent cytoplasm. The cytoplasm, related to its lipid content, has a finely vacuolated appearance. The tumor may have the appearance of a squamous cell carcinoma intermixed with sebaceous elements. Deep invasion and lymph node or other metastasis may be present on initial presentation (46,47).

Spindle cell squamous cell carcinomas consist of poorly differentiated neoplastic epithelial cells that have an elongated spindle shape and may mimic a spindle cell melanoma or a sarcoma (Fig. 19.7) (48). Squamous cell carcinoma with spindle cell stroma is a squamous cell carcinoma associated with a sarcoma-like stromal/dermal response that may mimic a primary sarcoma (49). Spindle cell squamous cell carcinomas can be differentiated from sarcomas by immunoperoxidase techniques. Like other squamous cell carcinomas, the spindle cell variant contains keratin and lacks the antigens distinctive to sarcomas of various origin. S100 antigen, HMB45, and Melan-A are usually immunoreactive in a spindle cell melanoma and lacking in a spindle cell squamous carcinoma.

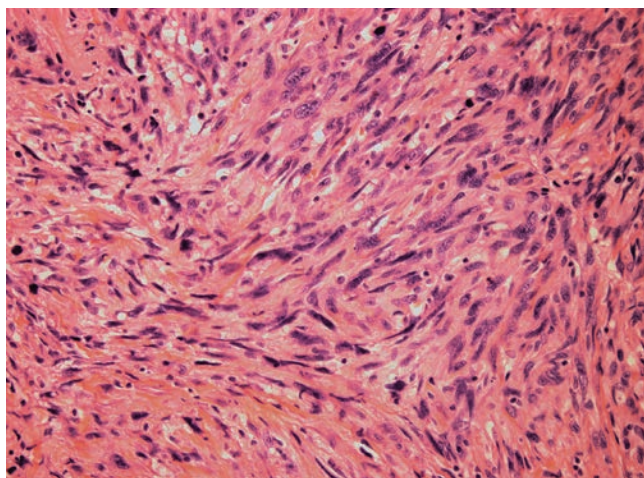


FIGURE 19.7. Spindle-cell squamous carcinoma. The tumor cells have a spindle shape and poorly defined cell junctions.

Verrucous Carcinoma

Verrucous carcinoma of the vulva typically presents as an exophytic-appearing growth that can be locally destructive. Clinically, it may resemble condyloma acuminatum. The so-called Buschke-Lowenstein giant condyloma is classified as a variant of verrucous carcinoma by the World Health Organization (30).

Microscopically, verrucous carcinoma is characterized by well-differentiated epithelial cells. The tumor growth pattern is characterized by a “pushing” tumor-dermal interface with minimal stroma between the acanthotic epithelium (Fig. 19.8). The surface is often hyperkeratotic, and there may be parakeratosis. Observed mitoses are characteristically normal. Within the dermis, a mild lymphocytic inflammatory cell response is usually seen. Vascular space involvement by tumor is characteristically lacking. Because of its excellent prognosis, strict histologic criteria should be used in the diagnosis of verrucous carcinoma. Squamous carcinomas with focal verrucous features should not be described or diagnosed as verrucous carcinoma.

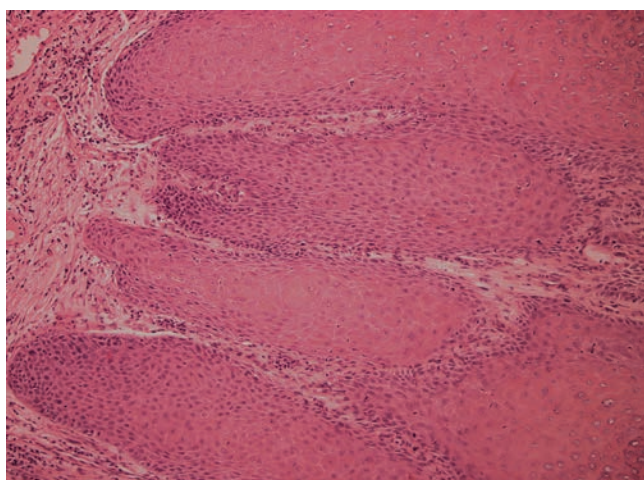


FIGURE 19.8. Verrucous carcinoma. The epithelial cells are well-differentiated, and the tumor has a “pushing border” with a delicate vascular core between the epithelial elements.

Verrucous carcinomas are characteristically diploid, unlike typical squamous cell carcinomas of the vulva, which are usually aneuploid by DNA analysis. Verrucous tumors may be associated with HPV 6 or its variants (50).

The major differential diagnosis of squamous cell carcinoma includes keratoacanthomas, pseudocarcinomatous (pseudoepitheliomatous) hyperplasia, epithelioid sarcoma, and malignant rhabdoid tumor.

Basal Cell Carcinoma

Basal cell carcinoma is a relatively rare tumor in the vulva, accounting for 2% to 4% of infiltrative neoplasms. These tumors are most commonly found in elderly women (51). The surface of the tumor appears granular and is well circumscribed; on palpation, the tumor is characteristically very firm. Vulvar basal cell carcinoma most commonly arises on the labia majora and is typically 2 cm or less in diameter.

The epithelial cells composing basal cell carcinoma are typically small and vary in form, with small hyperchromatic nuclei that may exhibit some nuclear pleomorphism. These tumors may have a variety of growth patterns (e.g., trabecular, insular), although peripheral nuclear palisading is a relatively consistent finding. Basal cell carcinomas often have an intraepithelial component that is contiguous with the infiltrative component, if present.

Metatypical basal cell carcinoma is a variant of basal cell carcinoma that usually occurs at mucocutaneous junctions. The term *basosquamous carcinoma* is applied to these tumors because of their microscopic features, which include basal cell carcinoma intermixed with a squamous cell carcinoma component. Nuclear pleomorphism is usually seen in metatypical basal cell carcinoma and in the basal cell and squamous cell components of the tumor. The deeper tumor cells, close to the underlying stroma, have the greatest degree of nuclear pleomorphism and the more prominent squamous features. These tumors have a more aggressive clinical behavior than typical basal cell carcinoma.

The differential diagnosis of basal cell carcinoma includes basaloid squamous cell carcinoma, Merkel cell tumor of the skin, and metastatic small cell carcinoma. Basaloid squamous cell carcinoma can be distinguished by its lack of characteristic basal cell growth pattern, and the presence of intracellular bridges. Nuclear pleomorphism is typically much greater in basaloid squamous cell carcinoma than in basal cell carcinoma. Basal cell carcinomas express BerEP4 on histochemical study, an antigen not expressed by basaloid squamous cell carcinomas (38). Basaloid squamous cell carcinomas are typically associated with HPV 16, which is not typically associated with basal cell carcinoma. Merkel cell tumors and other neuroendocrine tumors of the vulva are typically subcutaneous or dermal nodules, and not intraepithelial lesions (see the section on neuroendocrine tumors).

Neuroendocrine and Neuroectodermal Tumors: Merkel Cell Tumors and Peripheral Neuroectodermal Tumor/Extrasosseous Ewing Sarcoma

Merkel Cell Tumor. Merkel cell tumors are neuroendocrine tumors of the skin occurring usually within the dermis. The tumor is composed of small, relatively uniform cells with little cytoplasm and hyperchromatic nuclei with a punctate chromatin pattern, and it has a high mitotic count. The tumor is infiltrative and often involves vascular spaces. Merkel cell tumors have been associated with squamous cell carcinoma and vulvar intraepithelial neoplasia (52). Merkel cell tumors are subclassified as carcinoid-like (trabecular), intermediate type, and small cell (oat cell) type. These tumors typically express neuron-specific

enolase, synaptophysin, chromogranin, and low-molecular-weight keratin. Keratin study, such as with cytokeratin 20, demonstrates a distinct perinuclear cytoplasmic dot. Dense core neurosecretory granules are seen by electron microscopy. These features differentiate it from basal cell or squamous cell carcinoma (38). Merkel cell tumors frequently have both regional lymph node and distant metastases and are associated with a poor prognosis.

Peripheral Neuroectodermal Tumor/Extrasosseous Ewing Sarcoma. Peripheral neuroectodermal tumor/extrasosseous Ewing sarcoma (PNET) is a rare neuroendocrine vulvar neoplasm that has been reported in childhood and women of reproductive age. The tumor may present as a subcutaneous or polypoid mass and clinically may resemble a cyst or be ulcerated (53,54). On microscopic examination the tumor is circumscribed and multilobulated, without capsule but nonencapsulated, and contains small cells with little cytoplasm and nuclei with hyperchromatic and finely granular nuclear chromatin. Some cells have small nucleoli, and mitotic figures are usually common, with mitotic counts from 3 to exceeding 10 per 10 high power fields. Numerous patterns of growth may be seen with highly cellular undifferentiated areas, areas with cyst formation containing eosinophilic proteinous material, rosettes with Homer-Wright rosettes, and follicle-like structures.

The cells of PNET have periodic-acid Schiff (PAS) staining cytoplasm that digests with diastase, and typically express CD99 and vimentin. Although, as in Merkel cell tumors, focal reactivity for synaptophysin and neuron-specific enolase may be present, cytokeratin reactivity is not present but may be focally immunoreactive in some cases.

Dense core neurosecretory granules, as seen in Merkel cell tumor by electron microscopy, are not present. Cytogenetic study of these PNET tumors demonstrates translocation t(11;22)(q24;q12) in approximately 90% of cases. This translocation can also be demonstrated with fluorescence *in situ* hybridization, or reverse transcriptase polymerase chain reaction (RT-PCR) (53,54).

Urothelial/Transitional Cell Carcinoma

Urothelial carcinoma may be a primary tumor of the vulva, usually arising within the Bartholin's glands. More commonly, urothelial carcinoma is metastatic to the vulva, having arisen within the bladder or urethra. In rare instances, the tumor presents as a Paget-like lesion of the vulva (see section on Paget's disease) (55).

Microscopically, urothelial carcinomas are composed of relatively uniform cells; nuclear pleomorphisms may be marked in high-grade urothelial neoplasms. The cytoplasm is eosinophilic without apparent inclusions or keratin formations, although focal keratin formation may be seen. The tumors may exhibit papillary-like growth.

Adenocarcinoma and Carcinoma of Bartholin's Glands

Most primary adenocarcinomas of the vulva arise within Bartholin's glands. Adenocarcinoma may also arise from other glands or skin appendages of the vulva, including sweat glands and Skene's glands (56). Clear cell adenocarcinoma arising in endometriosis has been reported in the groin (57). Invasive vulvar Paget's disease has given rise to adenocarcinoma (Fig. 19.13). Primary malignant tumors arising within Bartholin's glands include adenocarcinoma and squamous cell carcinoma, which occur with approximately equal frequency and account for approximately 80% of all primary malignant tumors in this site. Adenoid cystic carcinomas compose approximately 15% of all primary carcinomas, with adenosquamous carcinomas and

transitional cell carcinomas each composing approximately 5% of the primary Bartholin's gland tumors (58).

Carcinoma of Bartholin's glands generally occurs in older women and is rare in women younger than 50. In clinical practice, it is generally advisable to excise an enlarged Bartholin's gland in a woman 50 years of age or older, especially if there is no known history of prior Bartholin's cyst. If a cyst is drained and a palpable mass persists, excision is also indicated. Fine needle aspiration of a Bartholin's mass for cytologic evaluation may help to establish a positive diagnosis.

Primary carcinomas within Bartholin's glands are usually solid tumors and are often deeply infiltrative. A variety of histologic types of adenocarcinoma have been described within Bartholin's glands. Mucinous, papillary, and mucoepidermoid carcinoma tumor types have been described, in addition to adenosquamous, squamous, and transitional cell carcinoma. Adenocarcinoma of Bartholin's glands is typically immunoreactive for carcinoembryonic antigen (38). Histopathologic features that identify a carcinoma arising in Bartholin's glands include a recognizable transition from a Bartholin's gland to tumor. The histopathologic tumor type must be consistent with an origin from a Bartholin's gland, and the tumor must not be metastatic to a Bartholin's gland.

These malignancies are characteristically deep and difficult to detect in their early growth. Approximately 20% of women with primary carcinoma of Bartholin's glands have metastatic tumor to the inguinofemoral lymph nodes at the time of primary tumor diagnosis.

Adenocarcinoma Arising in Vulvar Skin Appendages

The vulvar labia majora were once thought to be within the milk line, but this has been significantly challenged by Van der Putte, who observed that the milk line did not involve the vulva in the human (59). The breast-like tumors found are believed to arise from specialized anogenital glands that reside in the intralabial sulci and may be the origin of papillary hidradenoma. Both benign and malignant breast-like tumors have been observed within the vulva (60). Fibroadenoma, intraductal papilloma, and lactating adenoma have been observed. Primary adenocarcinoma of the vulva may arise in specialized anogenital glands, which reside in the intralabial sulcus and are believed to be the origin of papillary hidradenoma of the vulva, as well as the breast-like tumors seen within the vulva, and these glands may resemble breast tissue (59,60).

Adenosquamous Carcinoma

Adenosquamous carcinomas are epithelial tumors composed of both malignant squamous and gland-forming elements. Adenosquamous carcinomas account for approximately 5% of all tumors of Bartholin's glands. These tumors may be composed of a poorly differentiated squamous component mixed with cells bearing small glandular lumens containing mucin.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma arising within the vulva most commonly arises within the Bartholin's glands and composes approximately 15% of all carcinomas of Bartholin's glands. Microscopically, adenoid cystic carcinomas are composed of relatively uniform small cells with regular, round nuclei and minimal cytoplasm. The cord-like or "nested" arrangement contains gland-like lumens that include an acellular eosinophilic material. Electron microscopy has documented that this material is basement membrane-like material rather than a secretion. These tumors are therefore more properly considered a variant of squamous cell carcinoma than adenocarcinoma.

Carcinomas of Sweat Gland Origin

Primary carcinomas of sweat gland origin are relatively rare within the vulva, composing approximately 10% of all vulvar malignant tumors. A variety of sweat gland carcinomas in this site have been described, including eccrine adenocarcinoma, eccrine porocarcinoma, and clear cell hidradenocarcinoma (56). Primary adenocarcinomas of apocrine gland origin have also been described arising within the vulva, and some of these have been associated with vulvar Paget's disease. These should be distinguished from the benign papillary hidradenoma, which typically arises in the intralabial papillary sulcus from specialized anogenital glands and contains a myoepithelial cell population, distinguishing it from adenocarcinoma (59).

Vulvar Paget's Disease and Paget-Like Lesions

Vulvar Paget's disease typically presents as an eczematoid, red, weeping area on the vulva, often localized to the labia majora, perineal body, clitoral area, or other sites. This disease typically occurs in older, postmenopausal Caucasian women, although it has been described in a premenopausal woman. Because of its eczematoid, or "cake-icing" appearance, it is not unusual for vulvar Paget's disease to be misdiagnosed as eczema or contact dermatitis. Approximately 15% of women with vulvar Paget's disease have underlying primary adenocarcinoma, usually arising within apocrine glands or the underlying Bartholin's glands (Fig. 19.9). The Wilkinson and Brown etiologic classification of vulvar Paget's disease divides Paget's disease into 2 main groups: those of cutaneous origin and those of noncutaneous origin (55). The 2 most common types of noncutaneous Paget's disease are those associated with colorectal adenocarcinoma and those associated with bladder urothelial carcinoma. Women with Paget's disease of the colorectal type usually present with a lesion that involves the perianal skin, and this lesion is a manifestation of underlying colon or rectal adenocarcinoma. Women with Paget-like disease (Pagetoid urothelial intraepithelial neoplasia [PUIN]) typically present with a lesion involving the periurethral area and vulvar vestibule (55,61,62). In these cases there is associated bladder and/or urethral urothelial carcinoma with the extension of the neoplastic urothelial cells to the epithelium of the vulva (55,61). In cases of PUIN, total deep vulvectomy is not indicated because there is no associated underlying cutaneous adenocarcinoma. The tumor cells are from the bladder and/or urethra, representing an intraepithelial transitional cell

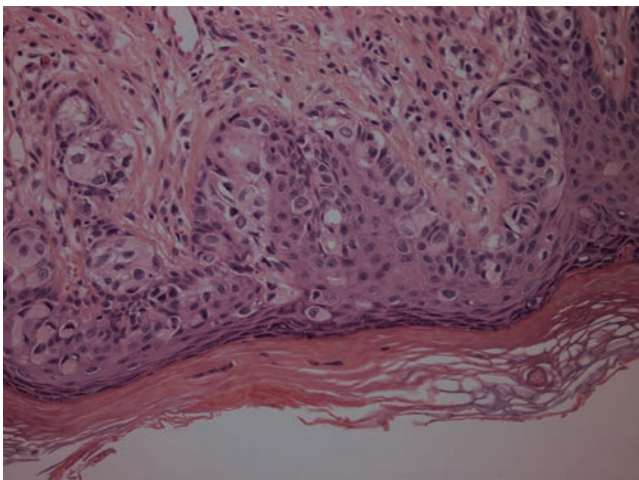


FIGURE 19.9. Paget's disease. The large cells with prominent cytoplasm and large nuclei represent the intraepithelial Paget's cells. A few small gland-like intraepithelial structures are formed by the Paget's cells.

neoplasm extending from the bladder and/or urethra (55). These cells have been reported from a vaginal cytology specimen from a woman with a PUIN lesion (63).

Cutaneous Paget's disease is most commonly a primary intraepithelial neoplasm. In such cases the intraepithelial Paget's disease may have an associated invasive Paget's disease. In rare cases, cutaneous Paget's disease may be a manifestation of an underlying cutaneous adenocarcinoma (55). Cutaneous Paget's disease is characterized by the presence of Paget's cells, which are found within the involved epithelium. A Paget's cell is relatively large, with a prominent nucleus that typically has coarse chromatin and a prominent nucleolus. On hematoxylin and eosin staining, the cytoplasm is distinctly pale compared with the surrounding keratinocytes. The cytoplasm may be vacuolated or appear foamy and typically is somewhat basophilic (Fig. 19.9).

Paget's cells of cutaneous origin are rich in carcinoembryonic antigen (CEA), which can be identified with immunoperoxidase techniques (55). Paget's cells also express cytokeratin 7 (CK-7) and gross-cystic-disease fluid protein-15 (GCDFFP-15) (55,64). Paget's cells infrequently express CA-125, and estrogen receptor is generally negative (65). Immunohistochemical study for CK-7 is useful in many cases to identify the Paget's cells that are strongly CK-7 positive, whereas the adjacent epithelial cells are negative (66). Invasive Paget's disease 1 mm or less in DOI has reportedly little risk for recurrence (65).

The differential diagnosis of Paget's disease of cutaneous origin includes PUIN/Paget's disease of urothelial origin, Paget's disease of colorectal origin/or other related adenocarcinoma, superficial spreading malignant melanoma, pagetoid reticulosis, and the pagetoid variant of vulvar intraepithelial neoplasia, which are keratinocytic cells resembling Paget's cells. These can all be differentiated by immunoperoxidase techniques because melanomas do not express cytokeratin, but usually express S100 protein, HMB45, and Melan-A, which are absent in Paget's cells (55,67). The Paget-like cells in PUIN express uroplakin-3, but do not express GCDFFP-15. Adenocarcinoma cells of colonic, anal, or rectal origin express CEA, as well as caudal homeobox (CDX), whereas Paget's disease of cutaneous origin does not express CDX. HSIL (VIN 3) of pagetoid type may microscopically resemble Paget's disease or melanoma, but the cells of LSIL or HSIL (VIN 1-VIN 2-3) do not express CEA, S100, or melanoma antigen (55,61).

Vulvar Malignant Melanoma

Malignant melanoma of the vulva accounts for approximately 9% of all primary malignant neoplasms on the vulva, and vulvar melanoma accounts for approximately 3% of all melanomas in women. This tumor occurs predominantly in Caucasian women, with approximately one-third of the cases occurring in women younger than 50, and the mean age at diagnosis is 55 years (68). The peak frequency occurs between the sixth and seventh decades, and the highest incidence is in women 75 years of age or older, where the age-specific incidence is reported to be 1.28 per 100,000 (69). The most common presenting symptom is bleeding; however, pruritus, pain, dysuria, and a palpable mass may all be symptoms (69,70,71). The tumor may arise from a preexisting pigmented lesion or from normal-appearing skin. The primary site on the vulva may be the clitoris, labia minora, and labia majora, where melanomas occur with approximately equal frequency (72). The tumor may be elevated, nodular, or ulcerated. Although tumors are usually pigmented, approximately one-fourth are nonpigmented, amelanotic melanomas, a melanoma type that clinically and pathologically may resemble squamous carcinoma. In the clinical setting, the differential diagnosis includes pigmented condyloma acuminatum, pigmented HSIL VIN, atypical genital nevus, large vulvar nevi, melanosis of the vulva, or other malignant tumors, including malignant soft-tissue tumors (61,73).

Vulvar malignant melanomas may be subclassified into 3 specific categories: superficial spreading malignant melanoma, nodular melanoma, and mucosal lentiginous melanoma, which is also referred to as mucosal/acral lentiginous melanoma (74). In the vulva, some cases are mixed or cannot be specifically classified. Mucosal lentiginous melanomas are the type most commonly reported on the vulva, accounting for over one-half of the cases in larger series (69,74). Nodular melanomas are second in frequency, accounting for approximately one-fifth of the cases, and have the overall worst prognosis of the melanoma types, usually related to the greater thickness and deeper invasion at the time of presentation. Superficial spreading melanomas are the least common type in the vulva. Some variation in the frequency of these types in the vulva is present in the literature, primarily related to some variations in pathologic classification (68–72,74,75,76).

Histopathologic differentiation of melanoma type is based on identification of a superficial spreading component. Mucosal lentiginous melanomas have the neoplastic melanocytes clustered in the dermal-epithelial junction and have both radial growth and vertical growth. Superficial spreading melanomas have radial growth involving 4 or more rete lateral to their vertical or infiltrative growth (61). Nodular melanomas show minimal or no radial growth. Superficial spreading malignant melanoma characteristically shows junctional melanocytes with radial growth, and a vertical growth pattern may be absent. The tumor cells are highly variable in appearance but commonly are relatively large, with nuclei showing minimal variation in size and containing prominent nucleoli (Fig. 19.10). These cells may

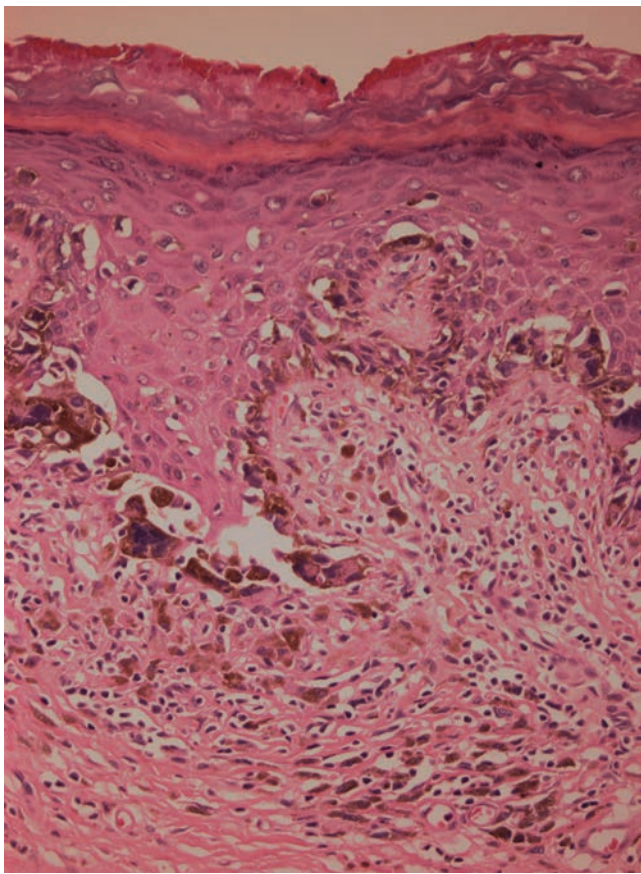


FIGURE 19.10. Malignant melanoma. The tumor is within the dermis and contains dark melanin pigment. Junctional growth is seen within the overlying epithelial dermal junction.

or may not contain pigment. The form of the cells ranges from epithelioid to spindle shaped; in some cases, the spindle cell type may predominate. The spindle cells may be relatively small, with oval nuclei and elongated cytoplasm. They may infiltrate the adjacent dermis in cords and sheets.

Malignant melanomas typically express S100 antigen, HMB45, and Melan-A and lack cytokeratin or CEA. The microscopic differential diagnosis for superficial spreading malignant melanoma is primarily vulvar Paget's disease, pagetoid reticulosis, and Kaposi's sarcoma. Immunohistochemical techniques are essential in discriminating superficial spreading melanoma from Paget's disease (see the section on vulvar Paget's disease) (67). Nonpigmented nodular melanomas may mimic squamous cell carcinoma or spindle cell neoplasms of various types. In these circumstances, immunoperoxidase procedures are of great value, because squamous cell carcinomas typically do not express S100 protein, HMB45, or Melan-A, and melanomas do not express cytokeratin (63).

Tumor thickness is the most important measurement in evaluating malignant melanoma (68). The Clark level definitions describe the extent of dermal and subcutaneous involvement by the melanoma (77). Measurements for vulvar melanomas can be applied as for skin and mucous membranes, as described by Breslow (78). With the Breslow method, the thickness measurement for cutaneous melanomas requires measurement from the top of the granular layer to the deepest point of invasion. Malignant melanomas that have a thickness of up to 1 mm are generally considered of minimal risk of recurrence. Melanomas at Clark level 2 or thickness of 1.49 mm or less, or tumor volume of 100 mm³, also correlate with good prognosis (79). A poor prognosis is correlated with Clark level 5, thickness >2 mm, or mitotic count exceeding 10/mm². Other prognostic factors include mitotic rate and reaction and surface ulceration (80).

Vulvar melanoma has been described as being associated with NRAS codon 12 mutation, as more commonly seen in sun-exposure-related melanomas; however, most mucosal non-sun-exposure-related melanomas do not express NRAS exon 2 mutations (81).

Melanomas arising in the vulva may metastasize to other sites within the lower female genital tract, including the cervix, vagina, urethra, and rectum. Distant metastasis is common with disseminated disease. Survival after recurrence is poor: approximately 5%.

Vulvar Sarcomas

Leiomyosarcoma. Leiomyosarcoma is the most frequent primary vulvar sarcoma. It most commonly arises in the labia majora or Bartholin's gland area, although these smooth muscle tumors may arise in the clitoris and labia minora. The tumors are generally larger than 5 cm in diameter when first diagnosed and may be deep within the subcutaneous tissue.

On microscopic examination, these tumors are composed of interlacing spindle shaped cells, sometimes with an epithelioid appearance. Features of leiomyosarcoma include an infiltrating border and metastasis. Microscopic criteria for diagnosis require determination of the mitotic figure count. In cases with minimal pleomorphism, it is generally accepted that the diagnosis of leiomyosarcoma can be made with a mitotic count of 10 or more per 10 high power fields. Tumors that have an infiltrating border or nuclear atypia with pleomorphism and mitotic count of 5 or more per 10 high power fields are classified as leiomyosarcoma. There are tumors that may show no significant atypia, have a diameter exceeding 5 cm, have an infiltrating margin, and have a low mitotic count, up to 5 per 10 high power fields. It is preferable to classify them as smooth muscle tumors of uncertain malignant potential, because the risk of recurrence is uncertain (38,82,83).

Malignant Fibrous Histiocytoma. Malignant fibrous histiocytoma (MFH) arises from histiocytes with fibroblastic differentiation. It is considered the second most common sarcoma of the vulva and has its peak frequency in middle age. MFH typically presents as a solitary mass that may appear somewhat brownish or pigmented, secondary to areas of focal hemorrhage within the tumor.

On microscopic examination, the tumor is characterized by a complex interlacing cellular growth pattern with marked nuclear pleomorphism, including multinucleated cells and large bizarre cells. Abnormal mitotic figures may be apparent. Microscopic variants of this tumor include inflammatory, giant cell, myxoid, and angiomatoid types (57,84). On immunoperoxidase study, these tumors contain α_1 antitrypsin and α_1 antichymotrypsin. MFH is typically infiltrative, with infiltrative margins, and may involve the underlying fascia. Involvement of the fascia is associated with a higher risk of local spread and distant metastasis.

Epithelioid Sarcoma. Epithelioid sarcoma may arise within the labia majora, subclitoral area, and clitoris (85). Its microscopic features may resemble squamous carcinoma, malignant melanoma, malignant rhabdoid tumor, or lymphoma. Epithelioid sarcoma is usually relatively superficial, arising in and involving the reticular dermis, but it may occur in deeper structures.

On microscopic examination, the tumor is nodular and may have areas of necrosis. The tumor cells have an epithelioid appearance with eosinophilic cytoplasm, but there may be metaplastic components, including cartilage and bone. On immunohistochemistry, this tumor contains cytokeratin, which does not distinguish it from epithelial tumors, but is of value in differentiating it from malignant melanoma or other types of soft-tissue tumors. Epithelioid sarcoma rarely metastasizes, although local recurrence is a risk. The differential diagnosis for this tumor includes squamous cell carcinoma, malignant melanoma, lymphoma, and malignant rhabdoid tumor, all of which are capable of distant metastasis and aggressive behavior (85). Immunoperoxidase studies are of value in differentiation but have not been of value in differentiating epithelioid sarcoma from malignant rhabdoid tumor. The distinction of these 2 tumors is based primarily on microscopic features.

Malignant Rhabdoid Tumor. Malignant rhabdoid tumor has been described in the vulva and, like epithelioid sarcoma, may be relatively superficial and contain tumor cells with an epithelioid appearance with eosinophilic cytoplasm. Unlike epithelioid sarcoma, malignant rhabdoid tumors have relatively pleomorphic nuclei. Metaplastic elements are usually not present. Malignant rhabdoid tumor also has eosinophilic cytoplasmic inclusions, which are not present in epithelioid sarcoma. These inclusions give some of the cells the appearance of signet ring cells. Malignant rhabdoid tumor has a lobulated architecture but lacks necrosis or granulomatous features, which are often found in epithelioid sarcoma (82,83,85).

Yolk Sac Tumor

Yolk sac tumor (endodermal sinus tumor) is a rare germ cell tumor of the vulva, primarily arising in the labia or clitoral areas (38,86). The age range of patients is from just under 2 to 26 years. Distinctive microscopic features are similar to endodermal sinus tumor in the ovary, including the Schiller-Duval bodies, distinctive eosinophilic globules that are PAS positive and contain α -fetoprotein, and the presence of α -fetoprotein within the tumor, as demonstrated by immunoperoxidase technique.

Other Sarcomas and Soft-Tissue Tumors

A partial list of primary sarcomas of the vulva includes angiosarcoma, Kaposi's sarcoma, hemangiopericytoma, rhabdomyosarcoma, alveolar soft part sarcoma, and liposarcoma. Sarcoma botryoides is a variant of rhabdomyosarcoma that may involve the vulva, but most cases arise within the vagina or base of the bladder. Kaposi's sarcoma and angiosarcoma should be differentiated from bacillary angiomatosis, which is a benign pseudo-neoplastic infectious process (87).

Aggressive angiomyxoma is well-documented as a primary soft-tissue tumor of the vulva and pelvis that occurs predominantly in women of reproductive age. It is locally aggressive but rarely metastatic (82,88). It typically presents as a deep soft-tissue mass or pelvic mass, sometimes mimicking a Bartholin's cyst or inguinal hernia. In the pelvis, it may displace other pelvic organs and may be best appreciated on radiologic studies.

The tumor is typically poorly circumscribed and difficult to discriminate from adjacent soft tissue. On microscopic examination, the tumor has many blood vessels. The tumor consists predominantly of spindle to stellate shaped cells, with relatively small uniform nuclei representing predominately fibroblasts and myofibroblasts. Mitotic figures are very rare. The tumor stroma varies from myxoid to densely collagenous. Nerves, small glandular structures with mucin-secreting columnar cells, and other epithelial elements may be found trapped within the tumor. The differential diagnosis is as for angiomyo-fibroblastoma (AMF), summarized below.

AMF is a rare, benign tumor of soft-tissue origin that occurs predominantly in the female genital tract (89). When involving the vulva, it usually presents as a soft subcutaneous mass, but may occasionally be pedunculated (89).

On microscopic examination, the tumor usually has well-demarcated borders. Variable cellularity is present with an edematous appearance. The cells are spindle shaped, plasmacytoid or epithelioid in appearance, and mitotic figures are rare. Cells were present in most cases. Cells may be clustered about blood vessels. The tumor is vascular with small to medium sized vessels. Some inflammatory cells, commonly lymphocytes or mast cells, may be seen around the vessels.

The differential diagnosis includes aggressive angiomyxoma, atypical myxoid fibroepithelial stromal polyp, Bartholin's cyst, lipoma, and leiomyoma. The reader is referred to additional texts on these and other soft-tissue tumors of the vulva (38,82,83).

Metastatic Tumors to the Vulva

Most metastatic tumors to the vulva involve the labia majora or Bartholin's glands. In the vulva, they usually present as single or multiple intradermal or subcutaneous nodules but may present as a Bartholin's gland mass (58,90,91,92). Metastatic tumors account for approximately 8% of all vulvar tumors, and in approximately one-half of the cases the primary tumor was in the lower genital tract, including the cervix, vagina, endometrium, and ovary. Cervical carcinoma is the most common origin of contiguous metastasis. Local metastasis secondary to contiguous involvement of the vulva from urothelial carcinoma of the bladder or urethra, or anorectal carcinoma, may involve the vulva and present as a Paget-like lesion (see Paget's disease and Paget-like lesions in this section) or a vulvar or groin node mass (55,93). Remote metastases have been observed from tumors arising in breast, kidney, stomach, lung, and other sites. Malignant melanoma and neuroblastoma can also metastasize to the vulva, as can gestational choriocarcinoma and malignant lymphomas. In approximately 10% of the cases, the primary site of the metastatic tumor cannot be identified.

PROGNOSTIC FACTORS (INFLUENCING CHOICE OF TREATMENT)

Prognostic information collected during the diagnostic work-up of squamous cell carcinomas of the vulva serves as a basis for both patient counseling and treatment decisions. Fundamental decisions regarding goals of therapy (cure vs. palliation) and sequencing of primary treatment (primary surgery vs. chemoradiation) should be based on 4 things: (a) historical and demographic risk factors; (b) characteristics of the primary tumor, including location, laterality, size (cm), DOI, and lymphovascular space invasion; (c) clinical $\pm$ radiographic assessment of the inguinal lymph nodes; and (d) The probability of distant metastatic disease.

After resection of the primary tumor and surgical evaluation of the inguinal lymph nodes, additional information obtained from intraoperative observations and the final pathologic specimens serve to guide decisions regarding adjuvant therapy. The most important prognostic factors for the adjuvant management of squamous cell carcinoma of the vulva have been incorporated into the FIGO and AJCC staging systems (Table 19.2). Among the many factors that affect recurrence risk and disease-specific mortality, *nodal status, particularly the number of positive nodes, size of the largest metastasis, and the presence or absence of extracapsular extension, are the most important*. Each of the above risk factors will be discussed below in relation to its temporal presentation (pre- vs. postsurgical resection). Prognostic factors associated with the resection specimen and inguinal lymph node evaluation following surgery are also discussed below.

Presurgery

DOI, tumor size, and lymphovascular space invasion are the primary determinants of a patient's risk for nodal metastases, and the presence of nodal involvement is the single most important determinant of disease-specific mortality. Multiple studies have demonstrated a direct correlation between lymphovascular space invasion, increasing stromal invasion and the presence of involved inguinal lymph nodes (6,22,94,95,96).

Postsurgery

Following surgery, intraoperative findings and final pathologic analysis are used to estimate recurrence risk and subsequently guide decisions regarding adjuvant therapy. Among the many pathologic findings (in addition to tumor size, lymphovascular space invasion, and DOI) that have been shown to affect recurrence risk, surgical nodal status is the most important (22,94,95).

Risk of local recurrence, although associated with tumor size and extent, is also related to the adequacy of the surgical resection margins. Heaps et al., in their analysis of formalin-fixed tissue specimens, were able to demonstrate a sharp rise in the incidence of local recurrence for tumors with microscopic margins less than 8 mm (97). They suggested that this would correspond to a minimum margin of 1 cm in fresh, unfixed tissue. These observations were confirmed in a retrospective multivariate analysis of clinical data by Chan et al., who showed that pathologic margin distance ≤ 8 mm is an important predictor of local recurrence (98). De Hullu et al. reported 9 local recurrences among 40 patients with tumor-free margins ≤ 8 mm compared to no local recurrences among 39 patients with margins > 8 mm (99). To aid the surgeon in planning surgical margins of resection, Hoffman et al. measured the radial occult microscopic spread of tumor in patients with invasive squamous cell carcinoma of the vulva. They found that the gross and microscopic peripheries of

most cancers were approximately the same; however, ulcerative tumors with an infiltrative pattern of invasion were more likely to extend beyond what is grossly apparent (100).

The single most important prognostic factor for recurrence and overall survival in women with vulvar cancer is metastasis to the inguinal lymph nodes; most recurrences will occur within 2 years of primary treatment (101). The presence of inguinal node metastasis portends a 50% reduction in long-term survival (102,103). A number of noninvasive imaging modalities have been studied for the evaluation of inguinofemoral lymph node metastasis, including MRI, CT, PET, SPECT, and ultrasound. There currently is no imaging modality with a sufficiently high negative predictive value to allow for exclusion of surgical groin lymph node evaluation (104,105).

GENERAL MANAGEMENT

General Management (By Stage, Including Algorithms)

Historical Background

Development of the radical vulvectomy with bilateral inguinofemoral lymphadenectomy during the 1940s and 1950s was a dramatic improvement over prior surgical options and greatly enhanced survival, particularly for women with smaller tumors and negative lymph nodes (106,107). The ability to successfully resect vulvar tumors eliminated prolonged survival marked by local and regional progression of disease and associated pain, drainage, and bleeding. Long-term survival of 85% to 90% can now be routinely obtained with radical surgery. However, radical surgery can be associated with postoperative complications such as wound breakdown and lymphedema. Indications for radical vulvectomy and bilateral inguinofemoral lymphadenectomy for the primary treatment of vulvar cancer are very rare.

Presently, smaller vulvar tumors can be acceptably managed by less radical surgical approaches, and many authors have proposed more limited resections for certain subsets considered to represent early or low-risk disease (49,108,109,110). Advantages of such an approach are retention of a significant portion of the uninvolved vulva, preservation of body image and sexual function, less operative morbidity, and fewer late complications. In contrast, radical surgery is frequently ineffective in curing patients with bulky tumors or positive groin nodes. Multimodality programs that incorporate radiation, surgery, and chemotherapy have now been validated in women with high-risk tumors, based upon success with similar approaches in women with squamous cancers of the cervix and anus (111,112–115).

Sentinel Inguinal Lymph Node Biopsy

The SLN is defined as the first draining lymph node of a tumor. The SLN is identified by lymphatic mapping. This is a peritumoral injection of a material that is taken up by superficial cutaneous lymphatic channels and transported to the SLN. A vital blue dye or radiocolloid can be used and the SLN identified by direct visualization or detection of low levels of radioactivity by a handheld device or imaging study (Figs. 19.11 and 19.12). The modern SLN concept was first described by Morton and colleagues (116) in patients with cutaneous melanoma and shortly thereafter in patients with vulvar cancer (117). Preliminary experience with both intraoperative lymphatic dye and radioisotope injections confirmed that the SLN of the vulva is always in the groin and can be identified in most patients (118,119,120). This early experience supports the concept that



FIGURE 19.11. Transdermal localization of sentinel node using a handheld gamma counter. The probe has a collimator and is pointed away from the primary tumor. Radioactivity will fall off rapidly until the sentinel node is encountered. Mark the site of an increase in activity.



FIGURE 19.12. A hot blue sentinel node identified through a small incision. Frozen section is requested only if the sentinel node is grossly suspicious. Immunohistochemical staining is performed if the routine hematoxylin and eosin staining does not reveal metastatic disease. After a sentinel node is removed, the wound is explored with the gamma counter to assure that there is not another sentinel node in the field.

the assessment of lymphatic metastases may ultimately be reduced to the biopsy of one or 2 identifiable nodes.

Based on these early results, 2 large multi-institutional trials were initiated to determine the utility of sentinel lymph node biopsy (SLNB) in women with vulvar cancer. The GROINS V trial used a prospective, observational design, enrolling 403 evaluable women with tumors ≤ 4 cm who underwent SLNB alone. Of these, 276 women had a negative SLNB and were closely observed for recurrence during a 2-year follow-up period. Eight patients (2.9%) suffered a groin relapse. When patients with multifocal primary tumors were removed from the analysis, the relapse rate was only 2.3% (121).

The second study, GOG 173, employed a validation design. All women underwent SLNB followed by unilateral or bilateral inguinofemoral lymphadenectomy. Five hundred and fifteen women were enrolled, and 418 were evaluable. If the primary

tumor was more than 2 cm from the midline, a unilateral SLNB and inguinofemoral lymphadenectomy were performed. If the tumor was within 2 cm of the midline, or involving the midline, bilateral inguinal lymphadenectomies were performed. The false-negative rate was 8.3%, and the false-negative predictive value (FNPV) was 3.7% for the entire cohort. The FNPV is a prediction of the chance of a positive nonsentinel lymph node when the SLN is free of tumor and a lymphadenectomy has not been performed. In GOG 173 the FNPV by groin was 2.7%; for patients with tumors less than 4 cm, it was 2.0%. This means that a patient with a tumor less than 4 cm, no palpable lymph nodes, and a negative SLNB has a 2% chance of a groin relapse (122). The results of these studies indicate that, for well-selected women in the care of a surgeon experienced with this technique, the risk of groin relapse following a negative SLNB is 2% to 3% (Table 19.4). This compares favorably with superficial inguinal lymphadenectomy,

Table 19.4 SLNB Sensitivity Analysis

Analysis	SLNB Result	Present	Absent	Total	Sensitivity	90% CI	NPV (%)	90% CI	FNPV (%)	90% CI
By patients	Positive	121	0	121						
	Negative	11	286	297						
	Total	132	286	418	91.7	86.7–95.3	96.3	93.9–97.9	3.7	2.1–6.1
By groin	Positive	140	0	140						
	Negative	12	441	453						
	Total	152	441	593	92.1	87.5–95.4	97.4	95.7–98.5	2.7	1.5–4.3
In tumors < 4.0 cm	Positive	67	0	67						
	Negative	4	198	202						
	Total	71	198	269					2.0	0.7–4.5
In tumors > 4.0 cm	Positive	54	0	54						
	Negative	7	88	95						
	Total	61	88	149					7.4	3.5–13.4

CI, confidence interval; FNPV, false-negative predictive value; NPV, negative predictive value; SLNB, sentinel lymph node biopsy.

Source: Reprinted with permission from Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a Gynecologic Oncology Group study. *J Clin Oncol*. 2012;30(31):3786–3191.

as reported by Stehman et al. for the GOG (123). As with all surgical innovations, individual practitioners must use care when implementing new procedures. Gynecologic oncologists can learn the procedure from peers or from surgical oncologists treating melanoma or breast cancer patients. Prior to adopting this as his / her standard, each gynecologic oncologist should determine his/her own false-negative rate by performing SLNB followed by inguinofemoral lymphadenectomy in approximately 10 cases. Some practices see very few vulvar cancer patients, in which case referral is appropriate. Considered together, the GROINS V and GOG 173 trials strongly support an assertion that, under the appropriate circumstances, SLNB should be offered to eligible women with vulvar cancer.

It is important to note that the SLN undergoes pathologic ultrastaging with serial sectioning and immunohistochemical staining if routine hematoxylin and eosin staging does not reveal metastatic disease. In most studies, including GOG 173 and GROINS V, approximately half of the lymph node metastases are detected by IHC. SLNB has the promise of reducing the number of unnecessary lymphadenectomies performed in node-negative women while at the same time identifying additional women who may benefit from adjuvant therapy.

The combination of local vulvar resection and SLNB holds the promise of improved outcomes for many women with vulvar cancer. Preservation of sexual function and body image, a reduction in the risk of lymphedema, and more focused use of adjuvant therapy are all possible.

Patients with Clinical Stage I/II Tumors at Presentation

Tumors demonstrating a DOI of the vulvar stroma of 1 mm or less (≤ 1 mm) have minimal risk for lymphatic dissemination. Excisional procedures that incorporate a 1-cm normal tissue margin are likely to provide curative results (124). Patients in this category represent the only subset for whom surgical evaluation of the inguinal lymph nodes can be omitted. These so-called superficially invasive carcinomas tend to arise in younger patients with intraepithelial squamous lesions (VIN) that are commonly associated with oncogenic HPV infections. Occult invasion in lesions thought to be intraepithelial is common (125,126). Consequently, the entire lower genital tract and vulva should be carefully evaluated before surgical resection of these lesions is attempted. The risk of vulvar recurrence or development of a new lesion at another vulvar site is significant. After primary therapy, these patients should undergo frequent follow-up examinations.

Management of clinical stage I and II vulvar cancer includes wide radical excision of the primary tumor with unilateral or bilateral SLNB plus or minus inguinofemoral lymphadenectomy. The operation removes the primary tumor with a wide radial margin of normal skin (2 cm), along with a deep margin to the deep perineal fascia; thus, the vulvar specimen will contain tumor, skin, subcutaneous fat, vascular perforators and dermal lymphatics. This approach provides excellent long-term survival and local control in approximately 88% of patients (127). Every attempt should be made to preserve structures such as the clitoris and urethral meatus. Deep margins are rarely a problem except on the perineum, where there is little or no subcutaneous fat. In this case, removal of the capsule of the anus or some of the sphincter muscle itself can be performed without a loss of anal function.

Closure of vulvar defects for small primary tumors can usually be achieved with simple mobilization of the skin and fat surrounding the vulva. In cases where primary closure is not possible, any one of a number of plastics closures are useful (discussed later). Consultation with a plastic surgeon in such cases can be invaluable.

A subanalysis of GOG 173 data also provides guidance regarding when unilateral groin evaluation is safe. GOG 173 required bilateral lymph node evaluation except when the tumor

was more than 2 cm from a midline structure. There were 234 women enrolled on GOG 173 who had a preoperative lymphoscintigraphy (LSG) and at least one SLN identified during surgery. There were 105 women with midline primary tumors and 32 women had unilateral drainage on preoperative LSG. Four of these patients had lymph node metastases on the side that did not have LSG drainage. There were 65 women with tumors located within 2 cm of the midline but not directly involving a midline structure. Twenty-seven women (42%) had unilateral drainage on LSG and bilateral surgical groin evaluation. None of these patients had metastases to the side without LSG drainage. These data support the time-honored oncologic surgical experience that midline tumors can have bilateral drainage and a unilateral LSG should not result in omission of one side. Conversely if the tumor looks lateralized and that is confirmed by LSG, unilateral SLNB is appropriate (128). The authors routinely obtain preoperative LSG, preferably by SPECT/CT (Fig. 19.16), regardless of the location of the primary, since it helps confirm the location of the SLN and the lymphatic drainage pattern.

The survival for women with adequate resection of a primary squamous carcinoma limited to the vulva and with negative nodes is 90% or better. Stage II patients who have negative margins and nodes but involvement of the lower vagina or urethra should obtain similar results.

Clinical Stage III and IV Cancers at Presentation

Some women have lymph node metastases detected by preoperative physical examination or diagnostic imaging or at the time of their primary surgery. If a node is grossly involved at this point, most gynecologic oncologists will proceed with inguinofemoral lymphadenectomy on the assumption that there is a high likelihood of additional positive lymph nodes.

Clinical stage II/III tumors often extend to adjacent mucosal structures $\pm$ the inguinal lymph nodes. Many are bulky; however, some are of limited volume but are considered high stage because of proximity to critical midline structures. Some primary tumors can be curatively excised by radical vulvectomy or by some variation of pelvic exenteration and vulvectomy. Surgical resection of 1 to 1.5 cm of the distal urethra in order to achieve a negative surgical margin does not appear to compromise bladder continence (128). Though radical surgery is an option for patients with locally advanced tumors, contemporary therapeutic strategies have centered upon sequenced radiotherapy or radiochemotherapy followed by radical surgery as a means to preserve either urinary or fecal continence or both. Vulvar cancers are sufficiently sensitive to therapeutic radiation such that function-sparing operations are feasible in selected patients with advanced disease who receive combined modality treatment (129). For patients with stage IVA tumors, similar experiences have been reported; ultraradical (exenterative) resections may also be considered for selected patients. Although occasional cures have been described with innovative combinations of surgery, radiation, and radiochemotherapy, treatment of patients with stage IVB vulvar cancer should be considered palliative.

Node-Positive Cancers

An optimal management strategy for clinically apparent node-positive patients is yet to be defined. Two factors impact management of regional disease: radiation can have a significant impact on sterilizing or eradicating small volume nodal disease, and surgical resection of bulky nodal disease also improves regional control and probably enhances the curative potential of irradiation. In multivariate analysis, Hyde et al. found that, for

patients with clinically positive groin nodes who underwent surgery followed by radiation therapy, the method of surgical groin node dissection (nodal “debulking” versus full groin dissection) had no prognostic significance (130).

Patients who undergo bilateral inguofemoral lymphadenectomy as initial therapy and are found to have positive nodes—particularly more than one positive node—are likely to benefit from postoperative irradiation to the groin and lower pelvis (131,132). Radiotherapy is superior to surgery in the management of patients with positive pelvic nodes. The morbidity of combining superficial and deep inguinal lymphadenectomy with radiation may be substantial. The highest incidences of chronic groin and extremity complications, primarily lymphedema, are seen in such cases (132).

Several management options are available for patients found to have positive nodes during the course of an inguinal lymphadenectomy when performed as a staging procedure: (a) no further surgical therapy may be performed; (b) the lymphadenectomy can be extended to include the ipsilateral deep nodes, the contralateral groin nodes, or both; or (c) postoperative irradiation can be added to any of these surgical options. Given the heterogeneity of vulvar cancer presentations, treatment individualization is necessary. If postoperative radiotherapy to the inguinal nodes ultimately is deemed to be necessary, it would be reasonable to limit resection to grossly positive nodes. Here the intent would be to minimize the likelihood of lymphedema following combined radical surgery and radiation. Excellent local control and minimal morbidity have been achieved when selective inguinal lymphadenectomy and tailored postoperative adjuvant therapy were administered to carefully selected patients (127).

The ideal management for a patient with a microscopically positive SLN who did not have a full lymphadenectomy at her primary surgery is unknown. This is the question being investigated in the GROINS VII/GOG 270 trial. In this trial, women with a negative SLN are observed, women with a metastasis ≤ 2 mm receive postoperative radiation therapy, and women with larger metastases are managed with inguofemoral lymphadenectomy and radiotherapy. Concurrent radio-sensitizing cisplatin is optional. Until these results are reported, uncertainty will remain about the management of SLNB positive patients.

Recurrent Cancer

Regardless of initial treatment, vulvar cancer recurrences can be categorized into 3 clinical groups: local (vulva), groin, and distant. The reported experience with local recurrence at the vulva is surprisingly good. Recurrence-free survival can be obtained in up to 75% of cases when the recurrence is limited to the vulva and can be excised with a gross clinical margin (133,134). The observation that many of these vulva recurrences occur at sites remote from the initial primary tumor or that they occur years after apparently successful primary treatment suggests that some recurrences probably represent new primary tumors rather than the development of new disease. Recurrences in the groin, however, are almost universally fatal. A few patients may be saved by resection of bulky disease and local radiation, perhaps even using intensity modulated radiotherapy (IMRT) in patients who have had prior pelvic radiation. Patients who develop distant metastases are candidates for palliative systemic cytotoxic or targeted chemotherapy or transition to comfort care.

Nonsquamous Histologies

Because nonsquamous vulvar malignancies are exceedingly rare, relatively little definitive information is available regarding optimal treatment and long-term outcome. Most available information is derived from isolated case reports or small series spanning long periods of time.



FIGURE 19.13. Nodular, darkly pigmented malignant melanoma of the left labium majus.

Malignant Melanoma

Malignant melanoma is the second most common vulvar malignancy, and it is most commonly seen in postmenopausal Caucasian women. Typical presentations include either an asymptomatic pigmented lesion identified during a routine exam or pruritic or painful vulvar mass (Fig. 19.13) (135). A definitive diagnosis is established by biopsy. Immunohistochemical staining for melanoma-specific antigen and S100 may be helpful in uncertain cases. Melanomas may arise from existing pigmented vulvar lesions or as new isolated primary tumors. Consequently, any pigmented vulvar lesion should be considered for biopsy. Cutaneous melanoma has evolved significantly over the past 45 years. Because of the rarity of vulvar melanoma, it has not been clear whether extrapolation of prognostic and treatment data from cutaneous nonvulvar disease is appropriate for vulvar melanoma patients. Thus, until recently multiple authors have described their experience with vulvar melanoma using one or more different staging systems (e.g., Breslow's depth, Clark's levels, AJCC staging), making standardization of prognostic groups and treatment strategies difficult. Recently, Moxley et al. reported a multi-institutional retrospective examination of 77 patients with vulvar melanoma. Presenting staging data (via AJCC, Breslow's thickness, and Clark's levels) and treatments were correlated with outcomes, specifically recurrence and overall survival. Among the 3 staging methods, only AJCC staging was significantly correlated with overall survival, although Breslow's thickness was significantly associated with likelihood of recurrence (34).

The primary treatment modality for vulvar melanoma is surgical excision. Radical vulvectomy with bilateral inguofemoral lymphadenectomy has been the historical treatment of choice (136,137). Because most failures are distant though, radical local resection does not appear to enhance survival. Furthermore, many patients with vulvar melanoma are elderly, with coexisting medical problems, making less radical and morbid surgery compelling. More recent reviews recommend some form of hemivulvectomy or wide local excision along with inguinal lymphadenectomy or SLN mapping (34,110,137). DOI and the presence of ulceration are significant prognostic factors and should be considered in treatment planning. Look et al.

reported a series of vulvar melanoma patients in whom none of the patients with lesion depth of ≤ 1.75 mm experienced a recurrence and suggested that these patients could be treated with wide local excision. In contrast, all patients with lesion depth of > 1.75 mm recurred despite radical tumor excision (75). Based on information derived from large series of patients with cutaneous melanomas at nongenital sites, regional lymphadenectomy should probably be considered a prognostic rather than a therapeutic procedure. In a multivariate analysis of 644 patients with vulvar melanoma, Sugiyama et al. reported 5-year disease-specific survival rates of 68%, 29%, and 19% for patients with zero, one, and 2 or more positive lymph nodes, respectively (135). Lymphadenectomy can be avoided in patients with superficial melanomas (< 1 mm, Tis, and Clark's level I), for whom the risk of metastatic disease is negligible. SLN identification and biopsy have been increasingly applied to the surgical management of cutaneous malignant melanomas, and multiple authors assert that for those surgeons who are competent with the technique, SLN mapping and biopsy should be considered a standard practice, with false-negative rates extrapolated from squamous carcinoma of the vulva comparable to other disease sites such as breast cancer and cutaneous, nonvulvar melanoma (34,138).

Radiation therapy may be useful in enhancing local and regional control for some high-risk patients. Despite reported complete clinical response rates and local tumor control rates of 50% to 70% for patients with localized recurrences treated with radiation therapy, alone or in combination with hyperthermia, these modalities have rarely been used in the primary treatment of vulvar melanoma (139,140).

Systemic chemotherapy, in either an adjuvant or salvage setting, is considered palliative; durable responses are rare, and adverse effects are usually considerable. Interferon alpha-2b has been shown to have activity in patients with small volume tumor burden; however, because of its narrow therapeutic index, its use is typically available only at high volume centers. Multiple cytotoxic chemotherapeutics have demonstrated activity. Most notable among these are dacarbazine (DTIC), temozolomide, and platinum-based regimens, which yield response rates from 7% to 12%. Novel combinations of IL-2 and cytotoxic chemotherapy are also commonly employed; however, to date, such approaches have not been shown to be superior to standard salvage therapies. Because of the relatively poor response rates to cytotoxic agents, in recent years much emphasis has been placed on using small molecule inhibitors, or biologic agents targeting well-characterized genetic mutations in melanomas. The best characterized melanoma mutations for which there are biologic inhibitors are B-Raf, c-Kit and CTLA-4 (141).

Overall survival rates in women with vulvar melanoma are approximately 50% (142,143). Patients with superficial lesions have an excellent chance for cure after surgical resection, but patients with deeper lesions or metastases at the time of diagnosis have a more limited prognosis. These patients are good candidates for investigational trials.

Verrucous Carcinoma

Verrucous carcinomas are locally invasive and rarely metastasize (144). Consequently, treatment by radical wide excision is usually curative (145). Local recurrence can occur, especially when the tumor has been inadequately resected.

Basal Cell Carcinoma

Basal cell carcinomas should be removed by excisional biopsy using a minimum surgical margin of 1 cm (146). Lymphatic or distant spread is exceedingly rare (147). Local recurrence may

occur, particularly in tumors removed with suboptimal resection margins.

Adenocarcinoma

Patients presenting with vulvar adenocarcinoma should first undergo an extensive clinical evaluation to determine whether the lesion in question represents a primary versus metastatic tumor. Despite the paucity of data regarding the evaluation and treatment of vulvar adenocarcinoma, resection of localized disease by radical wide excision, hemivulvectomy, or radical vulvectomy seems appropriate (148). The incidence of groin node metastases is approximately 30% (149). Some form of inguinal lymphadenectomy should be included with primary surgical resection. Radiation therapy may have a role in enhancing local control for women with large primary tumors or inguinal metastases. The effectiveness of chemotherapy is unknown, although a single case report documents a response with pegylated liposomal doxorubicin in adenocarcinoma of the vulva (150).

Paget's Disease

Paget's disease is associated with an underlying invasive adenocarcinoma component in approximately 15% of cases (151). As many as 20% to 30% of patients will have or will later develop an adenocarcinoma at another nonvulvar location (152), although more recent series suggest a lower incidence of secondary malignancies (153). Observed sites of nonvulvar malignancies developing in patients with extramammary Paget's disease include breast, lung, colorectum, gastric, pancreas, and upper female genital tract. Screening and surveillance for tumors at these sites should be considered in patients with Paget's disease.

Paget's disease should be resected with a wide margin. If underlying invasion is suspected, the deep margins should be extended to the perineal fascia. Some suggest careful assessment of the surgical margins using multiple frozen sections to ensure complete excision (154,155). This approach can be cumbersome and may not influence the long-term incidence of recurrence. Pierie et al. showed that patients with microscopically positive margins had a significantly higher rate of recurrence; however, with extended follow-up, all patients eventually recurred (154). Others have shown that despite surgical efforts to the contrary, microscopically positive margins are frequent, and disease recurrence is common regardless of margin status (156). Repeat local excision of recurrent disease is usually effective in the absence of invasion (157).

Nonsurgical Therapy

Imiquimod is an immune modulator that is believed to affect the function of the Toll-like receptor (TLR) as a costimulatory molecule for T-cell-mediated immune response to malignant cells. It has well-documented activity for treatment of genital warts as well as vulvar dysplasia. It also reportedly has activity in extramammary Paget's disease. In several small case series, complete response (CR) rates of as much as 92% have been reported (158,159,160).

Vulvar Sarcomas

The specific histologic types are described in the pathology section of this chapter. All types of vulvar sarcoma are rare, but leiomyosarcoma, MFH, and rhabdomyosarcoma predominate (161,162). Cures have occasionally been obtained with aggressive resection of either primary or locally recurrent disease. The results of regional and systemic therapy for leiomyosarcoma are disappointing. These patients are excellent candidates for



FIGURE 19.14. Multiple in-transit lymphatic metastases from a cloacogenic carcinoma of the rectum. A large constricting lesion was evident on rectal examination.

clinical trials. Rhabdomyosarcoma seems to be more responsive to both chemotherapy and radiation. The current treatment of choice is to combine chemoradiation with limited surgical resection of residual disease (162,163).

Metastatic Tumors to the Vulva

Treatment of secondary vulvar tumors should be directed against the primary tumor. As with bulky vulvar cancers, a multimodal approach seems to provide some opportunity for long-term survival, along with enhanced local tumor control and organ preservation.

Cutaneous vulvar lymphatic metastases may occur as in transit tumor emboli from anorectal tumors or as retrograde flow metastases when bulky tumors of the cervix or uterus obstruct the normal lymphatic drainage patterns (Fig. 19.14). These metastases are multiple and are often bilateral. Their histology reflects that of the primary tumor. Because this metastatic pattern is associated with advanced tumors, the primary tumor should be readily detectable by examination.

SURGICAL TECHNIQUES

Wide Radical Excision

Several names have been applied to the procedures used to resect small vulvar cancers: partial deep excision, radical wide excision, radical local excision, wide local excision, modified radical vulvectomy, and hemivulvectomy. Regardless of the preferred nomenclature, the surgical procedure should be adequately defined and described. Surgical incisions are devised to allow for at least a 1 to 2 cm resection margin encompassing



FIGURE 19.15. This is a picture of an early vulvar cancer identified in a background of VIN III. A planned 2-cm margin is outlined.

the primary lesion (Fig. 19.15). Dissection is carried to the deep perineal fascia. Tumors located close to the anus or anal sphincter can be managed by radical wide excision with sphincter or flap repair, or they can be treated with combined modality therapy as outlined under the radiation therapy section. Most wide radical excision sites can be closed primarily. In some patients, fasciocutaneous pedicle flaps can be used to facilitate coverage of the vulvar defect. Some form of inguinal lymphadenectomy, performed through a separate incision, is generally combined with radical wide excision.

Ambulation is begun on the day of surgery. Perineal irrigation and air (natural or forced) drying is started within 24 hours of the surgery. The average hospital stay for patients undergoing radical wide excision is usually 1 to 2 days. Wound breakdown, usually of minor degree, is reported in at least 15% of cases (49,108). The incidence and severity of groin complications is proportional to the extent of the lymphadenectomy.

Inguinofemoral Lymphadenectomy

Appropriate surgical management of the groin nodes has been evolving for many years. Original descriptions of radical vulvectomy included *en bloc* resection of the vulva with inguinal and pelvic lymph nodes. The extent of lymphadenectomy was steadily reduced, first eliminating the pelvic node dissection and then reducing the extent of the groin dissection. The concept of superficial inguinal lymph adenectomy was proposed in the late 1970s; however, this approach was ultimately rejected by gynecologic oncologists due to an unexpectedly high relapse rate (Table 19.5).

Table 19.5 Unanticipated Groin Failure in Patients with Negative Superficial Lymphadenectomy

Investigators	No.	%
Burke et al. (165)	4/76	5.2
Berman et al. (65)	0/50	0
Stehman et al. (166)	6/121	5.0
Gordinier et al. (170)	9/104	8.6
Total	19/351	5.4

The most common current approach starts with an incision parallel and just above or below the inguinal ligament. The incision is carried through Campers fascia and small flaps are elevated to expose the lymph node-bearing fat and preserve blood supply to the skin. There is no need to skeletonize the femoral artery; however, identification of the medial wall of the femoral vein helps assure removal of the medial fat pad, where the SLN is frequently found. The dissection can usually be performed solely with electrocautery or a small vessel-sealing device. The saphenous vein is encountered at the lower medial margin of the dissection, and whenever possible should be preserved to reduce the risk for postoperative lymphedema. The dissected specimen is forwarded for pathologic assessment. The skin incision can be closed with either staples or absorbable sutures. A closed-suction drain is placed and removed when output is <25 mL per day.

Cadaver studies identify 8 to 10 lymph nodes in the femoral triangle defined by the inguinal ligament, sartorius muscle, and adductor longus. Surgical node counts are dependent on the thoroughness of the surgeon and pathologist.

The nomenclature of groin lymph nodes is inconsistent and confusing. The authors find the terms “deep” and “superficial” especially troubling and, in the SLN era, largely meaningless. A satisfactory groin dissection has been performed when the inguinal ligament, adductor longus, saphenous vein, medial wall of the femoral vein, and the fossa ovalis have been identified.

Sentinel Lymph Node Biopsy Technique

As discussed previously, SLNB should be offered as an alternative to inguinofemoral lymphadenectomy as part of the primary management in women with tumors ≤ 4 cm with no suspicious lymph nodes on physical examination or imaging and no prior groin surgery or radiation that might interfere with lymphatic drainage pathways. The authors obtain an LSG in most patients. If possible, the surgeon should perform the injection for vulvar cancer or assure that the nuclear medicine specialist is comfortable with injecting the vulva. The injection is painful and EMLA cream can be helpful. The half-life of the radiocolloid is approximately 6 hours, so a patient can be injected in the morning and then operated on the same day. Frequently this is not possible and a second radiocolloid injection will be necessary in the operating room. The blue dye is visible in the SLN for as little as 45 minutes. The authors typically inject the radiocolloid prior to sterile prepping and draping and inject the blue dye only when the team is prepared to make an incision. All injections are intradermal, 0.5 to 1.0 cm from the tumor itself. Intratumoral or subcutaneous injections will most likely result in a failure to identify the SLN.

Transdermal localization of the SLN using a handheld gamma counter is possible in most patients. SPECT/CT is also valuable for locating the SLN in relation to the femoral vessels (Fig. 19.16). A small incision is made over the location of the SLN. Although data are limited, clinical experience indicates the SLN is commonly medial to the femoral vein and just above the adductor longus muscle. Once the SLN is removed, the wound is scanned for any residual radioactivity. It is imperative that all SLNs in the groin are removed. The gamma counter may detect second echelon nodes in the pelvis just above the inguinal ligament. If blue lymphatic channels lead to a node that is not hot or blue it is still considered an SLN.

Within the pathology laboratory, the evaluation of SLNs requires detailed and systematic evaluation of the submitted specimen. The lymph node sample submitted requires proper identification of patient name, source, name of the surgeon submitting, node location, date, and number of nodes identified.

In sectioning SLNs, it is recognized that to achieve close to 100% identification of all metastases the section spacing needs to be one-half the diameter of the tumor to be detected

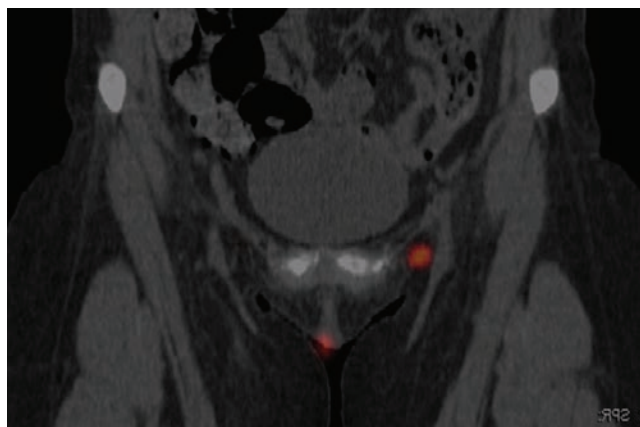


FIGURE 19.16 SPECT/CT demonstrating left sentinel lymph node just medial to femoral vein. SPECT/CT provides superior localization of sentinel lymph nodes compared with 2-dimensional lymphoscintigraphy. The number of sentinel nodes identified should correspond to the number removed at surgery.

(162). The lymph node or nodes are sliced in 1 to 2 mm slices, cutting the lymph node at right angles to the long axis of the node. All of the lymph node tissue (slices) should be submitted for study.

Once the nodal tissue is embedded in the paraffin block, the node slices can be cut at closer intervals to improve tumor detection. Although there are some variations on this sectioning method, our approach is to cut 3 sections from each block. After facing the block to get a full face of the sectioned nodal tissue, the first 5-micron section is cut. This section will be stained with hematoxylin and eosin (H&E). We then cut 100 microns into the block and cut another 5- μ m section. This second slide is held for additional H&E staining, or immunohistochemistry, if the first and last H&E sections have equivocal findings. We then cut an additional 100 microns into the block and take the third section. This slide is stained with H&E. The pathologist reviews the 2 H&E slides, and if the findings are equivocal, the held second slide is then studied.

Limited information is available regarding ideal surveillance following SLNB. Our preferred technique is ultrasound, since it is noninvasive and the internal architecture of the lymph nodes can be imaged (Fig. 19.17A, B). Early detection of a groin failure may help in improving outcomes with multimodality treatment.

Surgical Resection for Recurrent Disease

The site, extent, and volume of recurrent vulvar lesions dictate both resectability and potential for cure. Recurrences can be categorized as local (vulvar), inguinal, or distant (pelvis, lower extremity, or beyond). Surgical therapy plays a curative or palliative role in selected subsets of patients with recurrent disease.

Wide Radical Excision

As many as 75% of patients with recurrent disease limited to the vulva can be salvaged by radical wide excision (partial deep vulvectomy) or reexcision of the tumor (133,134). Surgical principles of recurrent vulvar tumors are identical to those for primary tumors: wide excision with a measured normal tissue margin of at least 1 to 2 cm. Particular attention is also focused on obtaining a clear deep margin. Because most patients have had prior operative therapy, primary closure of the vulvar defect is frequently more difficult. More complex reconstructive efforts may be needed to restore tissue integrity.

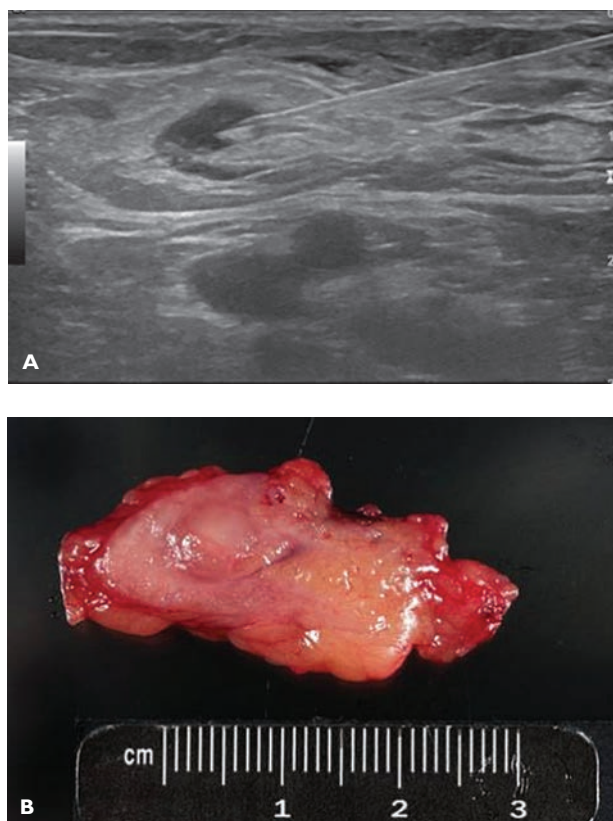


FIGURE 19.17 **A** and **B**: Close surveillance following sentinel lymph node biopsy is recommended since groin relapse is difficult to treat. Physical examination is very unreliable. Ultrasound can be very effective, as illustrated here. Six months after negative sentinel lymph node biopsy, ultrasound detected a 5-mm metastasis. Fine needle aspiration confirmed metastatic disease. The patient underwent inguinal femoral lymphadenectomy and radiation therapy. She remains disease-free at 2 years.

Radical Vulvectomy

In very rare circumstances, radical vulvectomy may be indicated for recurrent vulvar cancer. The classic description of radical vulvectomy and bilateral lymphadenectomy can be described as based on either a “butterfly” or “longhorn” approach. The butterfly incisions use convex “wings” over the groin and around the anus to facilitate closure of the defect (Fig. 19.18). The longhorn incisions were developed to limit skin resection over the groin in an attempt to reduce wound breakdown (164). The arcing superior incision is placed from the lateral margins of the groin dissection across the mons pubis. The lateral vulvar incisions are placed at the labiocrural folds, because these topographical landmarks represent the most lateral location of the superficial vulvar lymphatics. The perianal incision is placed to allow resection of the perineal body. These incisions are taken to the level of the deep inguinal and perineal fascia and permit *en bloc* removal of both superficial and deep groin nodes, the entire vulva, and an intervening skin bridge.

After removal of the specimen, the skin and mucosal edges are undermined to permit mobilization and primary closure with delayed absorbable suture. Some degree of tension at the suture lines is unavoidable, particularly in the perineal body and periurethral areas. Closed suction drains are usually placed in the groin sites to remove excess lymphatic- and serous-fluid accumulations and are usually removed when drain output is minimal (5 to 14 days).

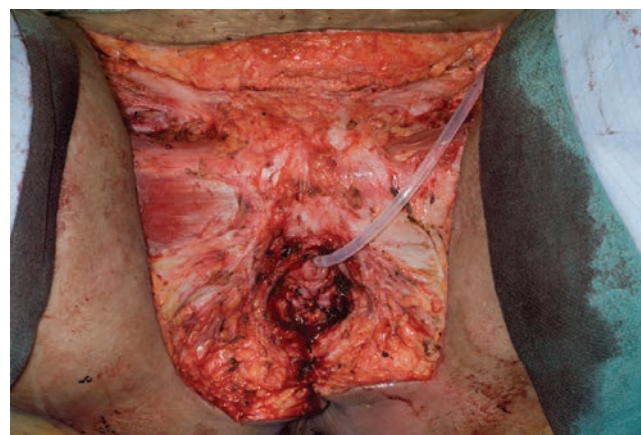


FIGURE 19.18: Butterfly incision described for a traditional radical vulvectomy with bilateral inguinal lymphadenectomy. Modern indications for radical vulvectomy are exceedingly rare. The patient shown in Figure 19.5 was treated with concurrent chemoradiation and still had bilateral gross tumor. This figure demonstrates the field following resection.

Some degree of wound breakdown is seen in approximately 50% of patients. Local wound care results in satisfactory secondary healing in most of these cases. Lymphocyst formation is relatively common and frequently presents as a tense but nontender groin mass. Percutaneous needle drainage is usually sufficient, but occasionally replacement of a groin drain may be required. Inguinal cellulitis, lower extremity lymphangitis, and lymphedema are uncommon late sequelae. The incidence of these complications is related to the extent of groin therapy and is highest in patients treated with superficial and deep lymphadenectomy along with groin irradiation. The 3-incision concept preserves the radicality of the vulvar resection while retaining skin over the groin. Consequently, the incidence of major wound breakdown is significantly reduced to approximately 15% to 20% of cases (165,166,167). As with other techniques, the incidence and severity of groin complications such as infection, wound breakdown, or lymphocyst formation is still high (168). There are few if any indications for radical vulvectomy as the primary treatment for vulvar cancer.

Pelvic Exenteration

Curative resection may still be possible when vulvar recurrence extends to the vagina, proximal urethra, or anus. Selected patients have achieved long-term survival after pelvic exenteration for such recurrences (169,170). The surgical approach in these cases should be individualized to the size and location of the recurrent tumor, prior therapies, and the age and overall health of the patient. Patients considered for pelvic exenteration should have a thorough preoperative evaluation to exclude the presence of regional and/or distant metastases. Frequently, anterior or posterior exenteration with an extended vulvar phase will provide excellent resection margins while allowing preservation of either urinary or fecal continence. The techniques used to perform the exenteration are identical to those routinely used for the treatment of women with recurrent cervical carcinoma. Multiple vulvar and perineal reconstructive techniques have been described for coverage of large surgical defects (171,172,173,174).

Resection of Groin Recurrence

Patients who develop isolated groin recurrence should be treated with multimodality treatment if radiotherapy is still an option. Surgical resection should be viewed with caution in the

previously irradiated patient. A resection with negative margins usually requires the resection of vessels or bone with plastic reconstruction. Ultraradical surgery attempted in young patients with outstanding performance status and a small relapse in an irradiated groin that appears resectable on preoperative imaging is associated with high morbidity. Extended survival is possible for the few patients who achieve control of recurrent disease in the groin and do not later manifest distant metastasis (175). Isolated groin recurrence is a rare event, so the data to support the efficacy of this treatment are anecdotal.

Vulvar Reconstruction

With careful planning and adequate tissue mobilization, most vulvar defects can be closed primarily. When large portions of the vulva have been resected, when tissue mobility is poor, or when radiation therapy has been administered previously, primary closure may not be feasible. Alternate tissue sources must be considered for these difficult cases. Categorically, the 2 types of techniques commonly employed for extensive vulvar reconstruction are fasciocutaneous flaps and myocutaneous flaps. Both categories of flaps have been well described as hearty and aesthetic options for patients who need a large tumor resected; however, the techniques referenced below should only be employed by surgeons who are regularly practiced in their use. Our practice routinely consults plastic surgery for patients in whom a complicated closure will be likely.

Fasciocutaneous Advancement Flaps

There are a number of different fasciocutaneous advancement flaps described for vulvar reconstruction. Nearly all of them are based on the rich, redundant blood supply from the internal pudendal artery and subsequent superficial perineal artery perforators that approach the vulva and perineum primarily from the posterior and lateral directions. The significance of this is that most vulvar fasciocutaneous flaps are designed with the intent to preserve fasciocutaneous perforators from these directions.

The most widely utilized pedicle flap among gynecologic oncologists has been the rhomboid flap; however, lotus pedicle flaps have also become more commonly used by plastic surgeons for closure of large vulvar defects. While detailed discussion of the techniques employed for these flaps is outside the intended scope of this chapter, references for multiple fasciocutaneous flaps that have been employed by these authors are referenced here (171–173,176).

Myocutaneous Flaps

Myocutaneous flaps, in comparison to fasciocutaneous advancement flaps, include a segment of muscle and usually receive their blood supply and innervation through an identifiable, named neurovascular pedicle. These are usually large, thick tissue sources that are best suited for the reconstruction of substantial defects. Each of the following listed flaps has notable advantages and disadvantage. Several types of myocutaneous flaps, namely the gracilis, gluteus maximus, tensor fascia lata, vastus lateralis, and vertical rectus abdominus flaps have been used to provide repair and reconstruction of large vulvar and groin defects (177). Historically, the gracilis flap was used to fill large vulvar and urogenital defects; however, in recent decades, the myocutaneous flap most commonly described for extensive vulvar reconstruction is the vertical rectus abdominus flap, which is based on the robust inferior epigastric pedicle. As with fasciocutaneous flaps, a detailed description of each flap is beyond the intended scope of this chapter; however, a number of techniques are referenced here (176–179).

RADIATION THERAPY

Early accounts of severe skin peeling and poor survival rates after primary radiation treatment of vulvar carcinomas led some investigators to surmise that radiotherapy had a narrow therapeutic role in the curative management of patients with vulvar cancer (180,181). The use of high doses of radiation alone, delivered with low-energy ⁶⁰cobalt photons and *en face* electron boosts, in patients who were mostly poor surgical candidates, resulted in a suboptimal therapeutic benefit between tumor control probability and normal tissue complications (182). More modern-day practices, such as incorporating consecutive daily fractionation, attention to dosimetric planning detail, and appreciation of vulvar and low pelvic radiation tissue tolerance limits, have undoubtedly shown that relatively high doses of irradiation can be delivered safely. In selected patients, treatment of the vulva and/or regional lymph nodes by fractionated radiation improves locoregional control rates and survival rates, and may even reduce overall treatment morbidity. Radiation therapy is now accepted as an important element in the multidisciplinary management of patients with advanced vulvar cancer involving the pelvis and groin.

Treating Locally Advanced Disease in the Vulva

Following initial resection of a vulvar primary tumor, various surgicopathologic features have been identified that are associated with a higher risk of local recurrence. Podratz et al. reported a 24% incidence of vulvar recurrence in 71 patients with stage III carcinoma (183). Recurrence was correlated with tumor size and nodal status. Heaps et al. reported that a close surgical margin was the most powerful predictor of local recurrence in their patients (97). They observed 21 vulvar recurrences in 44 patients with tumor margins <8 mm (deep or at the skin surface), compared with no local recurrences in 91 patients with margins ≥8 mm (after fixation). The importance of a pathologic margin distance ≥8 mm in optimizing local vulvar control and 5-year disease-specific survival has also been emphasized in a recent analysis by Chan et al. (98). Lymphovascular space invasion and deep tumor penetration are also associated with a greater and increased risk of recurrence (97,184,185). Although many local recurrences are controlled with additional surgery or irradiation, salvage surgery is often morbid, and local recurrences may provide additional opportunity for regional and distant tumor spread. While no prospective trials of postoperative vulvar site radiotherapy have been completed, adjuvant radiation of the primary tumor bed in selected patients with close margins or other high-risk features does improve vulvar tumor control (186).

Alternatively, in patients who present with more advanced primary tumors, radiation therapy may be delivered preoperatively. Advocates of this approach have listed several theoretical advantages for patients with locally advanced vulvar carcinomas:

1. Less radical resection of the vulva may be adequate to achieve local tumor control after preoperative treatment of the vulva with radiation;
2. Tumor regression during radiation may allow the surgeon to obtain adequate tumor-free surgical margins without sacrificing important pelvic structures such as the urethra, anus, and the clitoris; and
3. Radiation treatment alone may be sufficient to sterilize microscopic regional disease when the inguinal nodes are clinically normal and may mobilize fixed and matted nodes, facilitating subsequent surgical excision.

Table 19.6 Concurrent Chemoirradiation in the Management of Locally Advanced or Recurrent Carcinoma of the Vulva

Investigators	No. of Patients	Chemotherapy	RT Dose (Gy)	No. with Recurrent or Persistent Local Disease after RT Surgery	Follow-up (months)
Moore et al. (2012)	58	CDDP	57.6	21 (36%)	24.8
Moore et al. (154)	73	5-FU + CDDP	47.6	15 (21%)	22–72
Gerszten et al. (249)	18	5-FU + CDDP	44.6	3 (17%)	1–55
Cunningham et al. (234)	14	5-FU + CDDP	45–50	4 (29%)	7–81
Landoni et al. (240)	58	5-FU + Mito	54	13 (22%)	4–48
Akl et al. (246)	12	5-FU + Mito	30–36	0	8–125
Han et al. (247)	14	5-FU + CDDP or Mito	40–62	6 (43%)	4–273

Note: 5-FU, 5-fluorouracil; CDDP, cisplatin; Mito, mitomycin C; RT, radiation therapy.

Although the published experiences with preoperative single-modality radiation therapy are small, several investigators have reported excellent responses and high local control rates after treatment of advanced tumors with relatively modest doses of radiation therapy followed by local resection (187,188). These reports provided emerging evidence that radiation could significantly debulk advanced local disease and allow for more conservative, viscera-sparing surgery while preserving good local control.

Data have emerged supporting the therapeutic benefit of radiochemotherapy, typically followed by limited surgical resection, in addressing locally advanced disease (Table 19.6) (115,189,190). These trials were initially prompted by extrapolation from superior local control and survival outcomes after radiochemotherapy for anal cancer (189,190). Typical regimens have included combinations of radiation coadministered with 5-fluorouracil (5-FU), and cisplatin or mitomycin C. Most investigators have observed remarkable regressions of bulky lesions with radiochemotherapy, suggesting that therapeutic responses may be better than would be expected with radiation alone. Randomized trials of the role of radiochemotherapy have not been done and are unlikely to be feasible within this disease, given the small number of patients and heterogeneity of clinical presentation. However, recent single experimental arm trials have demonstrated improved local control and survival when concurrent cisplatin chemotherapy was added to radiation in locally advanced vulvar cancers (191,192).

The most compelling data in support of concurrent radiochemotherapy in the management of locally advanced disease come from 2 large prospective phase 2 trials performed by the Gynecologic Oncologic Group (GOG protocols 101 and 205). In the first study (GOG protocol 101), 71 evaluable patients with locally advanced T3 or T4 disease who were deemed not resectable by standard radical vulvectomy underwent preoperative radiochemotherapy. Chemotherapy consisted of 2 cycles of 5-FU and cisplatin. Radiation was delivered to a dose of 47.6 Gy, using a planned split-course regimen, with part of the radiation given twice daily during the 5-FU infusion. Patients underwent planned resection of the residual vulvar tumor, or incisional biopsy of the original tumor site in the case of complete clinical response, 4 to 8 weeks after chemoradiotherapy. A complete clinical tumor response was noted in 33 of 71 patients (47%). Following vulvar excision or biopsy, 22 patients (31%) were found to have no residual tumor in the pathologic specimen. In all, only 2 of 71 patients (3%) had unresectable disease after radiochemotherapy, and in only 3 patients was it impossible to preserve urinary and/or gastrointestinal continuity following complete resection of the primary tumor residuum. With a median follow-up interval of 50 months, 11 patients (16%) have developed locally recurrent

disease in the vulva (115). These results are all the more notable considering the relatively low dose of radiation used in these typically bulky, advanced tumors. Building on this experience, investigators sought to study weekly cisplatin chemotherapy coadministered with radiation (GOG protocol 205). On this trial, 58 evaluable patients with untreated locally advanced T3 or T4 disease not amenable to standard radical vulvectomy underwent preoperative radiochemotherapy (196). On this contemporary study, radiation totaled 57.6 Gy in 32 uninterrupted daily fractions of 1.8 Gy. Cisplatin (40 mg/m²) chemotherapy was administered weekly. Following vulvar excision or biopsy, 37 (64%) of 58 patients had no residual tumor in the pathologic specimen.

It is important to be cautious in designing aggressive treatment protocols for this group of patients, who are often elderly and have coexistent medical problems. Serious pulmonary toxicity has been observed in patients treated with bleomycin (193,194). In the largest published series of patients treated with mitomycin C and 5-FU, hematologic tolerance was acceptable, but the administered dose of mitomycin C was more conservative than is usually used in the treatment of anal cancers (195). Other investigators have confirmed the increased toxicity associated with concurrent radiochemotherapy, especially with the use of mitomycin C–based regimens (196).

Following radiochemotherapy for locally advanced disease, it remains undefined whether surgery is necessary in those who achieve complete clinical response. In GOG 101, approximately 70% of patients who achieved complete clinical response were found to have no pathologic residual in the surgical specimen. In GOG 205, 34 of 37 patients (92%) underwent surgical biopsy only to assess radiochemotherapeutic response. Of these 34 women, 29 (78%) had biopsies showing a complete response to radiochemotherapy. At this point, we continue to recommend biopsies of the original tumor bed in patients who achieve complete clinical response. In those with residual vulvar disease after radiochemotherapy, surgical resection would be individualized and tailored to the extent and location of residuum.

Treatment of Regional Disease

Although radical inguinal lymphadenectomy has historically been considered the treatment of choice for regional management of invasive vulvar carcinoma, a number of retrospective studies have suggested that regional prophylactic radiation therapy is an effective method of preventing groin recurrences with minimal morbidity (197,198). In a large single-institution retrospective analysis, Katz et al. reported no differences in the

inguinal relapse rates for patients treated with prophylactic groin irradiation compared with those undergoing lymph node dissection (195). Leiserowitz et al. observed no groin recurrences in 23 patients with locally advanced, clinically N0 vulvar cancers after prophylactic treatment of the groin with concurrent radiochemotherapy (198).

The GOG tried to define the optimal approach to clinically negative inguinal nodes in a trial that randomized patients between inguinal node irradiation and radical lymphadenectomy (followed by inguinopelvic radiation in patients with positive nodes) after resection of the primary tumor (199). This study was closed after entry of only 58 patients when there appeared to be a higher rate of groin recurrence in the radiation treatment arm. However, this study has been criticized because the treatment protocol was not CT-based, it recommended combination photon and electron dosing to a depth of 3 to 4 cm, and likely delivered an inadequate dose to the inguinal nodes (200,201).

While the role of prophylactic radiotherapy in the undissected but high-risk groin remains controversial, there is strong evidence that adjunctive radiation therapy improves regional tumor control and survival in patients who have documented nodal metastases following inguinal node dissection. Retrospective studies suggested that patients with metastases to multiple nodes or extranodal tumor extension had an increased risk of groin recurrence after radical surgery and therefore may benefit from radiation therapy (202,203). However, the critical role of radiation therapy was not appreciated until 1986, when Homesley et al. published results of a prospective GOG trial in 114 patients with inguinal metastases (131). In that study, all patients underwent radical vulvectomy and inguinal lymphadenectomy. Patients who had positive inguinal nodes were randomized intraoperatively to receive either pelvic node dissection or postoperative irradiation to the pelvis and inguinal nodes. This trial was closed before the projected accrual goal because an interim analysis revealed a statistically significant overall survival advantage for the radiation treatment arm ($p = 0.03$). The differences between the 2-year survival rates of patients treated with radiation therapy or pelvic dissection were most marked for patients presenting with clinically positive nodes (59% and 31%, respectively) and for those with 2 or more positive groin nodes (63% and 37%, respectively). Extended follow-up showed a narrow, nonsignificant 6-year overall survival rate (51% after radiation versus 41% after pelvic dissection) (132). Yet, the cancer-related death rate was significantly higher for pelvic node resection than for radiation (hazard ratio, 0.49 [95% CI, 0.28–0.87]; 51% versus 29% at 6 years, respectively) (132). Moreover, there was no significant difference in survival between the treatment groups for patients with only one microscopically positive node, although the authors commented that the number of patients in this subset was insufficient for reliable analysis. After long-term follow-up of patients on this study, those patients with one microscopically positive node had no survival benefit after radiation (132). The most striking difference in the patterns of recurrence for the 2 treatment groups was the much larger number of inguinal failures among patients who were treated with surgery alone (Fig. 19.19). These groin recurrences were rarely if ever salvageable. The vulva, regardless of tumor pathologic risk factors, was not included in the radiation treatment fields in this study, and approximately 8% of patients in both treatment arms had recurrences at the primary site at the time of the analysis, raising the question of whether selective radiation to the vulva may have decreased local recurrences. It is important to recall that while subset analysis showed the most dramatic benefit of adjuvant radiotherapy for clinically positive adenopathy or 2 or more pathologically involved nodes (131,204), the trial was closed early because of an overall survival benefit before subset analysis. The role of adjuvant radiation for patients with a single positive groin node following inguinal node dissection remains unresolved (132). Retrospective reviews of patients with only a

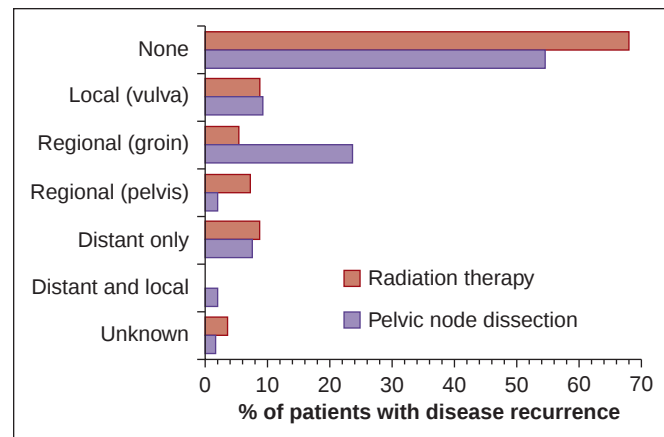


FIGURE 19.19. Sites of disease recurrence in patients treated with adjuvant radiation therapy to the pelvis and inguinal region or with pelvic node dissection following radical vulvectomy and bilateral inguinal lymphadenectomy. Source: Modified from Homesley HD, Bundy BN, Sedlis A, et al. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol.* 1986;68:733–740.

single positive inguinal nodal metastasis from vulvar cancer suggests that adjuvant radiation may provide therapeutic benefit if the groin node dissection was less extensive in scope or if a ratio of more than 20% positive ipsilateral groin nodes (number positive/number resected) was found at the time of surgery (132,205). Another indication that radiation may be useful in the single positive inguinal lymph node patient is derived from data in the GROningen International Study on Sentinel nodes in Vulva cancer (GROINSS-V) study (206). Patients with a single sentinel node metastasis larger than 2 mm had a lower disease-specific survival (69.5%) than those patients with a single sentinel node metastasis 2 mm or smaller (94.4%, $p = 0.001$).

The role of preoperative radiochemotherapy has been assessed in patients who present with bulky, unresectable inguinal adenopathy. In the GOG 101 study of preoperative radiochemotherapy for local regionally advanced vulvar cancer, there was a cohort of 42 evaluable patients with N2 or N3 nodal disease who were deemed initially unresectable. Patients received 47.6 Gy of radiotherapy in split-course fashion, with 2 concurrent cycles of 5-FU and cisplatin, as described above. Three to 8 weeks later, planned inguinofemoral lymph node dissection was performed. In only 2 patients (5%) did nodal disease remain unresectable. The surgical specimen showed histologic clearance of nodal disease in 15 patients (36%). At a median follow-up of 78 months, only 1 of 37 patients (3%) who completed the full prescribed regimen of preoperative radiochemotherapy and bilateral inguinofemoral node dissection relapsed in the groin (207). This study, while nonrandomized, provides further evidence of the efficacy of combined chemoradiotherapy in the management of local regionally advanced vulvar cancer and of patients with significant regional adenopathy. Given the high risk of distant relapse with node-positive vulvar cancer, especially in those with ≥ 2 involved nodes (132), it seems reasonable to consider adjuvant radiochemotherapy for such high-risk patients, provided that careful attention is paid to treatment planning and amelioration of toxicity. Results from GOG 205 echo these sentiments (189).

Radiation Therapy Technique

Radiation techniques used for treatment of vulvar carcinoma reflect a need to cover the vulva plus lower pelvic and inguinal nodes, while simultaneously minimizing radiation dose to the femoral heads. One approach is to treat with an anterior field that encompasses the inguinal regions, lower pelvic nodes, and

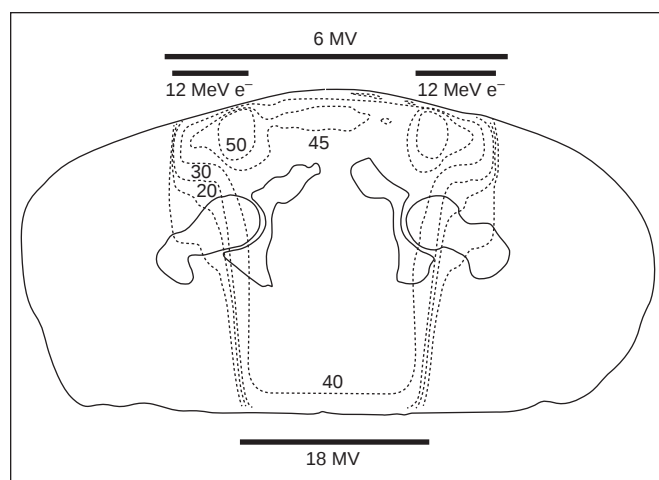


FIGURE 19.20. The radiation dose to the femoral heads can be reduced by delivering part of the dose to inguinal nodes with appropriate-energy electron fields. In this example, a wide anterior 6-MV field encompasses the primary site as well as the inguinal and pelvic nodes. Electron fields are placed anteriorly to overlap slightly with the exit of a narrower posterior 18-MV field that encompasses the primary and pelvic nodes

vulva, and a narrower posterior field that encompasses the lower pelvic nodes and vulva but excludes the majority of the femoral heads (Fig. 19.20). The intent here is to cover one nodal echelon proximal to the nodal echelon with metastatic vulvar cancer disease. The inferior-most borders of the fields should extend to the saphenous vein. If the fields are evenly weighted to the mid-plane of the pelvis using 6 MV photons, the contribution of the anterior field to the groin nodes at a depth of 3 to 5 cm will generally be 60% to 70% of the dose to the mid pelvis. The difference may be made up by supplementing the dose to the lateral groins with anterior electron fields of appropriate energy (Fig. 19.20). Currently, CT scans obtained in the process of radiation dose planning are used to detect enlarged nodes that may not be appreciated on clinical exam and to determine the appropriate electron energy. Gross disease in the groin or vulva may be boosted with *en face* electron fields. In some cases, interstitial implants or *en face* electron fields may be used to boost the dose to the primary site. If radiation is directed to the regional nodes only, with intentional sparing of the

vulva, care must be taken to avoid a large “midline” block, which may lead to higher medial groin and vulvar failures.

The complex anatomy of the vulva and its regional lymphatics has led some investigators to propose the use of IMRT in the management of vulvar cancer (Fig. 19.21) (207). To whom IMRT should be offered remains debated. In modern practice, IMRT may replace conventional external beam approaches used in the treatment of vulvar cancer; however, outcome data remain limited. Most data comes from experience extrapolated from the treatment of anal carcinoma in multi-institutional clinical trials (208,209) or single academic cancer center studies in this disease (210,211). IMRT is gradually being used more for radiotherapeutic management of gynecologic malignancies, including vulvar cancer. IMRT is an attractive approach to radiotherapy in the pelvis because of its ability to escalate radiation dose while lower radiation dose to nearby healthy normal tissue, improving the therapeutic window for radiation. An initial study has shown dosimetric and clinical benefits, with reduction in gastrointestinal and hematopoietic toxicity (210). Consensus indications and guidelines for vulvar IMRT are being written.

Although radiobiologically effective, IMRT has a number of practical limitations that must be acknowledged. Uncertainties in patient set-up and target volume definition when using IMRT techniques have been raised. Physical travel limits of IMRT multileaf collimators may be exceeded when targeting primary site disease and bilateral groin node basins. When travel limits are exceeded, IMRT radiation portals may have to be cut into 2 or more collimator carriage movements. Additive scatter and leakage radiation dose to normal tissues may occur. Vulvar and groin target motion resulting from quiet breathing during treatment is expected to be minimal, as is shifting bladder and rectal volumes unlikely to substantially modify primary disease position during beam-on time. Again borrowing from overall radiotherapy experience, it is not unreasonable to conclude that daily repositioning of women prior to radiation delivery, using such devices as on-board cone beam CT, will adjust for set-up inconsistencies. For vulvar cancer management, IMRT remains under inspection and an active area of research in this disease.

Furthermore, robotic stereotactic body radiosurgery has been attempted in patients with recurrent disease after previous irradiation. Here, radiation is delivered using a linear accelerator mounted on an industrial robotic arm. By allowing “pencil-beam” noncoplanar radiation delivery, robotic stereotactic body

Vulvar cancer – locally advanced T4N2



FIGURE 19.21. Intensity modulated radiation therapy in the management of vulvar cancer.

Source: Reprinted with permission from Beriwal S, Heron D, Kim H, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. *Int J Radiat Oncol Biol Phys*. 2006; 64:1395–1400.

radiosurgery delivers accurate and precise radiation (0.4 mm precision) at an escalated dose per fraction that is considered ablative (>8 Gy per fraction). In one report, 3 women underwent palliative stereotactic body radiosurgery (8 Gy × 3 fractions = 24 Gy) with complete regression of their bulky vulvar tumors (212). While the treatment was successful, inability to identify occult microscopic disease at the time of radiosurgical planning led to disease relapse outside and abutting the radiosurgical target in all 3 women. Incorporating advanced imaging, such as 2-[¹⁸F]fluoro-2-deoxy-D-glucose (¹⁸F-FDG) scans, improves target localization and is likely to improve the therapeutic usefulness of this approach (213).

Acute Complications of Radiation Therapy

Acute radiation reactions are brisk, and doses of 35 to 45 Gy routinely induce confluent moist desquamation. However, with adequate local care, this acute reaction usually heals within 3 to 4 weeks. Sitz baths, steroid cream, and treatment of possible superimposed *Candida* infection all help to minimize the discomfort. If the patient is sufficiently flexible, she may be placed in a frog-leg position during treatment to minimize the dose and ensuing skin reaction on the medial thighs; care must then be taken, however, to deliver an adequate dose to the vulvar skin. Although most patients will develop confluent mucositis by the fourth week of treatment, this is usually tolerated if the patient is warned in advance and assured that the discomfort will resolve after treatment is completed. Although a treatment break is occasionally required, delays should be minimized, because they may allow time for repopulation of tumor cells.

Late Complications of Radiation Therapy

Many factors add to the late morbidity of radiation treatment in patients with vulvar carcinoma. Patients with advanced vulvar carcinomas often are treated with radiation therapy following radical surgery, which may include extensive dissection of the inguinal and possibly pelvic nodes. Large ulcerative cutaneous lesions frequently have superimposed infection. Patients are often elderly and may have complicating medical conditions, such as diabetes, multiple prior surgeries, and osteoporosis. The contribution of concurrent chemotherapy to local morbidity is not yet clearly defined but may contribute to bowel and bone complications (208,209).

The incidence of lower extremity edema after inguinal irradiation alone is negligible (197,203). Radiation therapy is likely to contribute to the cumulative incidence of peripheral leg edema following radical node dissection, but there was no difference evident in the GOG randomized study of radiation (16%) versus pelvic node dissection (22%) (204). Femoral head fractures have occasionally been reported in patients treated with irradiation to the inguinal nodes (187,195). Techniques that limit the dose to

the femoral heads to less than 35 Gy should minimize the risk of this complication. It is not known whether severe osteoporosis contributes to femoral head complications. In general, with careful treatment planning techniques, the risk of major late complications following regional nodal radiation, either electively or adjuvant to lymph node dissection, is low (197). It has been suggested that concurrent chemotherapy may increase the risk, but this remains to be adequately substantiated (191,208).

The effect of radiation therapy on the long-term cosmesis and function of the vulva is poorly understood. Although treatment with radiation or radiochemotherapy and wide excision is becoming a more accepted alternative to extensive surgery for selected patients, and major complication rates appear to be acceptable, very little has been reported regarding more subtle late effects of such treatment in the vulva. Late effects are dose related. Better information will become available only as treating physicians record and report the late cosmetic and functional results of treatment (191,214).

CHEMOTHERAPY

Primary Treatment of Advanced Disease

The majority of patients diagnosed with vulvar cancer can be cured with surgery with or without postoperative radiation therapy; thus, chemotherapy monotherapy has traditionally been used solely for salvage therapy. Patients with advanced vulvar cancers tend to be older, with significant medical comorbidities, making them poor candidates for cytotoxic therapy because of concomitant diseases that increase the likelihood for significant adverse effects. Furthermore, recurrent vulvar cancer often occurs in the setting of extensive prior surgery and/or radiation therapy, making tolerance to cytotoxic therapy poor.

Squamous Cell Carcinoma

Cytotoxic Chemotherapy

Squamous carcinoma is the only histologic type of vulvar cancer for which there is significant data assessing the utility of cytotoxic chemotherapy in recurrent or advanced primary vulvar cancer not amenable to surgery or radiotherapy. A number of drugs have undergone phase 2 testing (Table 19.7) (215–218). Among these, only doxorubicin and bleomycin appear to have significant clinical activity. Cisplatin, a drug that has demonstrated broad activity in most gynecologic tumors (e.g., epithelial ovary, endometrial adenocarcinoma, and endometrial mixed mesodermal tumors and squamous carcinoma of the cervix), has notably little activity as monotherapy in vulvar and vaginal squamous tumors. Paclitaxel dosed at 175 mg/m² every 3 weeks

Table 19.7 Single-Agent Cytotoxics in Squamous Vulvar Cancer

Drug	Dose and Schedule	No. of Patients Complete	Response	Partial Response	Investigators
Doxorubicin	45 mg/m ² IV q 3 weeks	4	0	3	Deppe et al. (275)
Bleomycin	15 mg IM twice weekly	11	2	3	Trope et al. (111)
Cisplatin	50 mg/m ² q 3 weeks	22	0	0	Thigpen et al. (276)
Piperazinedione	9 mg/m ² IV q 3 weeks	13	0	0	Thigpen et al. (276)
Mitoxantrone	12 mg/m ² IV q 3 weeks	19	0	0	Muss et al. (277)
Etoposide	100 mg/m ² IV days 1, 3, 5	18	0	0	Slayton et al. (278)

Table 19.8 Combination Chemotherapy Regimens in Squamous Vulvar Cancer

Regimen	Dose and Schedule	No. of Patients			Investigators
		Entered	Complete Response	Partial Response	
Bleomycin	15 mg/m ² cont. IV days 1–3	22 ^a	2	4	Belinson et al. (279)
Vincristine	1.4 mg/m ² IV day 3				
Mitomycin C	10 mg/m ² IV day 3				
Cisplatin	60 mg/m ² IV day 3				
Bleomycin	5 mg IM days 1–5	28 ^b	3	15	Durrant et al. (280)
Methotrexate	15 mg PO days 1 and 4				
CCNU	40 mg PO days 5–7				
Bleomycin	5 mg IV days 1–6	1	1	0	Shimizu et al. (47)
Vincristine	1 mg IV day 6				
Mitomycin C	10 mg IV day 6				
Cisplatin	100 mg IV day 6				

^aFive of 6 responses with no prior therapy; one of 16 responses in refractory disease.

^bNo patient with prior radiation therapy or chemotherapy; responses were the same for primary therapy and recurrences; 8 patients had resectable disease after chemotherapy.

was evaluated in the EORTC phase 2 trial 55985. Thirty-one patients with metastatic or locally advanced carcinoma of the vulva were treated, and 29 were assessable for response. Grade 3 or 4 toxicity was seen in 27.6% of patients, and objective responses were seen in just 13.8% of patients.

Several drug combinations have also been used in squamous vulvar cancer, most commonly as neoadjuvant therapy for patients with inoperable disease. Combinations used in vulvar squamous cancer are detailed in Table 19.8 (219,220).

Recognition of the fact that Epidermal Growth Factor Receptor (EGFR) expression via immunohistochemical staining is elevated in malignant vulvar tumors has led to the use of EGFR tyrosine kinase inhibitors (TKIs) as monotherapy and in combination with cytotoxic chemotherapy for use in palliation of advanced and recurrent vulvar cancer patients. Olawaiye in 2007 reported 2 dramatic partial responses to single agent erlotinib in women with advanced, treatment refractory disease; Bacha in 2010 reported a PR in a woman with advanced disease (221,222). A phase 2 GOG trial using erlotinib in advanced or recurrent vulvar cancer patients is under way.

RESULTS OF THERAPY

The overall results of therapy for women with squamous cancers of the vulva are excellent based largely on the fact that approximately two-thirds of patients present with early-stage tumors. Five-year survival rates for vulvar cancer have improved over the past 2 decades. Landrum et al. used GOG data to perform an historical comparison between patients treated between 1977 and 1984 ($n = 577$) with patients treated between 1990 and 2005 ($n = 175$). Stratification into “minimal, low, intermediate, and high” risk groups was performed to enable comparisons. Patients treated in the era of less radical surgery and modern chemoradiation fared better than historical comparisons, with 5-year survival by risk group (minimal → high) of 100% versus 97.9%, 97% versus 87.4%, 82% versus 74.8%, and 100% versus 29.0% (96).

Several strategies to enhance survival for women with vulvar cancer are evident. High-risk patients can be educated and screened more consistently for the development of early cancer.

Women with HPV infections, *in situ* vulvar disease, long smoking history, and other genital neoplasms are at risk for developing vulvar cancer. Careful screening targeted at women with these high-risk factors may lead to improvements in early diagnosis.

The survival rate for women with nodal spread is one-half that for women without nodal disease who have similarly sized primary tumors (Fig. 19.22). Improvements in the use of molecular markers for metastatic disease and biologic aggressiveness would be helpful for triaging higher risk patients into more effective adjuvant therapies. And, of course, there is a dire need for better treatment options for node-positive patients.

SEQUELAE OF TREATMENT

Immediate complications such as wound infection and lymphocyst were common in the radical vulvectomy era. These complications occur much less frequently due to less radical surgery and innovations such as prophylactic antibiotics and closed suction drains. Breakdown of the vulvar incision is increased in patients who are smokers, have vasculopathy, and display chronic poor hygiene.

Lymphedema starts to appear within weeks of surgery. The severity is related to the extent of groin surgery, wound complications, postoperative radiation therapy, and preexisting conditions of the lower extremities. Lymphedema is not limited to the lower leg and thigh. It may also include the mons, groins, and hips. The use of SLNB reduces but does not eliminate wound complications and lymphedema.

Pressure stockings, sequential compression devices, lymphedema massage, and microvascular surgery have been used to manage lower extremity lymphedema, with limited results. Prevention of lymphedema with the use of SLNB is the best strategy for limiting the adverse effects of this complication.

All gynecologic surgery, especially surgery for vulvar cancer, can have an adverse effect on body image and sexual function. Informed consent obtained for vulvar cancer surgery should include a discussion regarding these risks. No assumptions regarding a woman's sexual activity should be made based on age or marital status. We have found that preoperative consultation with a sexual health expert can be invaluable for many women.

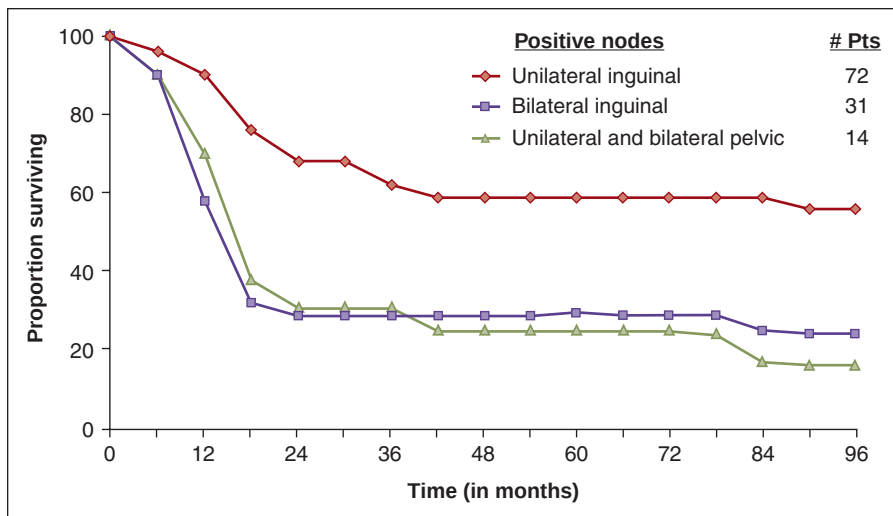


FIGURE 19.22. Invasive squamous vulvar carcinoma. Survival of patients with positive nodes. Source: Data courtesy of F. N. Rutledge.

FUTURE DIRECTIONS (RESEARCH, POTENTIAL MANAGEMENT CHANGES)

The incorporation of SLNB into the care of women with vulvar cancer raises many new questions regarding treatment of lymph node-positive patients. Should a woman with a microscopically positive SLN undergo full regional lymphadenectomy? How does the size of the metastasis impact the decision? Are isolated tumor cells clinically relevant? (223).

The GROINSVII/GOG 270 protocol, which is being conducted in Europe and North America, seeks to answer some of these questions. The original study design called for SLN-positive patients to be treated with 50-Gy radiation therapy to the groin. Early stopping rules were met because there was an unexpected number of patients with a groin relapse following SLNB and radiotherapy. On further analysis, there were no groin relapses among patients with metastases <2 mm. The study has been amended to require inguinofemoral lymphadenectomy for women with metastases over 2 mm and postoperative radiation therapy of 56 Gy. The role of adjuvant chemotherapy is unclear. GROINSVII/GOG 270 allows the use of concurrent cisplatin during radiotherapy, however, at the discretion of the treating physician.

Another area of interest will be targeted therapy. Phase 2 trials in vulvar cancer are unlikely; however, lessons learned from

squamous carcinomas of the anus or head and neck, as well as from cutaneous melanoma, may provide new options for patients with recurrent disease.

SUMMARY

Most patients with vulvar cancer are potentially curable at the time they present for care. The major challenge for providers is how to balance providing curative therapy with preserving quality of life, including organ function, sexual function, and body image.

The preferred therapy for patients with early disease is surgery alone. The morbidity of surgery can be reduced with the use of SLNB as an alternative to regional lymphadenectomy. This approach has proved very successful in the treatment of patients with breast cancer and cutaneous melanoma. There is now enough clinical evidence to support routine use in patients with vulvar cancer. Further investigation is needed to determine the ideal management of patients with a positive SLN.

Women with advanced disease usually benefit from multimodality therapy. The exact combination and order of treatment rely on consultation with a team including a gynecologic oncologist, radiation oncologist, pathologist, and diagnostic imager. Vulvar cancer is sufficiently infrequent that even busy clinicians should consider referral to a high-volume center when considering the care of women with vulvar cancer.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
2. Jones RW, Joura EA. Analyzing prior clinical events at presentation in 102 women with vulvar carcinoma: evidence of diagnostic delays. *J Reprod Med*. 1999;44:766–768.
3. Parry-Jones E. Lymphatics of the vulva. *J Obstet Gynecol Br Empire*. 1963;70:751–755.
4. Plentl AA, Friedman EA, eds. *Lymphatic System of the Female Genitalia*. Philadelphia, PA: WB Saunders; 1971.
5. Joura EA, Lössch A, Haider-Angeler MG, et al. Trends in vulvar neoplasia. Increasing incidence of vulvar intraepithelial neoplasia and squamous cell carcinoma of the vulva in young women. *J Reprod Med*. 2000;45(8):613–615.
6. Lanneau GS, Argenta PA, Lanneau MS, et al. Vulvar cancer in young women: demographic features and outcome evaluation. *Am J Obstet Gynecol*. 2009;200(6):645.e1–5.
7. Brinton LA, Nasca PC, Mallin K, et al. Case-control study of cancer of the vulva. *Obstet Gynecol*. 1990;75:859–866.
8. Blomberg M, Friis S, Munk C, et al. Genital warts and risk of cancer: a Danish study of nearly 50,000 patients with genital warts. *J Infect Dis*. 2012;205(10):1544–1553.
9. van de Nieuwenhof HP, van Kempen LC, de Hullu JA, et al. The etiologic role of HPV in vulvar squamous cell carcinoma fine tuned. *Cancer Epidemiol Biomarkers Prev*. 2009;18(7):2061–2067.
10. Basta A, Adamek K, Pityński K. Intraepithelial neoplasia and early stage vulvar cancer: epidemiological, clinical and virological observations. *Eur J Gynaecol Oncol*. 1999;20(2):111–114.
11. Brown JE, Sunborg MJ, Kost E, et al. Vulvar cancer in human immunodeficiency virus-seropositive premenopausal women: a case series and review of the literature. *J Low Genit Tract Dis*. 2005;9(1):7–10.
12. Hussain SK, Madeleine MM, Johnson LG, et al. Cervical and vulvar cancer risk in relation to the joint effects of cigarette smoking and genetic variation in interleukin 2. *Cancer Epidemiol Biomarkers Prev*. 2008;17(7):1790–1799.
13. Chaturvedi AK, Madeleine MM, Biggar RJ, et al. Risk of human papillomavirus-associated cancers

- among persons with AIDS. *J Natl Cancer Inst.* 2009;101(16):1120–1130.
14. Duong TH, Flowers LC. Vulvo-vaginal cancers: risks, evaluation, prevention and early detection. *Obstet Gynecol Clin North Am.* 2007;34(4):783–802, x.
 15. van de Nieuwenhof HP, Bulten J, Hollema H, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma. *Mod Pathol.* 2011;24(2):297–305.
 16. Carli P, De Magnis A, Mannone F, et al. Vulvar carcinoma associated with lichen sclerosus: experience at the Florence, Italy vulvar clinic. *J Reprod Med.* 2003;48:313–318.
 17. Jones RW, Rowan DM. Vulvar intraepithelial neoplasia III: a clinical study of the outcome in 113 cases with relation to the later development of invasive vulvar carcinoma. *Obstet Gynecol.* 1994;84:741–745.
 18. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol.* 2005;106:1319–1326.
 19. Trimble CL, Hildesheim A, Brinton LA, et al. Heterogeneous etiology of squamous carcinoma of the vulva. *Obstet Gynecol.* 1996;87:59–64.
 20. Mitchell MF, Prasad CJ, Silva EG, et al. Second genital primary squamous neoplasms in vulvar carcinoma: viral and histopathologic correlates. *Obstet Gynecol.* 1993;81:13–17.
 21. Homesley HD, Bundy BN, Sedlis A, et al. Prognostic factors for groin node metastasis in squamous cell carcinoma of the vulva (a Gynecologic Oncology Group study). *Gynecol Oncol.* 1993;49:279–285.
 22. Gonzalez Bosquet J, Magrina JF, Magtibay PM, et al. Patterns of inguinal groin metastases in squamous cell carcinoma of the vulva. *Gynecol Oncol.* 2007;105(3):742–746.
 23. Cohn DE, Dehdashti F, Gibb RK, et al. Prospective evaluation of positron emission tomography for the detection of groin node metastases from vulvar cancer. *Gynecol Oncol.* 2002;85(1):179–184.
 24. Beneder C, Fuechsel FG, Krause T, et al. The role of 3D fusion imaging in sentinel lymphadenectomy for vulvar cancer. *Gynecol Oncol.* 2008;109(1):76–80.
 25. Kobayashi K, Ramirez PT, Kim EE, et al. Sentinel node mapping in vulvovaginal melanoma using SPECT/CT lymphoscintigraphy. *Clin Nucl Med.* 2009;34(12):859–861.
 26. Kataoka MY, Sala E, Baldwin P, et al. The accuracy of magnetic resonance imaging in staging of vulvar cancer: a retrospective multi-centre study. *Gynecol Oncol.* 2010;117:82–87.
 27. de Bie RP, van de Nieuwenhof HP, Bekkers RL, et al. Patients with usual vulvar intraepithelial neoplasia-related vulvar cancer have an increased risk of cervical abnormalities. *Br J Cancer.* 2009;101(1):27–31.
 28. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009. May;105(2):103–104. Erratum in: *Int J Gynaecol Obstet.* 2010;108(2):176.
 29. Hacker NF. Revised FIGO staging for carcinoma of the vulva. *Int J Gynaecol Obstet.* 2009;105(2):105–106.
 30. Wilkinson EJ, Teixeira MR. Tumors of the Vulva. In: Tavassoli FA, Deville P, eds. *Tumours of the Breast and Female Genital Organs.* World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2003.
 31. Darragh TM, Colgan TJ, Cox JT, et al. The lower anogenital squamous terminology standardization project for HPV associated lesions: background and consensus recommendations from the college of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis.* 2012;16(3):205–242.
 32. Yoder B, Rufforny I, Massoll NA, et al. Stage IA vulvar squamous cell carcinoma: an analysis of tumor invasive characteristics and risk. *Am J Surg Pathol.* 2008;32(5):765–772.
 33. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual.* New York, NY: Springer; 2009.
 34. Moxley KM, Fader AN, Rose PG, et al. Malignant melanoma of the vulva: an extension of cutaneous melanoma? *Gynecol Oncol.* 2011;122(3):612–617.
 35. Wilkinson EJ, Stone IK. *Wilkinson and Stone: Atlas of Vulvar Disease.* 3rd ed. Wolters Kluwer, Lippincott Williams & Wilkins, Philadelphia, 2012.
 36. Dvoretzky PM, Bonfiglio TA, Helmkamp F, et al. The pathology of superficially invasive thin vulvar squamous cell carcinoma. *Int J Gynecol Pathol.* 1984;3:331–334.
 37. Jones RW, Sadler L, Grant S, et al. Clinically identifying women with vulvar lichen sclerosus at increased risk of squamous cell carcinoma: a case-control study. *J Reprod Med.* 2004;49:808–813.
 38. Kurman RJ, Ronnett J, Sherman ME, et al. Tumors of the cervix, vagina, and vulva. In: Rosai J, et al, eds. *Atlas of Tumor Pathology, Fascicle 3rd series.* Armed Forces Institute of Pathology, Washington, American Registry of Pathology, District of Columbia, 2010:44.
 39. Wilkinson EJ. Superficial invasive carcinoma of the vulva. *Clin Obstet Gynecol.* 1985;28:188–192.
 40. Wilkinson EJ. Protocol for the examination of specimens from patients with carcinomas and malignant melanomas of the vulva: a basis for checklists. Cancer Committee of the American College of Pathologists. *Arch Pathol Lab Med.* 2000;124:51–56.
 41. Drew PA, Al-Abbadi MA, Orlando C, et al. Prognostic factors in carcinoma of the vulva: a clinicopathologic and DNA flow cytometric study. *Int J Gynecol Pathol.* 1996;15:235.
 42. Kurman RJ, Toki T, Schiffman MH. Basaloid and warty carcinomas of the vulva: distinctive types of squamous cell carcinoma frequently associated with human papillomaviruses. *Am J Surg Pathol.* 1993;17:133–136.
 43. Carter JJ, Koutsky LA, Wipf GC, et al. The natural history of human papillomavirus type 16 capsid antibodies among a cohort of university women. *J Infect Dis.* 1996;174:927–934.
 44. Horn L-C, Liebert U, Edelmann J, et al. Adenoid squamous carcinoma (pseudoangiosarcomatous carcinoma) of the vulva: a rare but highly aggressive variant of squamous cell carcinoma. *Int J Gynecol Pathol.* 2008;27:288–291.
 45. Wilkinson EJ, Croker BP, Friedrich EG Jr, et al. Two distinct pathologic types of giant cell tumor of the vulva: a report of two cases. *J Reprod Med.* 1988;33:519–522.
 46. Carlson J, McGlennen R, Gomez R, et al. Sebaceous carcinoma of the vulva: a case report and review of the literature. *Gynecol Oncol.* 1996;60:489–491.
 47. Escanilla P, Grilli R, Canamero M, et al. Sebaceous carcinoma of the vulva. *Am J Dermatol.* 1999;21:468–472.
 48. Copas P, Dyer M, Comas FV, et al. Spindle cell carcinoma of the vulva. *Diagn Gynecol Obstet.* 1982;4:235–238.
 49. Berman ML, Soper JT, Creasman WT, et al. Conservative surgical management of superficially invasive stage I vulvar carcinoma. *Gynecol Oncol.* 1989;35:352–356.
 50. Rando RF, Sedlacek TV, Hunt J, et al. Verrucous carcinoma of the vulva associated with an unusual type 6 human papillomavirus. *Obstet Gynecol.* 1986;67:705–755.
 51. De Giorgi V, Salvini C, Massi D, et al. Vulvar basal cell carcinoma: retrospective study and review of literature. *Gynecol Oncol.* 2005;97:192–194.
 52. Bottles K, Lacey CG, Goldberg J, et al. Merkel cell carcinoma of the vulva. *Obstet Gynecol.* 1984;63:61S–65S.
 53. Takeshima N, Tabata T, Hishida H, et al. Peripheral primitive neuroectodermal tumor of the vulva: report of a case with imprint cytology. *Acta Cytol.* 2001;45:1049–1052.
 54. Vang R, Taubenberger JK, Mannion CM, et al. Primary vulvar and vaginal extraosseous Ewing's sarcoma/peripheral neuroectodermal tumor: diagnostic confirmation with CD99 immunostaining and reverse transcriptase-polymerase chain reaction. *Int J Gynecol Pathol.* 2000;19:236–242.
 55. Wilkinson EJ, Brown HM. Vulvar Paget disease of urothelial origin: a report of three cases and a proposed classification of vulvar Paget disease. *Hum Pathol.* 2002;33:549–554.
 56. Taylor RN, Lacey CG, Shuman MA. Adenocarcinoma of Skene's duct associated with a systemic coagulopathy. *Gynecol Oncol.* 1985;22:250–253.
 57. Klein AE, Bauer TW, Marks KE, et al. Papillary clear cell adenocarcinoma of the groin arising from endometriosis. *Clin Orthop Relat Res.* 1999;361:192–195.
 58. Woolcott RJ, Henry RJ, Houghton CR. Malignant melanoma of the vulva: Australian experience. *J Reprod Med.* 1988;33:699–711.
 59. Van der Putte SCJ, van-Gorp HM. Cysts of mammary-like glands in the vulva. *Int J Gynecol Pathol.* 1995;14:184–188.
 60. Cho D, Buscema J, Ronsenshein NB, et al. Primary breast cancer of the vulva. *Obstet Gynecol.* 1985;66:79S–87S.
 61. Malik S, Wilkinson EJ. Pseudopaget's disease of the vulva: a case report. *J Lower Genital Dis.* 1999;3:201–206.
 62. Powell FC, Bjornsson J, Doyle JA, et al. Genital Paget's disease and urinary tract malignancy. *J Am Acad Dermatol.* 1985;13:84–87.
 63. Brown H, Wilkinson EJ. Cytology of secondary vulvar paget disease of urothelial origin. *Acta Cytol.* 2005;49:71–74.
 64. Chen CH, Ji H, Suh KW, et al. Control of HPV-associated malignancies grown in liver with DNA vaccine. *Mod Pathol.* 1999;112:53A–55A.
 65. Crawford D, Nimmo M, Thomson T, et al. Vulvar Paget's disease: prognostic factors. *Mod Pathol.* 1999;12:114A–115A.
 66. Brainard JA, Hart WR. Proliferative squamous cell lesions in anogenital Paget's disease. *Mod Pathol.* 1999;12:113A–115A.
 67. Shah KD, Tabibzadch SS, Gerber MA. Immunohistochemical distinction of Paget's disease from Bowen's disease and superficial spreading melanoma with the use of monoclonal cytokeratin antibodies. *Am J Clin Pathol.* 1987;88:689–693.
 68. Panizzon RG. Vulvar melanoma. *Semin Dermatol.* 1996;15:67–70.
 69. Ragnarsson-Olding BK, Nilsson BR, Kanter-Lewensohn LR, et al. Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: predictors of survival. *Cancer* 1999;86:1285–1293.
 70. Raspagliesi F, Ditto A, Paladini D, et al. Prognostic indicators in melanoma of the vulva. *Ann Surg Oncol.* 2000;7:738–742.
 71. Wechter ME, Reynolds RK, Haefner HK, et al. Vulvar melanoma: review of diagnosis, staging, and therapy. *J Low Genit Tract Dis.* 2004;8:58–69.
 72. Piura B, Rabinovich A, Dgani R. Malignant melanoma of the vulva: report of six cases and

- review of the literature. *Eur J Gynaecol Oncol*. 1999;20:182–186.
73. Sison-Torre EQ, Ackerman AB. Melanosis of the vulva: a clinical simulator of malignant melanoma. *Am J Dermatopathol*. 1985;7:51–55.
 74. Benda JA, Platz CE, Anderson B. Malignant melanoma of the vulva: a clinical pathologic review of 16 cases. *Int J Gynecol Pathol*. 1986;5:202–216.
 75. Look KY, Roth LM, Sutton GP. Vulvar melanoma reconsidered. *Cancer*. 1993;72:143–146.
 76. Morgan L, Joslyn P, Chafe W, et al. A report on 18 cases of primary malignant melanoma of the vulva. *Colposcopy Gynecol Laser Surg*. 1988;4:161–170.
 77. Mihm MC Jr, Clark WH Jr, From L. The clinical diagnosis, classification and histogenetic concepts of the early stages of cutaneous malignant melanomas. *N Engl J Med*. 1971;284:1078–1082.
 78. Breslow A. Thickness, cross-sectional area and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg*. 1970;172:902–907.
 79. Beller U, Demopoulos RI, Bechnan EM. Vulvovaginal melanoma: a clinicopathologic study. *J Reprod Med*. 1986;31:315–321.
 80. Johnson TL, Kumar N, White CD. Prognostic features of vulvar melanoma: a clinicopathologic analysis. *Int J Gynecol Pathol*. 1986;5:110–119.
 81. Jiveskog S, Ragnarsson-Olding B, Platz A, et al. N-ras mutations are common in melanomas from sun-exposed skin of humans but rare in mucosal membranes or unexposed skin. *J Invest Dermatol*. 1998;111:757–762.
 82. Nielsen GP, Young RH. Mesenchymal tumors and tumor-like lesions of the female genital tract: a selective review with emphasis on recently described entities. *Int J Gynecol Pathol*. 2001;20:105–127.
 83. Nucci MR, Fletcher CDM. Vulvovaginal soft tissue tumors: update and review. *Histopathology*. 2000;36:97–108.
 84. Taylor RN, Bottles K, Miller TR, et al. Malignant fibrous histiocytoma of the vulva. *Obstet Gynecol*. 1985;66:145–150.
 85. Perrone T, Swanson PE, Twigg L, et al. Malignant rhabdoid tumor of the vulva: is distinction from epithelioid sarcoma possible? *Am J Surg Pathol*. 1989;13:848–851.
 86. Ungerleider RS, Donaldson SS, Warnke RA, et al. Endodermal sinus tumor: the Stanford experience and the first reported case arising in the vulva. *Cancer*. 1978;41:1627–1634.
 87. Cockerell CJ, LeBoit PE. Bacillary angiomatosis: a newly characterized, pseudoneoplastic, infectious, cutaneous vascular disorder. *J Am Acad Dermatol*. 1990;22:501–504.
 88. Ehrmann RL, Dwyer IM, Yavner BA, et al. An immunoperoxidase study of laminin and type IV collagen distribution in carcinoma of the cervix and vulva. *Obstet Gynecol*. 1988;72:257–260.
 89. Sims (Mandani-Sims) S, Stinson S, McLean FW, et al. Angiomyofibroblastoma of the vulva: a case report of a pedunculated variant and review of the literature. *J Lower Genital Tract Dis*. 2012;16(2):149–154.
 90. Lerner LB, Andrews SJ, Gonzalez JL, et al. Vulvar metastases secondary to transitional cell carcinoma of the bladder: a case report. *J Reprod Med*. 1999;8:729–732.
 91. Neto AG, Deavers MT, Silva EG, et al. Metastatic tumors of the vulva: a clinicopathologic study of 66 cases. *Am J Surg Pathol*. 2003;27:799–812.
 92. Vang R, Medeiros LJ, Malpica A, et al. Non-Hodgkin's lymphoma involving the vulva. *Int J Gynecol Pathol*. 2000;19:236–242.
 93. Levine RL. Urethral cancer. *Cancer*. 1980;45:1965–1969.
 94. Maggino T, Landoni F, Sartori E, et al. Patterns of recurrence in patients with squamous cell carcinoma of the vulva. A multicenter CTF Study. *Cancer*. 2000;89(1):116–122.
 95. Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. *Gynecol Oncol*. 2007;104(3):636–641.
 96. Landrum LM, Lanneau GS, Skaggs VJ, et al. Gynecologic Oncology Group risk groups for vulvar carcinoma: improvement in survival in the modern era. *Gynecol Oncol*. 2007;106(3):521–525.
 97. Heaps JM, Fu YS, Montz FJ, et al. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. *Gynecol Oncol*. 1990;38:309–315.
 98. Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinicopathologic prognostic factors in vulvar carcinoma: a multivariate analysis. *Gynecol Oncol*. 2007;104:636–641.
 99. De Hullu JA, Hollema H, Lolkema S, et al. Vulvar carcinoma. The price of less radical surgery. *Cancer*. 2002;95:2331–2338.
 100. Hoffman MS, Gunesakaran S, Arango H, et al. Lateral microscopic extension of squamous cell carcinoma of the vulva. *Gynecol Oncol*. 1999;73:72–75.
 101. Gonzalez Bosquet J, Magrina JF, Gaffey TA, et al. Long-term survival and disease recurrence in patients with primary squamous cell carcinoma of the vulva. *Gynecol Oncol*. 2005;97:828–833.
 102. Farias-Eisner R, Cirisano FD, Grouse D, et al. Conservative and individualized surgery for early squamous carcinoma of the vulva: the treatment of choice for stage I and II (T1-2 N0-1 M0) disease. *Gynecol Oncol*. 1994;53:55–58.
 103. Figge DC, Tamimi HK, Greer BE. Lymphatic spread in carcinoma of the vulva. *Am J Obstet Gynecol*. 1985;152:387–392.
 104. Oonk MH, Hollema H, de Hullu JA, et al. Prediction of lymph node metastases in vulvar cancer: a review. *Int J Gynecol Cancer*. 2006;16:963–971.
 105. Bipat S, Fransen GA, Spijkerboer AM, et al. Is there a role for magnetic resonance imaging in the evaluation of inguinal lymph node metastases in patients with vulva carcinoma? *Gynecol Oncol*. 2006;103:1001–1006.
 106. Taussig FJ. Cancer of the vulva: an analysis of 155 cases. *Am J Obstet Gynecol*. 1940;40:764–770.
 107. Way S. Carcinoma of the vulva. *Am J Obstet Gynecol*. 1960;79:692–699.
 108. Burke TW, Stringer CA, Gershenson DM, et al. Radical wide excision and selective inguinal node dissection for squamous cell carcinoma of the vulva. *Gynecol Oncol*. 1990;38:328–334.
 109. DiSaia PJ, Creasman WT, Rich WM. An alternative approach to early cancer of the vulva. *Am J Obstet Gynecol*. 1979;133:825–829.
 110. Nasu K, Kai Y, Ohishi M, et al. Conservative surgical treatment for early-stage vulvar malignant melanoma. *Arch Gynecol Obstet*. 2010;281(2):335–338.
 111. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. *Gynecol Oncol*. 2012;124(3):529–533.
 112. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340:1154–1162.
 113. Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*. 2000;18:1606–1610.
 114. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340:1144–1147.
 115. Moore DH, Thomas GM, Montana GS, et al. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. *Int J Radiat Oncol Biol Phys*. 1998;42:1317–1321.
 116. Morton DL, Wen DR, Foshag LJ, et al. Intraoperative lymphatic mapping and selective cervical lymphadenectomy for early-stage melanomas of the head and neck. *J Clin Oncol*. 1993;11(9):1751–1756.
 117. Levenback C, Burke TW, Gershenson DM, et al. Intraoperative lymphatic mapping for vulvar cancer. *Obstet Gynecol*. 1994;84:163–167.
 118. Levenback C, Burke TW, Morris M, et al. Potential applications of intraoperative lymphatic mapping in vulvar cancer. *Gynecol Oncol*. 1995;59:216–220.
 119. Barton DPJ, Berman C, Cavanagh D, et al. Lymphoscintigraphy in vulvar cancer: a pilot study. *Gynecol Oncol*. 1992;46:341–347.
 120. DeCesare SL, Fiorica JV, Roberts WS, et al. A pilot study utilizing intraoperative lymphoscintigraphy for identification of the sentinel lymph nodes in vulvar cancer. *Gynecol Oncol*. 1997;66:425–429.
 121. Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol*. 2008;26(6):884–889.
 122. Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. *J Clin Oncol*. 2012;30(31):3786–3791.
 123. Stehman FB, Ali S, DiSaia PJ. Node count and groin recurrence in early vulvar cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2009;113(1):52–56.
 124. Kelley JL 3rd, Burke TW, Tornos C, et al. Minimally invasive vulvar carcinoma: an indication for conservative surgical therapy. *Gynecol Oncol*. 1991;144:240–245.
 125. Chafe W, Richards A, Morgan L, et al. Unrecognized invasive carcinoma in vulvar intraepithelial neoplasia (VIN). *Gynecol Oncol*. 1988;31:154–157.
 126. Modesitt SC, Waters AB, Walton L, et al. Vulvar intraepithelial neoplasia III: occult cancer and the impact of margin status on recurrence. *Obstet Gynecol*. 1998;92:962–970.
 127. Burke TW, Levenback C, Coleman RC, et al. Surgical therapy of T1 and T2 vulvar carcinoma: further experience with radical wide excision and selective inguinal lymphadenectomy. *Gynecol Oncol*. 1995;57:215–219.
 128. De Mooij Y, Burger MP, Schilthuis MS, et al. Partial urethral resection in the surgical treatment of vulvar cancer does not have a significant impact on urinary continence. A confirmation of an authority-based opinion. *Int J Gynecol Cancer*. 2007;17:294–297.
 129. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. *Gynecol Oncol*. 2012;124(3):529–533.
 130. Hyde SE, Valmadre S, Hacker NF, et al. Squamous cell carcinoma of the vulva with bulky positive groin nodes—nodal debulking versus full groin

- dissection prior to radiation therapy. *Int J Gynecol Cancer*. 2007;17:154–158.
131. Homesley HD, Bundy BN, Sedlis A, et al. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol*. 1986;68:733–739.
 132. Kunos C, Simpkins F, Gibbons H, et al. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. *Obstet Gynecol*. 2009;114(3):537–546.
 133. Hopkins MP, Reid GC, Morley GW. The surgical management of recurrent squamous cell carcinoma of the vulva. *Obstet Gynecol*. 1990;75:1001–1007.
 134. Piura B, Masotina A, Murdoch J, et al. Recurrent squamous cell carcinoma of the vulva: a study of 73 cases. *Gynecol Oncol*. 1993;48:189–194.
 135. Sugiyama VE, Chan JK, Shin JY, et al. Vulvar melanoma: a multivariate analysis of 644 patients. *Obstet Gynecol*. 2007;110:296–301.
 136. Morrow CP, Rutledge FN. Melanoma of the vulva. *Obstet Gynecol*. 1972;39:745–750.
 137. Phillips GL, Bundy BN, Okagaki T, et al. Malignant melanoma of the vulva treated by radical hemivulvectomy: a prospective study of the Gynecology Oncology Group. *Cancer*. 1994;73:2626–2630.
 138. Wechter ME, Reynolds RK, Haefner HK, et al. Vulvar melanoma: review of diagnosis, staging, and therapy. *J Low Genit Tract Dis*. 2004;8:58–69.
 139. Emami B, Perez CA. Combination of surgery, irradiation, and hyperthermia in treatment of recurrences of malignant tumors. *Int J Radiat Oncol Biol Phys*. 1987;13:611–615.
 140. Singhal RM, Narayana A. Malignant melanoma of the vulva: response to radiation. *Br J Radiol*. 1991;64:846–850.
 141. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999;17(7):2105–2116.
 142. Podratz KC, Gaffey TA, Symmonds RE, et al. Melanoma of the vulva: an update. *Gynecol Oncol*. 1983;16:153–157.
 143. Trimble EL, Lewis JL Jr, Williams LL, et al. Management of vulvar melanoma. *Gynecol Oncol*. 1992;45:254–258.
 144. Gallousis S. Verrucous carcinoma: report of three vulvar cases and a review of the literature. *Obstet Gynecol*. 1972;40:502–506.
 145. Japaze H, Dinh TV, Woodruff JD. Verrucous carcinoma of the vulva: study of 24 cases. *Obstet Gynecol*. 1982;60:462–467.
 146. Breen JL, Neubecker RD, Greenwald E, et al. Basal cell carcinoma of the vulva. *Obstet Gynecol*. 1975;46:122–125.
 147. Hoffman MS, Roberts WS, Ruffolo EH. Basal cell carcinoma of the vulva with inguinal lymph node metastases. *Gynecol Oncol*. 1988;29:113–117.
 148. Copeland LJ, Sneige N, Gershenson DM, et al. Bartholin gland carcinoma. *Obstet Gynecol*. 1986;67:794–799.
 149. Leuchter RS, Hacker NF, Voet RL, et al. Primary carcinoma of the Bartholin gland: a report of 14 cases and a review of the literature. *Obstet Gynecol*. 1982;60:361–367.
 150. Huang GS, Juretzka M, Ciaravino G, et al. Liposomal doxorubicin for treatment of metastatic chemorefractory vulvar adenocarcinoma. *Gynecol Oncol*. 2002;87:313–317.
 151. Creasman WT, Gallager HS, Rutledge F. Paget's disease of the vulva. *Gynecol Oncol*. 1975;3:133–137.
 152. Fanning J, Lambert L, Hale TM, et al. Paget's disease of the vulva: prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. *Am J Obstet Gynecol*. 1999;180:24–30.
 153. Niikura H, Yoshida H, Ito K, et al. Paget's disease of the vulva: clinicopathologic study of type 1 cases treated at a single institution. *Int J Gynecol Cancer*. 2006;16:1212–1215.
 154. Kodama S, Kaneko T, Saito M, et al. A clinicopathologic study of 30 patients with Paget's disease of the vulva. *Gynecol Oncol*. 1995;56:63–67.
 155. Stacy D, Burrell MO, Franklin EW 3rd. Extramammary Paget's disease of the vulva and anus: use of intraoperative frozen-section margins. *Am J Obstet Gynecol*. 1986;155:519–524.
 156. Black D, Tornos C, Soslow RA, et al. The outcomes of patients with positive margins after excision for intraepithelial Paget's disease of the vulva. *Gynecol Oncol*. 2007;104:547–550.
 157. Bergen S, DiSaia PJ, Liao SY, et al. Conservative management of extramammary Paget's disease of the vulva. *Gynecol Oncol*. 1989;33:151–155.
 158. Feldmeyer L, Kerl K, Kamarashev J, et al. Treatment of vulvar Paget disease with topical imiquimod: a case report and review of the literature. *J Dermatol Case Rep*. 2011;5(3):42–46.
 159. Ho SA, Aw DC. Extramammary Paget's disease treated with topical imiquimod 5% cream. *Dermatol Ther*. 2010;23(4):423–427.
 160. Cohen PR, Schulze KE, Tschén JA, et al. Treatment of extramammary Paget disease with topical imiquimod cream: case report and literature review. *South Med J*. 2006;99(4):396–402.
 161. Tavassoli FA, Norris HJ. Smooth muscle tumors of the vulva. *Obstet Gynecol*. 1979;53:213–215.
 162. Hays DM, Shimada H, Raney RB, et al. Clinical staging and treatment results in rhabdomyosarcoma of the female genital tract among children and adolescents. *Cancer*. 1988;61:1893–1899.
 163. Bell J, Averette H, Davis J, et al. Genital rhabdomyosarcoma: current management and review of the literature. *Obstet Gynecol Surv*. 1986;41:257–262.
 164. Abitbol MM. Carcinoma of the vulva: improvements in the surgical approach. *Am J Obstet Gynecol*. 1973;117:483–489.
 165. Hacker NF, Leuchter RS, Berek JS, et al. Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions. *Obstet Gynecol*. 1981;58:574–578.
 166. Burrell MO, Franklin EW 3rd, Campion MJ, et al. The modified radical vulvectomy with groin dissection: an eight-year experience. *Am J Obstet Gynecol*. 1988;159:715–719.
 167. Siller BS, Alvarez RD, Conner WD, et al. T2/3 vulva cancer: a case-control study of triple incision versus en bloc radical vulvectomy and inguinal lymphadenectomy. *Gynecol Oncol*. 1995;57:335–340.
 168. Gaarenstroom KN, Kenter GG, Trimbois JB, et al. Postoperative complications after vulvectomy and inguino-femoral lymphadenectomy using separate groin incisions. *Int J Gynecol Cancer*. 2003;13:522–527.
 169. Miller B, Morris M, Levenback C, et al. Pelvic exenteration for primary and recurrent vulvar cancer. *Gynecol Oncol*. 1995;58:189–193.
 170. Forner DM, Lampe B. Exenteration in the treatment of stage III/IV vulvar cancer. *Gynecol Oncol*. 2012;124(1):87–91.
 171. Buda A, Confalonieri PL, Rovati LC, et al. Better anatomical and cosmetic results using tunneled lotus petal flap for plastic reconstruction after demolitive surgery for vulvar malignancy. *Int J Gynecol Cancer*. 2012;22(5):860–864.
 172. Yii NW, Niranjan NS. Lotus petal flaps in vulvo-vaginal reconstruction. *Br J Plast Surg*. 1996;49(8):547–554.
 173. Sawada M, Kimatu Y, Kasamatsu T, et al. Versatile lotus petal flap for vulvoperineal reconstruction after gynecological ablative surgery. *Gynecol Oncol*. 2004;95:330–335.
 174. McMenamin DM, Clements D, Edwards TJ, et al. Rectus abdominis myocutaneous flaps for perineal reconstruction: modifications to the technique based on a large single-centre experience. *Ann R Coll Surg Engl*. 2011;93:375–381.
 175. Cormio G, Loizzi V, Carriero C, et al. Groin recurrence in carcinoma of the vulva: management and outcome. *Eur J Cancer Care*. 2010;19(3):302–307.
 176. Franchelli S, Leone MS, Bruzzone M, et al. The gluteal fold fascio-cutaneous flap for reconstruction after radical excision of primary vulvar cancers. *Gynecol Oncol*. 2009;113(2):245–248.
 177. McMenamin DM, Clements D, Edwards TJ, et al. Rectus abdominis myocutaneous flaps for perineal reconstruction: modifications to the technique based on a large single-centre experience. *Ann R Coll Surg Engl*. 2011;93(5):375–381.
 178. Mathes SJ, Bostwick J 3rd. A rectus abdominis myocutaneous flap to reconstruct abdominal wall defects. *Br J Plast Surg*. 1977;30(4):282–283.
 179. Petrie N, Branagan G, McGuinness C, et al. Reconstruction of the perineum following anorectal cancer excision. *Int J Colorectal Dis*. 2009;24(1):97–104.
 180. Ellis F. Cancer of the vulva treated by radiation. *Br J Radiol*. 1949;22:513.
 181. Helgason NM, Hass AC, Latourette HB. Radiation therapy in carcinoma of the vulva. *Cancer*. 1972;30:997–1004.
 182. Busch M, Wagener B, Duhmke E. Long term results of radiotherapy alone for carcinoma of the vulva. *Adv Ther*. 1999;16:89–94.
 183. Podratz KC, Symmonds RE, Taylor WF. Carcinoma of the vulva: analysis of treatment failures. *Am J Obstet Gynecol*. 1982;143:340–346.
 184. Binder SW, Huang I, Fu YS, et al. Risk factors for the development of lymph node metastasis in vulvar squamous carcinoma. *Gynecol Oncol*. 1990;37:9–16.
 185. Boyce J, Fruchter RG, Kasambilides E, et al. Prognostic factors in carcinoma of the vulva. *Gynecol Oncol*. 1985;20:364–367.
 186. Faul CM, Mirmow D, Huang Q, et al. Adjuvant radiation for vulvar carcinoma: improved local control. *Int J Radiat Oncol Biol Phys*. 1997;38:381–385.
 187. Hacker NF, Berek JS, Julliard GJF, et al. Preoperative radiation therapy for locally advanced vulvar cancer. *Cancer*. 1984;54:2056–2064.
 188. Jafari K, Magalotti M. Radiation therapy in carcinoma of the vulva. *Cancer*. 1981;47:686–691.
 189. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. *Gynecol Oncol*. 2012;124(3):529–533.
 190. Mak RH, Halasz LM, Tanaka CK, et al. Outcomes after radiation therapy with concurrent weekly platinum-based chemotherapy or every-3-4-week 5-fluorouracil-containing regimens for squamous cell carcinoma of the vulva. *Gynecol Oncol*. 2011;120(1):101–107.
 191. Cummings B. Anal canal carcinomas. In: Meyer JL, Vaeth JM, eds. *Frontiers in Radiation*

- Oncology*. Vol 26. Basel, Switzerland: Karger; 1992:131–135.
192. Rich TA, Ajani JA, Morrison WH, et al. Chemoradiation therapy for anal cancer: radiation plus continuous infusion of 5-fluorouracil with or without cisplatin. *Radiother Oncol*. 1993;27:209–212.
 193. Iversen T. Irradiation and bleomycin in the treatment of inoperable vulvar carcinoma. *Acta Obstet Gynecol Scand*. 1982;61:195–200.
 194. Scheistroyen M, Trope C. Combined bleomycin and irradiation in preoperative treatment of advanced squamous cell carcinoma of the vulva. *Acta Oncol*. 1992;32:657–663.
 195. Thomas G, Dembo A, DePetrillo A, et al. Concurrent radiation and chemotherapy in vulvar carcinoma. *Gynecol Oncol*. 2004;93:659–666.
 196. Mulayim N, Silver DF, Schwartz PE, et al. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. *Gynecol Oncol*. 2006;103:1095–1099.
 197. Katz A, Eifel PJ, Jhingran A, et al. The role of radiation therapy in preventing regional recurrences of invasive squamous cell carcinoma of the vulva. *Int J Radiat Oncol Biol Phys*. 2003;57:409–413.
 198. Leiserowitz GS, Russell AH, Kinney WK, et al. Prophylactic chemoradiation of inguino-femoral lymph nodes in patients with locally extensive vulvar cancer. *Gynecol Oncol*. 1997;66:509–514.
 199. Stehman F, Bundy B, Thomas G, et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys*. 1992;24:39–42.
 200. Eifel PJ. Vulvar carcinoma: radiotherapy or surgery for the lymphatics? *Front Radiat Ther Oncol*. 1994;28:218–221.
 201. Koh WJ, Chiu M, Stelzer KJ, et al. Femoral vessel depth and the implications for groin node radiation. *Int J Radiat Oncol Biol Phys*. 1992;27:969–973.
 202. Origoni M, Sideri M, Garsia S, et al. Prognostic value of pathological patterns of lymph node positivity in squamous cell carcinoma of the vulva stage III and IVA FIGO. *Gynecol Oncol*. 1992;45:313–317.
 203. Simonsen E, Nordberg UB, Johnsson JE, et al. Radiation therapy and surgery in the treatment of regional lymph nodes in squamous cell carcinoma of the vulva. *Acta Radiol Oncol*. 1984;23:433–437.
 204. Hacker NF, Van der Velden J. Conservative management of early vulvar cancer. *Cancer*. 1993;71:1673–1678.
 205. Parthasarathy A, Cheung MK, Osann K, et al. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. *Gynecol Oncol*. 2006;103:1095–1099.
 206. Oonk MH, van Hemel BM, de Hullu JA, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancers: results from GROINSS-V, a multicentre observational study. *Lancet Oncol*. 2010;11(7):646–652.
 207. Beriwal S, Heron D, Kim H, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. *Int J Radiat Oncol Biol Phys*. 2006;64:1395–1400.
 208. Defoe SG, Beriwal S, Jones H, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal carcinoma – clinical outcomes in large national cancer institute-designated integrated cancer centre network. *Clin Oncol (R Coll Radiol)*. 2011;24:424–431.
 209. Bazan JG, Hara W, Hsu A, et al. Intensity-modulated radiation therapy versus conventional radiation therapy for squamous cell carcinoma of the anal canal. *Cancer*. 2011;117(15):3342–3351.
 210. Beriwal S, Coon D, Heron DE, et al. Preoperative intensity-modulated radiotherapy and chemotherapy for locally advanced vulvar carcinoma. *Gynecol Oncol*. 2008;109(2):291–295.
 211. Ghia AJ, Gaffney DK. Radiotherapy for vulvar and vaginal cancers. In: Ayhan A, Reed N, Gultekin M, eds. *Textbook of Gynaecological Oncology*. Ankara, Turkey: Güneş Publishing, 2009;pp. 878–886.
 212. Kunos C, von Gruenigen V, Waggoner S, et al. Cyberknife radiosurgery for squamous cell carcinoma of the vulva after prior pelvic radiation therapy. *Technol Cancer Res Treat*. 2008;7:375–380.
 213. Kunos C, Debernardo R, Fabien J, et al. ¹⁸FDG-PET/CT definition of clinical target volume for robotic stereotactic body radiosurgery treatment of metastatic gynecologic malignancies. *J Nucl Med Radiat Ther*. 2011; <http://dx.doi.org/10.4172/2155-9619.S4-001>
 214. Barton DPJ. The prevention and management of treatment related morbidity in vulvar cancer. *Best Pract Res Clin Obstet Gynecol*. 2003;17:683–701.
 215. Deppe G, Bruckner HW, Cohen CJ. Adriamycin treatment of advanced vulvar carcinoma. *Obstet Gynecol*. 1977;50:13–17.
 216. Thigpen JT, Blessing JA, Homesley HD, et al. Phase II trials of cisplatin and piperzinedione in advanced or recurrent squamous cell carcinomas of the vulva: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1986;23:358–362.
 217. Muss HB, Bundy BN, Christopherson WA. Mitoxantrone in the treatment of advanced vulvar and vaginal carcinoma. *Am J Clin Oncol*. 1989;12:142–147.
 218. Slayton RE, Blessing JA, Beecham J, et al. Phase II trial of etoposide in the management of advanced or recurrent squamous cell carcinoma of the vulva and carcinoma of the vagina: a Gynecologic Oncology Group study. *Cancer Treat Rep*. 1987;71:869–872.
 219. Belinson JL, Stewart JA, Richards A, et al. Bleomycin, vincristine, mitomycin C, and cisplatin in the management of gynecologic squamous cell cancer. *Gynecol Oncol*. 1985;20:387–392.
 220. Durrant KR, Mangione C, Lacave AJ, et al. Bleomycin, methotrexate, and CCNU in advanced inoperable squamous cell carcinoma of the vulva: a phase II study of the EORTC Gynecological Cancer Cooperative Group (GCGC). *Gynecol Oncol*. 1990;37:359–363.
 221. Olawaiye A, Lee LM, Krasner C, et al. Treatment of squamous cell vulvar cancer with the anti-EGFR tyrosine kinase inhibitor Tarceva. *Gynecol Oncol*. 2007;106(3):628–630.
 222. Bacha OM, Levesque E, Renaud MC, et al. A case of recurrent vulvar carcinoma treated with erlotinib, an EGFR inhibitor. *Eur J Gynaecol Oncol*. 2011;32(4):423–424.
 223. Oonk MH, van Hemel BM, Hollema H, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. *Lancet Oncol*. 2010;11(7):646–652.

20 Vagina

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ANATOMY

The vagina is a muscular dilatable tubular structure averaging 7.5 cm in length that extends from the cervix to the vulva. It lies dorsal to the base of the bladder and urethra, and ventral to the rectum. The vagina forms from the upward spread of the epithelium from the urogenital sinus. The fused müllerian ducts meet the urogenital sinus at the müllerian tubercle. The hymen marks where the tubercle later opens up to establish the vaginal orifice. The upper portion of the posterior wall is separated from the rectum by a reflection of peritoneum, the pouch of Douglas. At its uppermost extent, the vaginal wall attaches to the uterine cervix at a higher point on the posterior wall than on the anterior wall. During embryonic development, there is no obvious demarcation between the portion of the fused müllerian ducts destined to form the uterus and those destined to form the upper vagina. In the later part of the third month of development, the uterine wall begins to be set off from the upper vagina at the cervical portion. A groove begins to form. This circular groove, formed at the juncture of the vagina and the cervix, is called the *forix*.

The vaginal wall is composed of 3 layers: the mucosa, muscularis, and adventitia. The inner mucosal layer is formed by a thick, nonkeratinizing, stratified squamous epithelium overlying a basement membrane containing many papillae. The epithelium normally contains no glands, but is lubricated by mucous secretions originating in the cervix. The epithelium changes little in response to the reproductive cycle. Beneath the mucosa lies a submucosal layer of elastin and a double muscularis layer, highly vascularized with a rich innervation and lymphatic drainage. The muscularis layer is composed of smooth muscle fibers, arranged circularly in the inner portion and longitudinally in the outer portion. A vaginal sphincter is formed by skeletal muscle at the introitus. The adventitia is a thin, outer connective tissue layer that merges with that of adjacent organs.

The proximal vagina is supplied by the vaginal artery branch from the uterine or cervical branch of the uterine artery. It runs along the lateral wall of the vagina and anastomoses with the inferior vesical and middle rectal arteries from the surrounding viscera (1). The accompanying venous plexus, running parallel to the arteries, ultimately drains into the internal iliac vein. The lumbar plexus and pudendal nerve, with branches from the sacral roots 2 to 4, provide innervation to the vaginal vault.

The lymphatic drainage of the vagina is complex, consisting of an extensive intercommunicating network. Fine lymphatic vessels coursing through the submucosa and muscularis coalesce into small trunks running laterally along the walls of the vagina. The lymphatics in the upper portion of the vagina drain primarily via the lymphatics of the cervix; the upper anterior vagina

drains along cervical channels to the interiliac and parametrial nodes; the posterior vagina drains into the inferior gluteal, presacral, and anorectal nodes. The distal vagina lymphatics follow drainage patterns of the vulva into the inguinal and femoral nodes and from there to the pelvic nodes. Lymphatic flow from lesions in the mid-vagina may drain either way (Figure 20.1) (2). However, because of the presence of intercommunicating lymphatics along the terminal branches of the vaginal artery and near the vaginal wall, the external iliac nodes are at high risk, even in lesions of the lower third of the vagina.

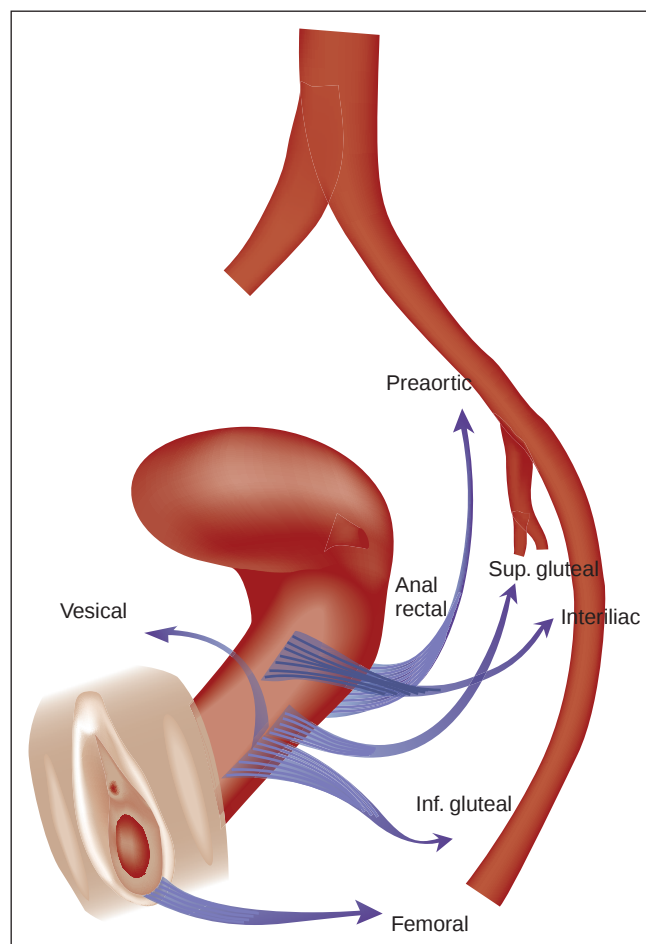


FIGURE 20.1. Lymphatic drainage of the vagina.

Source: Reprinted from Plentl AA, Friedman EA. Lymphatic system of the female genitalia. In: Plentl AA, Friedman EA, eds. *The Morphologic Basis of Oncologic Diagnosis and Therapy*. Philadelphia, PA:WB Saunders; 1971:55, Figure 5-2. Used with permission.

Such a complex lymphatic drainage pattern has significant implications for therapeutic planning. Therefore, bilateral pelvic nodes should be considered at risk in any invasive vaginal carcinoma, and bilateral groin nodes considered at risk in those lesions involving the distal third of the vagina. Although these drainage patterns serve as a general rule, recent data utilizing lymphatic mapping in women with vaginal cancer challenges the established drainage patterns (3). Frumovitz et al. found unexpected lymphatic drainage from primary lesions in the vagina, including 3 of 5 women with lesions located at the introitus that were found to have a sentinel node in the pelvis on pretreatment lymphoscintigraphy, when anatomic site would predict drainage to the inguinal triangle. Conversely, 2 of 4 women who had lesions in the upper third of the vagina were found to have a sentinel node in the inguinofoveal region when anatomic site would predict for involvement of pelvic lymph nodes.

EPIDEMIOLOGY AND RISK FACTORS

Primary vaginal cancer is a rare entity, representing only 1% to 2% of all female genital neoplasias. As cervical squamous cell carcinoma (SCC) is approximately 50 times more common than vaginal SCC, absence of concurrent cervical SCC or a history of cervical SCC within 5 years is usually considered a requirement for a tumor to be considered a vaginal primary, rather than involvement, or recurrence, of a cervical primary (54,55). Most vaginal neoplasms, 80% to 90%, represent metastasis from other primary gynecologic (cervix or vulva) and nongynecologic sites, involving the vagina by direct extension or lymphatic or hematogenous routes.

Creasman et al. (5) published the National Cancer Data Base (NCDB) report in 1998, based on 4,885 patients with primary diagnosis of vaginal cancer registered from 1985 to 1994. Approximately 92% of the patients were diagnosed with *in situ* or invasive SCC or adenocarcinomas, 4% with melanomas, 3% with sarcomas, and 1% with other or unspecified types of cancer. In the NCDB report, invasive carcinomas accounted for 72% of the carcinoma cases, or 66% of all vaginal cancers. *In situ* carcinomas accounted for 28% of invasive vaginal carcinomas, SCC represented 79%, and adenocarcinomas represented 14%. Adenocarcinomas represent nearly all the carcinomas in patients younger than 20 years of age and are seen less frequently with advanced age (5). In a more recent Surveillance, Epidemiology, and End Results program (SEER) study by Shah et al. (6), 2,149 women with primary vaginal cancer were diagnosed between 1990 and 2004. Squamous cell histology represented 65% of all cases, followed by adenocarcinomas 14%, melanoma 6%, and the other category representing the remaining 15% (6).

Carcinoma of the vagina is considered to be associated with advanced age, with the peak incidence occurring in the sixth and seventh decades of life. However, vaginal cancer is increasingly being seen in younger women, possibly due to human papillomavirus (HPV) infection or other sexually transmitted diseases. In the NCDB report, only 1% of the carcinoma patients were less than 20 years old at the time of diagnosis, and over 80% of those patients had *in situ* lesions. As patient age increased, the number of invasive tumors increased, reaching a peak in patients aged 70 to 79 years. The percentage of *in situ* carcinomas decreased to only 11% in patients over 80 years old (5). A decrease in the incidence of primary vaginal tumors has been noted in recent years, possibly because of early detection with cervical cytology or more rigid diagnostic criteria, which have eliminated from this category primary cancers arising from adjacent organs, such as the cervix, vulva, or endometrium.

Vaginal Intraepithelial Neoplasia and Squamous Cell Carcinoma

Potential risk factors for SCC include prior history of HPV infection, cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), immunosuppression, and possibly previous pelvic irradiation. HPV is the likely etiologic agent of SCC and its precursor lesion, vaginal intraepithelial neoplasia (VAIN). However, in contrast to cervical SCC, where almost all tumors contain detectable HPV-DNA, many vaginal SCCs are HPV negative. HPV has been detected in about 80% of VAIN lesions and 60% of invasive SCC of the vagina (7). In a case-control study of VAIN and early-stage cancer of the vagina, Brinton et al. (8) reported a 2.9-fold increase in therapy for genital warts and a 3.8-fold increase in prior abnormal Papanicolaou (Pap) smears in patients with VAIN compared to controls. The process most commonly occurs in the upper vagina, and it is frequently multifocal. Approximately one-half of the lesions are associated with concomitant CIN or VIN (9).

In studies reporting on groups of women with VAIN and SCC of the vagina, the following risk factors have been identified: 5 or more sexual partners, sexual debut before age 17 years, smoking, low socioeconomic status, a history of genital warts, prior abnormal cytology, and prior hysterectomy (7,8). Weiderpass et al., in a population-based study of 36,856 women, found that alcoholic women had an excess risk for cancer of the vagina, probably related to higher incidence of HPV infection associated with lifestyle factors such as promiscuity, smoking, use of contraceptive hormones, and dietary deficiencies (10). Iversen et al. (11) found no positive correlation between cancer of the penis in husbands and gynecologic cancer in their wives.

Patients with previous cervical carcinoma have a substantial risk of developing vaginal carcinoma, presumably because these sites share exposure and/or susceptibility to endogenous or exogenous carcinogenic stimuli. About 10% to 50% of patients with VAIN–carcinoma *in situ* (CIS) or invasive carcinoma of the vagina have undergone prior hysterectomy or radiotherapy (RT) for CIS or invasive carcinoma of the cervix (12–23). The interval from therapy for cervical cancer or preinvasive disease to the development of carcinoma of the vagina averages nearly 14 years, but there have been cases with the vaginal primary manifesting 50 years after therapy for cervical cancer (15,24).

It is controversial as to whether or not prior pelvic RT is a risk factor. Boice et al. (126) reported a 14-fold increased risk of cancer of the vagina in previously irradiated women before the age of 45 years, and a dose–response relationship was found to be significant. However, Lee et al. (25), in an analysis of 1,200 patients treated over a 20-year period at Washington University for carcinoma of the cervix, did not find prior RT to be associated with an increase in the incidence of pelvic second neoplasms. It is biologically plausible that there could be an apparent increase in risk given that prior pelvic RT would have likely been given for HPV-associated cervical carcinoma, and the antecedent HPV infection would increase the risk of SCC in the vagina. Such an association has led to the recommendation that patients treated for CIN or carcinoma of the cervix continue to undergo lifelong surveillance with vaginal cytological evaluation even after hysterectomy (26). In addition, Bornstein et al. (27) reported an incidence of CIN and VAIN after *in utero* exposure to diethylstilbestrol (DES) twice as high as in unexposed women. The putative mechanism is an enlargement of the transformation zone at risk, which is then at risk for infection with HPV (27).

Clear Cell Adenocarcinoma

Adenocarcinomas comprise approximately 14% of primary malignancies at this anatomic site (5,52). Primary adenocarcinomas

of the vagina may be associated with several presumed precursor lesions including adenosis, endometriosis, and mesonephric rests.

Clear cell adenocarcinoma (CCA) related to *in utero* DES continues to receive attention as the prototypical example of disease caused by an endocrine-disrupting chemical (61). The incidence of CCA of the vagina and cervix is increased 24-fold in daughters of women who were exposed to DES *in utero* during the first 16 weeks of pregnancy (28,62). Specific suggested mechanisms of carcinogenesis focus on the retention of nests of abnormal cells of müllerian duct origin, which, after stimulation by endogenous hormones during puberty, are promoted into adenocarcinomas. The median age at diagnosis in the DES-exposed patients is 19 years (28,61), whereas prior to this report, most patients with CCA of the vagina were elderly. The incidence of CCA in the exposed female population from birth to 34 years is estimated to be between 0.14 and 1.4 per 1,000. Approximately 90% of the patients had stage I–II disease at diagnosis and most cases involved the anterior upper third of the vaginal wall. Fortunately, the incidence of this tumor has decreased in recent years, and may decrease even more since the practice of prescribing DES during pregnancy has been discontinued. Palmer et al. (30) assessed the influence of postnatal factors on the development of CCA in women exposed to DES in 244 cases compared with 244 age-matched non-DES-exposed women. Neither oral contraceptive use nor pregnancy was associated with risk of CCA (30).

NATURAL HISTORY OF THE DISEASE (PATTERNS OF SPREAD)

The majority (57% to 83%) of vaginal primaries occur in the upper third or at the apex of the vault, most commonly in the posterior wall; the lower third may be involved in as many as 31% of patients (15,21,33). Lesions confined to the middle third of the vagina are uncommon. The location of the vaginal carcinoma is an important consideration in planning therapy and determining prognosis. Vaginal tumors may spread along the vaginal walls to involve the cervix or the vulva. However, if biopsies of the cervix or the vulva are positive at the time of initial diagnosis, the tumor cannot be considered a primary vaginal lesion. Because of the absence of anatomic barriers, vaginal tumors readily extend into surrounding tissues, such that a lesion on the anterior wall may infiltrate the vesicovaginal septum and/or the urethra; those on the posterior wall may eventually involve the rectovaginal septum and subsequently infiltrate the rectal mucosa. Lateral extension toward the parametrium and paracolpal tissues is not uncommon in more advanced stages of the disease as well as involvement of the obturator fossa, cardinal ligaments, lateral pelvic walls, and uterosacral ligaments.

The issue of regional nodal metastasis, both the incidence of occult nodal disease and the anatomic pathways of lymphatic spread, is somewhat controversial. The incidence of positive pelvic nodes at diagnosis varies with the stage and location of the primary tumor. Because the lymphatic system of the vagina is so complex, any of the nodal groups may be involved, regardless of the location of the lesion (2). Involvement of inguinal nodes is most common when the lesion is located in the lower third of the vagina. There does seem to be a significant risk of nodal metastasis for patients with disease beyond stage I. Although data on staging lymphadenectomy are sparse, 2 studies reported a significant incidence of nodal disease in early-stage vaginal carcinoma. In Al-Kurdi and Monaghan's series (34), the incidence of pelvic nodal metastasis was 14% and 32% for stages I and II, respectively, whereas in the Davis et al. series (24), the incidence was 6% and 26% for stages I and II, respectively. The incidence is expected to be higher for stage

III, although no substantial data are available. Chyle et al. (14) noted a 10-year actuarial pelvic nodal failure rate of 28% and a 16% inguinal failure rate in patients who had local recurrence, in contrast to 4% and 2%, respectively, in the group without local recurrence ($p < 0.001$). The incidence of clinically positive inguinal nodes at diagnosis as reported by several authors ranges from 5.3% to 20% (19,35).

Distant metastasis may occur, primarily in patients with advanced disease at presentation, or those who recurred after primary therapy. In the Perez et al. series (19), the incidence of distant metastasis was 16% in stage I, 31% in stage IIA, 46% in stage IIB, 62% in stage III, and 50% in stage IV. In the largest series reported to date by Hellman et al., distant metastases at diagnosis were rare at 2%, and in 5 of the 7 patients with distant metastases, the tumor involved the entire vagina (36). Robboy et al. reported that metastases to the lungs or supraclavicular lymph nodes represented 35% of recurrences in young women with CCA, a proportion much greater than found with SCC of the cervix or vagina (37).

CLINICAL PRESENTATION

Vaginal Intraepithelial Neoplasia—Carcinoma *In Situ*

VAIN most often is asymptomatic (17). In modern practice, VAIN is usually detected by cytological evaluation performed following hysterectomy as part of a surveillance strategy in patients with a history of CIN or invasive cervical carcinoma. In these cases, VAIN has a predilection for involvement of the upper vagina, likely secondary to a “field effect.” A discharge may be present, but is likely secondary to superimposed vaginal infections. It should be noted that evidence-based guidelines do not support routine cytological studies following hysterectomy for noncervical pathology. The American Cancer Society 2012 guidelines indicated that surveillance cytology in such patients is *not* necessary. Rather, surveillance cytology post hysterectomy should be limited to those patients with a prior history of CIN or invasive cervix cancer (38).

Invasive Squamous Cell Carcinoma

In patients with invasive disease, irregular vaginal bleeding, often postcoital, is the most common presenting symptom followed by vaginal discharge and dysuria. Pelvic pain is a relatively late symptom generally related to tumor extent beyond the vagina (12). In a series of 84 patients with invasive carcinoma, including 55 with SCC, Tjalma et al. noted that 62% of patients had vaginal discharge, 16% had positive cytology, 13% had a mass, 4% had pain, and 2% had dysuria. Forty-seven percent of the lesions were located on the posterior wall and 24% on the anterior wall; 29% had involvement of both walls (39). In 10% to 20% of the patients, no symptoms were reported, and the diagnosis was made by cytological examination.

Other Histologies

The most common presenting symptom in patients with CCA is vaginal bleeding (50% to 75%) or abnormal discharge. More advanced cases may present with dysuria or pelvic pain (26). Cytology is abnormal in only 33% of cases. Therefore, in addition to 4-quadrant cytology, Hanselaar et al. recommended palpation of the entire vaginal vault to assess for submucosal irregularity (40). The majority of CCA lesions are exophytic,

superficially invasive in the upper third of the vault near the cervix.

Embryonal rhabdomyosarcoma, the most common malignant vaginal tumor in children, presents as a protruding, edematous grape-like mass. Ninety percent of these sarcomas present before the age of 5 years. The average age at presentation was 23.5 months in the Maurer et al. series (304). In adults, symptoms most commonly noted were pain accompanied by a mass.

DIAGNOSTIC WORKUP

In general, in patients with suspected vaginal malignancy, thorough physical examination with detailed speculum inspection, digital palpation, colposcopy and cytological evaluation, and biopsy constitute the most effective procedure for diagnosing primary, metastatic, or recurrent carcinoma of the vagina. In symptomatic patients, biopsy of any abnormal exophytic or endophytic lesion noted at the time of the examination is indicated. Examination under anesthesia is recommended for the thoroughness of evaluation of all of the vaginal walls and local extent of the disease, primarily if the patient is in great discomfort because of advanced disease, in order to obtain a biopsy. Biopsies of the cervix, if present, are recommended to rule out a primary cervical tumor. The speculum must be rotated as it is slowly withdrawn from the vaginal fornix, so that the total vaginal mucosa may be visualized, and, in particular, posterior wall lesions, which occur frequently, are not overlooked.

The patient with a history of preinvasive or invasive carcinoma of the cervix found to have abnormal cytology following prior hysterectomy or RT should be offered vaginotomy with application of acetic acid to the entire vault, followed by biopsies as indicated by areas of white epithelium, mosaicism, punctation, or atypical vascularity. It can be very helpful for the menopausal patient or the patient previously irradiated to use a short course of topically applied estrogen (Premarin®) into the vaginal vault once or twice a week for 1 month prior to the colposcopy in order to foster epithelial maturation. Another method of identifying the area(s) most in need of biopsy would be, after application of acetic acid, to apply half-strength Schiller's iodine to determine if the Schiller-positive (nonstaining) areas correspond with the involved areas identified following acetic acid application.

Table 20.1A FIGO Staging System for Carcinoma of the Vagina

Stage	Description
Stage I	Limited to the vaginal wall
Stage II	Involvement of the subvaginal tissue but without extension to the pelvic side wall
Stage III	Extension to the pelvic side wall
Stage IV	Extension beyond the true pelvis or involvement of the bladder or rectal mucosa. Bullous edema as such does not permit a case to be allotted to Stage IV
IVA	Spread to adjacent organs and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

Source: From FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynaecol Obstet.* 2009;105(1):3–4. Used with permission.

STAGING

The 2 commonly used staging systems for carcinoma of the vagina are the International Federation of Gynecology and Obstetrics (FIGO) (Table 20.1A) (43) and the American Joint Commission on Cancer (AJCC) classifications (Table 20.1B) (44). According to FIGO and AJCC guidelines, cases should be classified as vaginal carcinomas only when “the primary site of the growth is in the vagina.” A tumor of the vagina that involves the cervix or vulva should be classified as a primary cervical or vulvar cancer, respectively. It may be difficult or impossible histologically to distinguish a primary vaginal SCC from recurrent cervical or vulvar disease. In this setting, it is unclear whether the vaginal lesion represents a new carcinoma of the vagina, recurrent cervical cancer, or a HPV-related field effect in these

Table 20.1B American Joint Commission on Cancer Staging of Vaginal Cancer

Primary Tumor(T)/FIGO	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis/	Carcinoma <i>in situ</i> (preinvasive carcinoma)
T1/I	Tumor confined to the vagina
T2/II	Tumor invades paravaginal tissues but not to the pelvic wall
T3/III	Tumor extends to the pelvic wall
T4/IVA	Tumor invades mucosa of the bladder or rectum and/or extends beyond the pelvis (Bullous edema is not sufficient to classify a tumor as T4)
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1/III	Pelvic or inguinal lymph node metastasis
Distant Metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1/IVB	Distant metastasis
AJCC Stage Groupings	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1–3 N1 M0, T3 N0 M0
Stage IVA	T4, any N, M0
Stage IVB	Any T, any N, M1

Source: American Joint Committee on Cancer (AJCC). Vagina. In: Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer-Verlag; 2010:469–472. Used with permission.

patients. Therefore, cervical cytology should be obtained, and directed biopsies if indicated based on abnormal cytology. If a cervical abnormality is visualized or palpated, biopsy is recommended to rule out a primary cervical malignancy. Similarly, the vulva should be carefully inspected, including application of acetic acid, with directed biopsies of abnormally staining epithelium.

Additionally, in the setting of a prior gynecologic malignancy, a neoplasm would be classified as primary carcinoma of the vagina if the current vaginal tumor occurred 5 or more years after the initial cancer diagnosis and if there is no other clinical evidence of recurrence of the initial gynecologic lesion (45).

Perez et al. (46) proposed in 1973 that FIGO stage II vaginal cancer should be subdivided into stage IIA (tumor infiltrating the subvaginal tissues but not extending into the parametrium) and stage IIB (tumor infiltrating the parametrium but not extending to pelvic side walls). However, most investigators do not use this classification, and there are few published data to support the prognostic significance of this subclassification (19,47). In addition, FIGO does not assign a specific stage for those patients with inguinofemoral lymphadenopathy. Some authors assign these patients to stage III, whereas others consider them stage IVB. In the AJCC staging system, patients with T1–3 and positive nodes (pelvic or inguinal) are assigned to stage III (44).

At present, primary malignancies of the vagina are all staged clinically. In addition to a complete history and physical examination, routine laboratory evaluations including complete blood cell count (CBC) with differential and platelets, and assessment of renal and hepatic function should be undertaken. In order to determine the extent of disease, the following tests are allowed by International Federation of Gynecology and Obstetrics (FIGO) criteria: chest radiograph, a thorough bimanual and rectovaginal examination, cystoscopy, proctoscopy, and intravenous pyelogram. Cystoscopy and/or proctosigmoidoscopy should be performed on patients with symptoms suggestive of bladder and/or rectal infiltration, respectively. If the patient is in significant discomfort, the examination should be conducted under anesthesia, preferably by a radiation oncologist and gynecologic oncologist who will be involved in her ongoing care. However, it can be difficult even for the experienced examiner to differentiate between disease confined to the mucosa (stage I) and disease spread to the submucosa (stage II) (13,33,48).

Pelvic computed tomography (CT) scan is generally performed to evaluate inguinofemoral and/or pelvic lymph nodes, as well as extent of local disease. In patients with vaginal melanoma or sarcoma, chest, abdomen, and pelvic CT scans are often part of the workup. Magnetic resonance imaging (MRI) has emerged as a potentially important imaging modality in the evaluation of vaginal cancers, predominantly intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images (49). Taylor et al. (49) concluded that MRI identified over 95% of primary vaginal tumors and enabled radiologic staging, which correlated with outcomes. An additional role of MRI is differentiation of tumor from fibrotic tissue in patients with suspected recurrent vaginal carcinoma (50).

Positron emission tomography (PET) is evolving as a modality of potential use in the evaluation of vaginal cancer that allows detection of the extent of the primary as well as abnormal lymph nodes more often than does CT scan. PET/CT was evaluated in a prospective registry study in 23 patients comparing the results of CT and whole-body PET (51). CT visualized the intact primary tumor in 43% of patients as compared to PET, which visualized 100% of all intact primary tumors. Furthermore, all abnormal lymph nodes visualized by CT were also detected by PET, with the addition of 4 additional foci consistent with nodal metastasis found on PET imaging (51).

In modern practice, for the majority of patients with disease volume and/or location requiring definitive RT to achieve

Table 20.2 Pathological Classification

Squamous cell carcinoma and precursors

Squamous cell carcinoma

Variants

Squamous dysplasia/squamous cell carcinoma *in situ*/vaginal intraepithelial neoplasia

Glandular tumors and precursors

Clear cell carcinoma

Endometrioid adenocarcinoma

Serous adenocarcinoma

Mucinous adenocarcinoma

Adenocarcinoma of intestinal type

Mesonephric adenocarcinoma

Metastatic adenocarcinoma

Other epithelial tumors

Adenosquamous carcinoma

Glassy cell carcinoma

Adenoid cystic carcinoma

Small cell (neuroendocrine) carcinoma

Paraganglioma

Mixed epithelial and mesenchymal tumors

Carcinosarcoma/malignant mixed müllerian tumor

Myoepithelial neoplasms

Mesenchymal tumors

Rhabdomyosarcoma (sarcoma botryoides)

Leiomyosarcoma

Gastrointestinal stromal tumor

Solitary fibrous tumor

Synovial sarcoma

Endometrial stromal sarcoma

Malignant peripheral nerve sheath tumor

Angiomyofibroblastoma

Other mesenchymal tumors

Miscellaneous tumors

Melanoma

Yolk sac tumor (endodermal sinus tumor)

Peripheral primitive neuroectodermal tumor/Ewing sarcoma

Wilms tumor

Hematolymphoid tumors

Non-Hodgkin's lymphoma

Leukemia/myeloid sarcoma

cure, therapeutic planning will be guided by disease volume assessment utilizing CT, MRI, and/or PET/CT, even though such radiologic modalities are not “allowed” for purposes of staging.

PATHOLOGIC CLASSIFICATION

Table 20.2 illustrates the current pathologic classification.

SCC and Precursors

SCCs (Fig. 20.2) comprise 67% to 80% of vaginal malignant tumors (52,53). SCCs of various sites are very difficult or impossible to differentiate on either a morphologic or an immunohistochemical basis. Vaginal invasive and *in situ* SCCs both occur with greatly increased frequency in patients with a history of cervical SCC. The standardized incidence ratio, the observed vaginal invasive cancer cases in patients with a history of cervical cancer divided by the number of expected cases based on demographic factors, is 29.9 (54). For vaginal SCC *in situ*, the standardized incidence ratio is 53.8 (54).

In contrast to cervical SCC, many vaginal SCCs are HPV negative. HPV has been detected in 50% to 80% of primary vaginal SCCs (56–59). Type 16 is the most common, present in 33% to 56% of cases (57–59). HPV positive tumors are likely to be associated with a history of previous SCC of the cervix or vulva, while patients with HPV negative carcinomas will usually not have a history of a previous HPV-related carcinoma (59). As in some other anatomic sites, immunohistochemical staining for p16^{INK4A} is highly sensitive (96%) and specific (86%) for the presence of HPV (59).

HPV-related carcinomas are frequently nonkeratinizing and of basaloid or warty subtypes (59). The presence of HPV does not correlate with clinical stage, tumor grade, or tumor size (56). In one study, overall prognosis did not differ significantly between the HPV positive and HPV negative groups (56). Among high stage (FIGO III or higher) patients, however, those positive for HPV had improved disease-free and overall survival (56).

SCCs may be subdivided into keratinizing and nonkeratinizing types and basaloid, warty (condylomatous), and papillary squamotransitional variants have been described (53,55). Basaloid carcinomas are composed of nests of high nucleus-to-cytoplasm ratio cells with very little evidence of squamous differentiation. Warty carcinomas have exophytic growth with papillae with fibrovascular cores and prominent koilocytotic atypia. Papillary squamotransitional carcinomas histologically closely resemble papillary urothelial carcinomas. The prognostic significance, if any, of these variants is not yet established. In a recent study, all the variants evaluated were strongly associated with HPV infection (58).

Verrucous carcinoma is a distinct type of very well differentiated SCC that presents as an exophytic, fungating mass and microscopically has very bland nuclear cytology, usually lacks stromal cores in the papillae, usually lacks koilocytotic atypia, and has a tendency to recur locally rather than metastasize (53,55). It is so well differentiated that it is notoriously difficult to diagnose on small or superficial biopsies that do not allow recognition of the pushing border of the broad epithelial cell nests at the deep aspect of the lesion. These tumors are resistant to radiation treatment and may, following irradiation, appear as a higher-grade SCC, and so treatment is usually surgical (53).

Tumors are graded based on their degree of differentiation, with keratinizing tumors with abundant cytoplasm being considered well-differentiated (grade 1), those with less abundant cytoplasm yet easily recognizable as squamous being considered moderately differentiated (grade 2), and nonkeratinizing tumors that are not easily recognizable as squamous being considered poorly differentiated (grade 3). Squamous carcinomas may have areas of sarcomatoid change, considered a pattern of poorly differentiated carcinoma. Grade is not a significant predictor of prognosis (53,56).

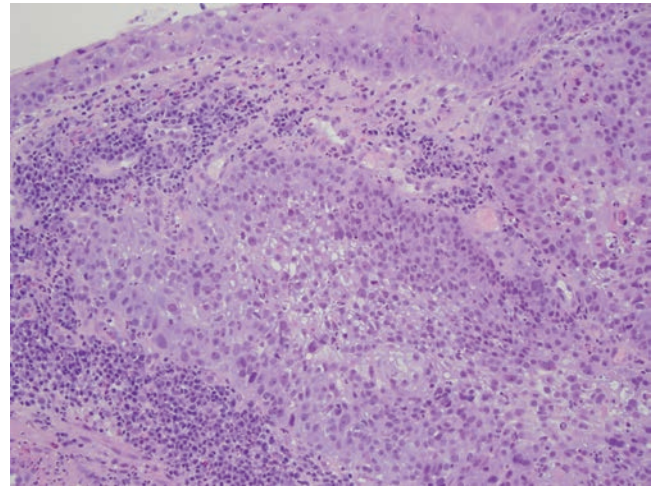


FIGURE 20.2. Primary vaginal squamous cell carcinoma with focal clear cytoplasm. Some examples of squamous cell carcinoma may have focally prominent clear cytoplasm. This should not be mistaken for clear cell carcinoma or other types of adenocarcinoma. There is a dense lymphoplasmacytic infiltrate surrounding the invasive carcinoma and there is overlying dysplastic squamous epithelium.

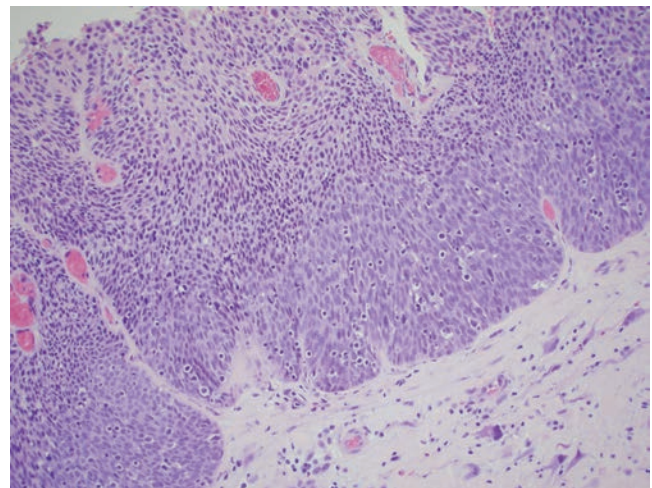


FIGURE 20.3. Vaginal squamous cell carcinoma *in situ* (vaginal intraepithelial neoplasia 3). There is full thickness loss of squamous cell maturation in the form of cells with large, atypical nuclei and very scant cytoplasm extending up to the surface of the epithelium. This patient previously had a cervical adenocarcinoma and was treated with radiation therapy. Stromal cell atypia consistent with the history of radiation treatment, seen as stromal cells with markedly enlarged nuclei and a stellate appearance, can be seen in the lower right corner of the photograph.

The histological diagnosis of VAIN depends on nuclear atypia, loss of squamous cell maturation, and the presence of suprabasilar mitoses in the squamous epithelium of the vagina. Hyperkeratosis, papillomatosis, and atypical mitotic figures are seen in some cases. VAIN is graded on a 3-grade scale similar to cervical intraepithelial neoplasia, based on whether the abnormality is primarily limited to the lower one-third of the epithelium (VAIN1/mild squamous dysplasia), the lower two-thirds (VAIN2/moderate squamous dysplasia), or nearly the full thickness (VAIN3/severe squamous dysplasia/SCC *in situ*) (Fig. 20.3). Human papillomavirus effect/koilocytotic atypia, while seen near the surface of the epithelium, is not considered loss of maturation and is equivalent to VAIN1. Some authors have advocated use of Bethesda System terminology: low-grade

squamous intraepithelial lesion (LSIL) being equivalent to VAIN1 and high-grade squamous intraepithelial lesion (HSIL) being equivalent to VAIN2–3 (55).

VAIN1 is appropriately considered a premalignant lesion as high risk HPV types have been identified in 76% of VAIN1 lesions, with low-risk types in the remainder (60). VAIN2–3 almost always has detectable high risk HPV DNA, with HPV type 16 being the most common type, present in 50% to 54% of cases (55,60). The natural history of untreated VAIN is not well understood, but with treated cases there is an approximately 5% risk of progression to invasive SCC (53).

Glandular Tumors and Precursors

Vaginal CCS (Fig. 20.4) are grossly nodular or polypoid. Microscopically, these tumors are similar to clear cell carcinoma (CCC) of the ovary or endometrium and they are composed of variable sized glands lined by cuboidal epithelium with variable nuclear enlargement and atypia (53). The cytoplasm may be clear due to cytoplasmic glycogen, but this is not a requirement for diagnosis and some cases may have scant or predominantly eosinophilic cytoplasm. Some tumor cells may have large nuclei that protrude into the glandular lumens (“hobnail cells”). A tubulocystic pattern, with variable sized glands, sometimes with areas of flattened epithelium and papillary tufting, is characteristic, but solid and papillary patterns may also be seen (55). Most cases will have associated vaginal adenosis.

The most critical histological differential diagnostic consideration is Arias-Stella reaction (such as in vaginal endometriosis), so patient history concerning the presence or absence of current or recent pregnancy should be obtained. Microglandular hyperplasia, which may occur in adenosis as well as in the endocervix, may also enter the differential diagnosis (53). Vaginal metastases of renal cell carcinoma have been reported with some frequency, sometimes preceding the diagnosis of a renal tumor, and may need to be excluded with immunohistochemical evaluation (53).

Vaginal adenosis, the presence of müllerian-type glandular epithelium in the vagina, is related to prenatal DES exposure

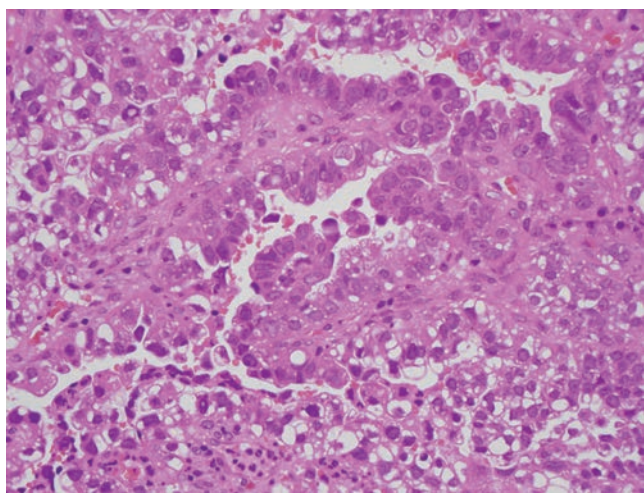


FIGURE 20.4. High magnification view of a vaginal clear cell carcinoma. The characteristic tubulopapillary architecture is seen with glands lined by cuboidal epithelium with prominent scalloped luminal surfaces and nuclei that protrude into the gland lumens (“hobnail nuclei”). There are occasional papillae that extend into the spaces and single tumor cells that appear to lie unattached within the gland lumens. There is high-grade nuclear atypia and marked hyperchromatism in some of the nuclei. Typically, clear cytoplasm is focally present but much of the malignant epithelium has scant or eosinophilic cytoplasm.

and is the precursor lesion for CCC, but can also be seen in non-DES-exposed women. Microscopically, the involved mucosa may have glandular epithelium at the surface or glands in the lamina propria. The glandular epithelium may be mucinous, tuboendometrial (which may be ciliated), or composed of cuboidal embryonic type cells (55). While a risk factor for CCC, most cases will spontaneously regress (55). When adenosis is seen in association with a CCC, the adenosis is likely to be cytologically atypical and of the tuboendometrial type (53).

Primary vaginal adenocarcinomas not associated with DES exposure have a much higher median age at presentation (54 years) than DES-associated cases (63). Prognosis is significantly worse than other primary carcinomas, with a 5-year survival rate of 34%, compared to 58% for SCC (63) and 93% for DES-associated CCC (53).

While endometrioid adenocarcinoma involving the vagina is most commonly of endometrial origin, primary endometrioid adenocarcinoma also occurs. It is the second most common type of primary vaginal adenocarcinoma (after CCC) (64). In one series of 18 cases, the mean patient age was 60 years, 16 patients had previously had a hysterectomy, 14 patients had vaginal endometriosis (a presumed precursor lesion), and none of the patients had a history of DES exposure (64). These tumors have histologic features typical of endometrial endometrioid adenocarcinomas: glandular architecture with columnar cells and flat luminal borders and squamous or mucinous metaplasia in some cases (64). In some cases, papillary architecture may suggest a diagnosis of serous carcinoma or squamous metaplasia with cytoplasmic glycogen may suggest a diagnosis of CCC, but careful attention to the morphology of the glandular areas and the usual presence of associated endometriosis may be helpful in diagnosing endometrioid adenocarcinoma. As primary vaginal adenocarcinomas are much less common than secondary tumors, the possibility of a primary tumor in the endometrium, ovary, and colon must be carefully excluded (64).

Primary serous adenocarcinoma has been reported as a primary tumor in the vagina. Metastasis from the endometrium or ovary must be excluded. CCC is also in the differential diagnosis as it may have papillary architecture and lack clear cytoplasm and may easily be confused with serous carcinoma. A recent carcinoma in a patient with possible *in utero* DES exposure was reported as “grade 2/3 clear cell and focal papillary serous carcinoma,” but not histologically illustrated (65).

Primary vaginal mucinous adenocarcinoma resembling cervical mucinous adenocarcinoma (lacking goblet cells) has been reported following hysterectomy, presumably arising from adenosis or endocervicosis (66). Exclusion of a metastasis, especially from the endocervix, endometrium, or ovary, is necessary to establish this diagnosis.

Very rare cases of primary vaginal adenocarcinoma of intestinal type have been reported (67). These tumors are not related to DES exposure and are composed of mucin-producing malignant glands, often with intraluminal nuclear debris (“dirty necrosis”) (67). Immunohistochemically, these tumors are diffusely positive for CDX-2 and cytokeratin 20, markers of intestinal differentiation (not necessarily origin), so clinical, endoscopic, and radiologic exclusion of origin from a colorectal, endometrial, ovarian, or other primary is necessary to establish this diagnosis (67).

Mesonephric adenocarcinoma, carcinoma thought to arise from the remnants of the mesonephric ducts, is one of the rarest primary vaginal tumors. The mean patient age in one series was 41 years, and the presentation may be a multicystic vaginal mass (68). The tumors histologically are seen as crowded glands or tubules composed of low columnar or cuboidal epithelium containing eosinophilic secretion (69). A variety of patterns may be seen, but the glandular (ductal) pattern is the most common and may closely resemble an endometrioid adenocarcinoma (68). Association with mesonephric remnants, present in the lateral wall of the vagina, or mesonephric hyperplasia, is key

to recognizing a tumor as a mesonephric carcinoma (68). The tumor cells lack clear cytoplasm and staining for mucin and glycogen are negative, but PAS staining may demonstrate basement membrane material around the tubules (55). The immunohistochemical profile, positive for cytokeratin AE1/AE3, cytokeratin 5/6, CD10, vimentin, and calretinin and negative for carcinoembryonic antigen, cytokeratin 20, estrogen receptor protein, and progesterone receptor protein, may be useful for differentiating this tumor from other adenocarcinomas (68,69). The prognosis of these rare tumors is not yet well established, but may be better than that of müllerian adenocarcinomas (68). Some cases may have an associated spindle cell component (malignant mixed mesonephric tumor) and may have heterologous elements such as rhabdomyosarcoma or atypical cartilage (68).

As primary vaginal carcinomas are rare and metastases relatively common, metastatic carcinoma should always be considered in the differential diagnosis of a glandular vaginal tumor. Metastases may be from a number of sites that may have relatively large undiagnosed primary tumors, such as the uterus, ovary, and kidney. Pancreatic carcinoma may also present with vaginal metastases (70). Isolated vaginal metastases of rectal adenocarcinoma have been seen and may respond well to local excision and chemotherapy (71).

Pagetoid adenocarcinoma *in situ* has been seen involving vaginal epithelium, believed to represent direct extension from origin in the cervix (72). The cells are admixed with the squamous epithelium, have pale cytoplasm, and stain immunohistochemically with cytokeratin 7 and p16 (73). Extension of Paget's disease of the vulva into the vaginal epithelium is also a consideration.

Other Epithelial Tumors

Adenosquamous carcinomas compose approximately 2% of primary vaginal carcinomas (55). These tumors are composed of a mixture of glandular and squamous components, lack associated adenosis or endometriosis, and may behave aggressively.

Primary glassy cell carcinoma has been the subject of a single case report (73). Glassy cell carcinoma is considered a variant of poorly differentiated adenosquamous carcinoma with poor prognosis (73). The tumors are histologically composed of nests of cells with abundant eosinophilic or amphophilic cytoplasm with a "ground glass" appearance, prominent cell membranes, large nuclei, and cytoplasmic mucin positivity (73).

Adenoid cystic carcinoma may involve the vagina, but if seen on a biopsy, it is likely to be of Bartholin gland origin and would be considered a vulvar, rather than vaginal, primarily (74). These tumors are composed of nests of basaloid epithelial cells with cribriform architecture with hyaline stroma (composed of basement membrane-like material and mucin) within the rounded spaces. Perineural invasion is commonly seen.

Primary vaginal small cell (neuroendocrine) carcinoma is very rare with fewer than 25 cases reported (75). The mean age at presentation is 59 years and postmenopausal bleeding is the usual presenting symptom (75). Most small cell carcinomas will express a neuroendocrine marker such as synaptophysin. Secondary involvement of the vagina by a cervical or other neuroendocrine carcinoma must, of course, be excluded in order to establish this diagnosis. TTF-1, an immunohistochemical stain often used as a marker of lung or thyroid origin is frequently positive in extrapulmonary small cell carcinomas so immunoreactivity does not prove that a tumor is metastatic at this site. Prognosis is very poor with only about 15% of patients surviving more than 1 year (75). Primary vaginal small cell carcinoma may cause Cushing syndrome due to adrenocorticotrophic hormone production by the tumor (76).

Vaginal paraganglioma is another epithelioid tumor that has been the subject of single case reports (77,78). These tumors have a characteristic nested pattern with round or polygonal cells

with granular eosinophilic cytoplasm, expression of chromogranin and synaptophysin, and absence of expression of keratin AE1/AE3, actin, desmin, and HMB-45 (77,78). Catecholamine hypersecretion is a potential concern during biopsy or surgical treatment (78).

Mixed Epithelial and Mesenchymal Tumors

Carcinosarcoma/malignant mixed müllerian tumor (MMMT) has been reported as a primary vaginal tumor (79). The epithelial component in the reported cases of primary vaginal MMMT is usually SCC (79). Absence of sarcomatoid component keratin staining has been suggested as a criterion for differentiating MMMT (sarcomatoid component keratin negative) from sarcomatoid carcinoma (sarcomatoid component keratin positive) (79). Because the epithelial component is usually squamous and because a recent case was associated with VAIN3 and high-risk human papillomavirus infection (79), it could be argued that these cases likely represent sarcomatoid carcinomas with loss of sarcomatoid component keratin expression.

Myoepithelial neoplasms similar to those more commonly seen in the salivary glands, with oval epithelioid cells with co-expression of keratin and desmin and/or smooth muscle actin, have been reported (80). The examples from the vagina have been benign (80).

Mesenchymal Tumors

Sarcomas represent 3% of primary vaginal cancers. There are several primary mesenchymal tumors that may occur in the vagina and the histologic diagnosis of this group of tumors may be very challenging. There are 2 tumors, rhabdomyosarcoma and leiomyosarcoma, that are of special interest because of their relative frequency at this site. Before establishing a diagnosis of a primary vaginal sarcoma, however, a variety of other lesions with spindle cell morphology must be excluded including sarcomatoid carcinoma, spindle cell melanoma, leiomyosarcoma or endometrial stromal sarcoma of uterine origin, and metastatic sarcoma. Mesenchymal tumors can be grouped as predominantly round cell tumors, spindle cell tumors with high cellularity, and spindle cell tumors with low cellularity.

The most important round cell mesenchymal tumor at this site is rhabdomyosarcoma (also known as sarcoma botryoides), the most common sarcoma of childhood (Fig. 20.5). Genital tract rhabdomyosarcoma may involve the vagina or the cervix and accounts for only 0.003% of genital tract malignancies (81). The median patient age at presentation is 2 years (82), but rare cases may occur in adults (55). Pediatric rhabdomyosarcomas are of embryonal subtype in 95% of cases and the botryoid variant was the most common, 80% of the total cases (82).

The tumors are commonly polypoid (or similar in appearance to a bunch of grapes, leading to the designation "botryoides") and are composed histologically of poorly differentiated tumor cells with overlying benign squamous epithelium. There may be a hypercellular band composed of cells with very little visible cytoplasm immediately deep to the squamous epithelium (cambium layer). Below this, the cellularity is variable and may be sparse with cytologically atypical round or occasionally spindle-shaped nuclei widely spaced in edematous stroma. Mitotic figures are usually frequent and the Ki-67 labeling index is high. Histologically recognizable skeletal muscle differentiation in the form of strap cells is not always seen and is not a requirement for diagnosis. Immunohistochemical staining for desmin and muscle-specific actin (muscle markers) and myoglobin and myogenin (striated muscle markers) may be useful in confirming the diagnosis (53,55).

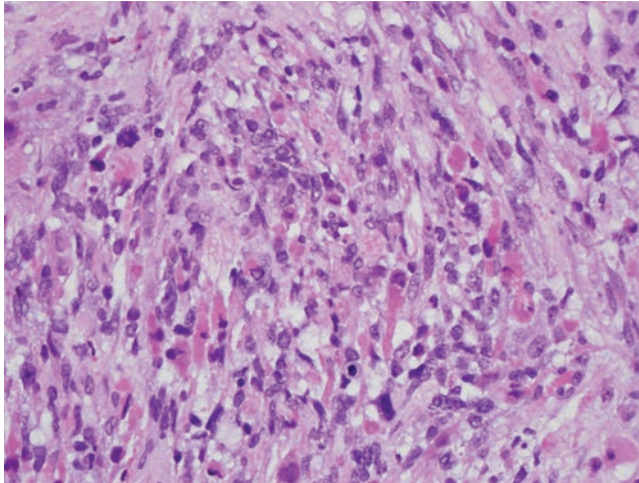


FIGURE 20.5. High magnification view of a primary vaginal rhabdomyosarcoma showing markedly pleomorphic nuclei and occasional cylindrical cells with eosinophilic cytoplasm representing skeletal muscle differentiation (“strap cells”). The patient was an elderly woman who presented with a vaginal mass. An endometrial curettage was negative for tumor, so the tumor was believed to represent a vaginal primary. There was extensive necrosis so it is possible that this tumor is a component of a malignant mixed müllerian tumor, with the epithelial component being unsampled or entirely necrotic.

The highly cellular spindle cell mesenchymal tumors include leiomyosarcoma, gastrointestinal stromal tumor, solitary fibrous tumor, and synovial sarcoma. In some cases, particularly when presented with a small biopsy specimen, immunohistochemical stains may be very helpful in this differential diagnosis. Smooth-muscle neoplasms will stain for actin, desmin, and caldesmon; gastrointestinal stromal tumor for c-Kit/CD117 and CD34; solitary fibrous tumor for CD34 (but not c-Kit/CD117); and synovial sarcoma will sometimes, unusually for a sarcoma, stain for epithelial membrane antigen and/or keratin.

Smooth muscle neoplasms are composed of fascicles of cells with oval to elongated nuclei and eosinophilic cytoplasm. Vaginal smooth muscle tumors may be benign or malignant. Leiomyomas are the most common vaginal stromal tumors, may have a similar presentation compared to leiomyosarcoma, and may enlarge rapidly during pregnancy (55). Histologic criteria have varied over time, but a smooth muscle tumor over 3 cm with 5 or more mitotic figures per 10 high power fields and moderate to marked cytologic atypia should be considered a leiomyosarcoma (53,55). Some leiomyomas from pregnant women may have increased mitotic activity (55).

Leiomyosarcomas are the most common vaginal sarcoma in adults and present most commonly with vaginal bleeding in a patient above the age of 40 (53,55). Histologically, they are similar to the much more common uterine leiomyosarcomas. These tumors invade locally and have hematogenous metastases. Primary treatment is surgical and the 5-year survival of approximately 35% (53).

Gastrointestinal stromal tumors (GIST) may rarely present as a rectovaginal septal mass and in this situation they are likely to be misdiagnosed as a smooth muscle tumor (83,84). Correct diagnosis of this tumor is important because of the malignant potential of this tumor, the lack of effectiveness of conventional chemotherapy and radiotherapy, and because of the existence of specific treatment (Imatinib mesylate) for this tumor (83,84). GISTs in this location are spindle cell tumors with a median mitotic count of 15 per 10 high power fields (83). Immunohistochemical stains for KIT (CD117) and CD34 are positive and stains for desmin and estrogen receptor protein are negative (84).

Primary vaginal solitary fibrous tumors are extremely rare, but have been reported as a single case report (85). These are spindle cell tumors with bland nuclear cytology, disorganized architecture (“patternless pattern”), and dilated branching blood vessels. Immunohistochemical staining for CD34 is positive and staining for muscle markers is either negative or only focally positive (85). Despite the absence of key indicators of malignant behavior in stromal tumors such as mitotic activity and necrosis, recurrence may be seen following excision (85).

Synovial sarcoma, more common in the extremities, has recently been reported in a variety of other sites including the female genital tract (86,87). The tumors may be monophasic with only a highly cellular, mitotically active spindle cell component or they may be biphasic and also have foci of gland-like structures lined by a single layer of cuboidal epithelium (87). Expression of keratin by a spindle cell carcinoma may be helpful in suggesting the diagnosis and molecular genetic demonstration of the X;18 translocation or rearrangement of the *SYT* gene is confirmatory (86,87).

A variety of malignant or potentially malignant mesenchymal tumors, more commonly seen at other sites, may very rarely present as a vaginal mass. Primary low-grade endometrial stromal sarcoma, arising in endometriosis, has been reported (55). CD10 immunoreactivity and absence of staining for muscle markers would be important in establishing this diagnosis. Primary malignant peripheral nerve sheath tumor has been reported, in association with neurofibromatosis, type 1 (88). The reported case was initially misdiagnosed as a smooth-muscle neoplasm, but immunohistochemical staining for S-100 protein and lack of expression of smooth muscle markers, CD10, and HMB-45 helped to exclude a smooth muscle neoplasm, endometrial stromal sarcoma, or spindle cell melanoma (88).

Several spindle cell mesenchymal tumors of lower cellularity may be seen. Within this morphologic grouping of tumors, the major consideration is distinguishing aggressive angiomyxoma from the other, less aggressive, lesions. Aggressive angiomyxoma is an infiltrative neoplasm with frequent local recurrence. The tumor has been clinically mistaken for a vaginal cyst (89). This tumor is characterized grossly by poor circumscription and a gelatinous consistency and histologically by spindle and stellate cells in myxoid stroma and blood vessels of varying size including thick-walled vessels (84, 89). Immunohistochemical staining for estrogen receptor protein, progesterone receptor protein, desmin, and CD34 are positive, but these markers also label the other tumors in this differential diagnosis (84). HMGA2, the product of a transcription factor gene subject to rearrangement in aggressive angiomyxoma, may prove to be useful in the differential vs. the histologically similar lesions (84). Initial treatment is surgical, but treatment of recurrent tumors with hormonal therapy or radiotherapy has also been attempted (89).

Angiomyofibroblastoma and myofibroblastoma are related mesenchymal tumors that may occur in the vulva or vagina and may be related to tamoxifen treatment (90,91). Angiomyofibroblastoma is a circumscribed, nonencapsulated, cytologically bland, spindle cell tumor with variable cellularity, edematous zones, prominent thin-walled vessels, and insignificant mitotic activity (84,90). Stromal lymphocytes and mast cells, multinucleate cells, and tumor cell aggregation around blood vessels may be seen in some cases (84). Immunohistochemical staining for vimentin, desmin, PTEN, CD34, estrogen receptor protein, and progesterone receptor protein are expected to be positive, and that for smooth-muscle actin and S-100 protein will be negative (90). Angiomyofibroblastoma is benign but must be distinguished from the aggressive angiomyxoma (90).

Myofibroblastoma is a spindle cell tumor that arises from the subepithelial stroma of the vagina and is usually not associated with tamoxifen treatment (91). The cells may be ovoid or stellate, are arranged among thick collagen bands, and stain immunohistochemically for vimentin, desmin, and CD99 while

staining for smooth muscle actin is negative (91). These tumors may recur locally, but metastasis has not been reported (91).

Occasional stromal tumors may have epithelioid morphology, composed of round or polygonal cells with abundant cytoplasm in a solid pattern. Once the possibility of a carcinoma, a neuroendocrine tumor (such as carcinoid tumor or paraganglioma), or a melanoma have been excluded, there are a variety of epithelioid stromal tumors that are potential diagnostic possibilities. These include a smooth-muscle tumor or GIST with epithelioid morphology, granular cell tumor, alveolar soft part sarcoma, and perivascular epithelioid cell tumor.

Primary vaginal perivascular epithelioid cell tumor has been the subject of reports of single cases in an adult (92) and in a child (93). These tumors, also known as PEComa, clear cell myomelanocytic tumor, or extrapulmonary clear cell sugar tumor, are composed of sheets of tumor cells with central round nuclei, prominent nucleoli, and abundant eosinophilic or clear cytoplasm (92,93). Pigment production by the tumor may be prominent and the tumors stain immunohistochemically for HMB-45, desmin staining is variable, and they are negative for S-100 protein, keratin, chromogranin, and synaptophysin (92,93). The cellular morphology, pigment, and HMB-45 expression could potentially lead to confusion with melanoma, but the absence of staining for S-100 and variable staining for desmin may be helpful.

Miscellaneous Tumors

Primary vaginal malignant melanomas comprise 3% to 8% of primary vaginal malignant tumors (52,55). In the NCDB report by Creasman et al. (5), vaginal melanomas represented 4% of primary vaginal cancers. Trimble's examination of the Surveillance, Epidemiology, and End Results (SEER) data on 30,295 melanomas found 51 vaginal melanomas (0.3% of all melanomas), with an annual incidence of 0.026 per 100,000 (32). They most commonly present with vaginal bleeding, usually involve the distal one-third of the vagina, and have a mean age at presentation of 61 years (94). The tumors are commonly nodular, ulcerated, and pigmented, but they may also be amelanotic (55). Microscopically, melanomas may have rounded, epithelioid cells or be composed of spindle-shaped cells. Adenocarcinoma or poorly differentiated squamous carcinoma (in the case of melanomas with rounded cells) or sarcoma or sarcomatoid carcinomas (in the case of spindle cell melanoma) may be differential diagnostic considerations and immunohistochemical staining for S-100 protein, HMB-45, and MelanA are often helpful in confirming the diagnosis of melanoma. Excluding metastatic melanoma may be difficult, but the presence of an extensive lateral junctional component would favor a primary melanoma (53) and a history of melanoma elsewhere would certainly raise the possibility of metastasis.

Clark's level, assigned based on histologic levels in the skin, is not appropriate at this site, but depth of invasion (measured in mm) should be reported. Almost all cases are greater than 2 mm in depth (53). In a recent series of stage I cases, the median tumor size was 3.0 cm and the median depth of invasion was 7 mm (94). Of the patients surgically treated with lymph node dissection, 25% had positive pelvic or inguinal lymph nodes (94). The reported prognosis is worse than that of cutaneous melanoma, with 5-year survival rates of 5% to 20% for vaginal melanoma (53,55).

The vagina is the primary site of rare pediatric extragonadal yolk sac tumors. These tumors (also known as endodermal sinus tumor) may clinically present similarly to rhabdomyosarcoma, with a friable polypoid mass associated with vaginal bleeding in a child (95,96). Most of the reported tumors have been in patients 4 years of age or younger (53). Serum α -fetoprotein elevation may be helpful in suspecting the diagnosis. Histologically,

these tumors may have a variety of histologic patterns, but a mesh-like microcystic pattern with hyaline globules is commonly seen (96). Reticular, solid, and papillary patterns, sometimes with columnar cells surrounding a fibrovascular core (Schiller-Duval bodies) may also be seen (53,96). Immunohistochemical staining for α -fetoprotein may be helpful if positive, but is poorly sensitive. Glypican 3 and SALL4 are newer, more sensitive, markers for yolk sac tumor that have recently been used investigated at other sites and may also be useful for vaginal yolk sac tumor (97–99). Correct diagnosis is critical as these tumors respond well to platinum-based chemotherapy and surgical treatment may not be necessary (95).

Along with rhabdomyosarcoma (see above) and hematolymphoid neoplasms (see below), a few rare sarcomas are possible considerations in the small round cell tumor differential diagnosis. Peripheral primitive neuroectodermal tumor and Ewing sarcoma are considered related neoplasms that show neuroectodermal differentiation and share characteristic chromosomal translocations, usually t(11;22), which result in fusion of the *EWSR1* and *FLI-1* genes (100). These are very rare tumors, which usually present in young adults (100,101). Histologically, the tumors are lobulated at low magnification with solid cellular aggregates separated by fibrous septae. At high magnification, the tumor cells have relatively uniform hyperchromatic nuclei and scant to moderately abundant eosinophilic cytoplasm. Squamous and glandular differentiations are not seen and only a minority of cases will have rosette formation by the tumor cells (100). Immunoreactivity for *CD99* and *FLI-1*, absence of staining for muscle markers, and molecular identification of the characteristic t(11;22) are confirmatory (100,101). Reverse transcriptase polymerase chain reaction or fluorescent *in situ* hybridization molecular studies are considered the “gold standard” for the diagnosis of these tumors (100).

A single case of primary vaginal extrarenal teratoid Wilms tumor (nephroblastoma) has recently been reported (102). This tumor had areas of undifferentiated malignant cells (blastoma component), but the spindle cell and epithelial/tubular component typical of Wilms tumor were also present along with heterologous cartilage, skeletal muscle, squamous epithelium, and mucinous epithelium (103).

Hematolymphoid Tumors

Primary non-Hodgkin's lymphoma of the female genital tract is rare, less than 1% of extranodal lymphomas, but secondary involvement in advanced lymphoma is significantly more common. The mean patient age is approximately 52 years and patients may present with a mass, vaginal bleeding, or urinary symptoms (104). Lymphoma limited to the vagina has been the subject of occasional case reports and may clinically closely mimic a carcinoma (105,106). Very rare reports of other tumors such as plasmacytoma and eosinophilic granuloma also exist (55).

Correct preoperative diagnosis of extranodal non-Hodgkin's lymphomas is essential to avoid radical surgery and allow specific treatment. “B symptoms” such as fever, weight loss, night sweats, and fatigue are usually absent (105). The differential diagnosis may include inflammatory conditions and a variety of tumors that may have inconspicuous cytoplasm including small cell carcinoma, melanoma, endometrial stromal sarcoma, and primitive neuroectodermal tumors (104). The tumors may be diffuse large B-cell lymphomas or follicular lymphomas (104,105). One recently reported case of primary vaginal diffuse large B-cell lymphoma was associated with immune thrombocytopenic purpura (107).

Myeloid sarcoma, a tumor composed of malignant myeloblasts, is also known as granulocytic sarcoma and chloroma. These tumors may present as a vaginal mass in the absence of a history of acute myeloid leukemia (AML), although patients

presenting with myeloid sarcoma will generally progress to AML relatively rapidly (108). Histologically, the tumors are composed of small to intermediate size cells with scant cytoplasm, fine chromatin, and frequently with crush artifact (108). Immunohistochemical staining for keratin and neuroendocrine markers, muscle markers, melanoma markers, and B- and T-cell markers will be negative (108). Myeloperoxidase, lysozyme, CD43, and CD68 are among the useful positive markers for this potentially difficult to diagnose neoplasm (108).

PROGNOSTIC FACTORS INFLUENCING CHOICE OF TREATMENT

Invasive SCC

As with most primaries, stage of disease is the dominant prognostic factor in terms of ultimate outcome (14,16,18,19,35, 109–120). In Perez's series, including 212 patients with primary vaginal carcinomas treated with definitive RT, the 10-year actuarial disease-free survival was 94% for Stage 0, 80% for Stage I, 55% for Stage IIA, 35% for Stage IIB, 38% for Stage III, and 0% for those with Stage IV (35). In a recent SEER analysis of over 2000 patients by Shah et al., the 5-year disease-specific survival was 84% for stage I, 75% for stage II tumors, and 57% for women with advanced disease (121).

The impact of lesion location has been controversial. Several investigators (14,23,122,123) have shown better survival and decreased recurrence rates for patients with cancers involving the proximal half of the vagina when compared with those in the distal half or those involving the entire length of the vagina. Tarraza et al. (124) reported that upper-third lesions develop local recurrences more frequently, and lower-third lesions develop a disproportionate number of sidewall and distant recurrences. Chyle et al. (14) observed a 17% rate of pelvic relapse in patients with upper vaginal tumors, 36% in those with middle or lower vaginal tumors, and 42% with whole-vaginal involvement. However, a larger series failed to note any difference in site of recurrence based on primary lesion location (3,35). In addition, lesions of the posterior wall have a worse prognosis than those involving other vaginal walls (10-year recurrence rates of 32% and 19%, respectively) (14), which probably reflect the greater difficulty of performing adequate brachytherapy procedures in this location.

The prognostic importance of lesion size has been controversial, with an adverse impact noted with increasing size on multivariate analysis in several series (14,16,39,117,121) contrary to Perez et al.'s (3,35) findings. In the Chyle et al. series (14), lesions measuring less than 5 cm in maximum diameter had a 20% ten-year local recurrence rate compared to 40% for those lesions larger than 5 cm. Similarly, in the Princess Margaret Hospital experience, tumors larger than 4 cm in diameter fared significantly worse than smaller lesions (16). In the Perez et al. series (35), stage was an important predictor of pelvic tumor control and 5-year disease-free survival, but the size of the tumor in stage I patients was not a significant prognostic factor. However, in stage IIA disease, lower pelvic tumor control and survival were noted with tumors larger than 4 cm. In stages IIB and III, tumor size was not a significant prognostic factor, probably related to the difficulty in assessing size and the fact that higher doses of RT were delivered for larger tumors. Stock et al. (21) reported that disease volume, a likely surrogate for stage or lesion size, adversely impacted survival as well as local control.

Age has also been reported as a significant prognostic factor with increasing age correlating with poorer survival (23,117,125). In the Urbanski et al. series (23), the 5-year

survival was 63.2% for patients below the age of 60 years compared with 25% for those over 60 years of age ($p < 0.001$). Similar findings were reported by Eddy et al. (113) and in the NCDB of the American College of Surgeons (5), showing better survival in younger patients (90% versus 30%, respectively). However, most of these series do not correct for death secondary to intercurrent disease in the elderly population. No statistical significance of age to survival was found in the series of Dixit et al. (114) and Perez et al. (35).

With regard to the histological type and grade, several series (16,123,126) have shown the histological grade to be an independent, significant predictor of survival. However, the histology of the tumor (SCC vs. other) has not been found to be a prognostic factor for survival among the patients with invasive tumors. Chyle et al. (14) noted a higher incidence of local recurrence in patients with adenocarcinoma compared with SCC (52% and 20%, respectively, at 10 years), as well as a higher incidence of distant metastases (48% and 10%, respectively), and lower 10-year survival rate (20% vs. 50%). A report by Frank et al. (63) compared outcome of patients with non-DES-associated adenocarcinoma of the vagina to that of patients with SCCs. They found a 5-year overall survival rate of 34% in the adenocarcinoma group compared to 58% for the patients with SCC ($p > 0.01$) (63).

An increased propensity for distant metastases to the lung and supraclavicular nodes has been reported in patients with CCA (37). Stage, tubulocystic pattern, size less than 3 cm, and depth of invasion less than 3 mm were all noted to be associated with superior survival (40).

Vaginal melanoma has a higher propensity for development of distant metastases, and affected patients do more poorly than patients with SCC. A review by Reid et al. of 115 vaginal melanoma patients noted that depth of invasion and size of lesion (>3 cm) adversely impacted survival, but stage did not, perhaps because it was known for only 42 of the 115 patients in the series. (31) Patients with malignant mesenchymal tumors of the vagina do worse than those with invasive SCC due to a higher propensity for development of local recurrence and distant metastases. Specific, adverse prognostic factors for vaginal sarcoma identified by Tavassoli and Norris (127) included infiltrative versus pushing borders, high mitotic rate of 5 or more mitoses per 10 HPFs, size greater than 3 cm in diameter, and cytological atypia. However, in a SEER analysis by Shah et al. (121), there was no difference in 5-year disease specific survival between all histological types, although vaginal melanoma was associated with an increased risk of mortality in their multivariate model (HR 1.51).

Overexpression of *HER2/neu* oncogenes in squamous cancer of the lower genital tract is a rare event that may be associated with aggressive biologic behavior (128). Waggoner et al. (129), in a group of 21 women with CCA of the vagina and cervix, observed a more favorable prognosis in gynecologic tumors with an overexpression of wild-type p53 protein than in tumors containing mutated *TP53* genes.

Lymph node metastasis at diagnosis portends a poor prognosis. However, this has not been extensively evaluated in vaginal cancer. The only report of outcome based on lymph node status is by Pingley et al. (130). They reported a 56% DFS for patients without lymph node involvement and 33% for those with metastatic lymphadenopathy at presentation.

In a recent series by Tran et al., which included only invasive SCC, prior hysterectomy as well as normal pretreatment/treatment hemoglobin levels were favorable prognostic factors on multivariate analysis in the treatment of vaginal cancer (119). In their review, it is recommended to consider transfusion with packed red blood cells to maintain normal hemoglobin levels as this approach has had some success in cervical cancer patients. Possible explanations for improved outcomes in women with previous hysterectomies included possible increased surveillance

with detecting vaginal cancer at an earlier stage, or simply less vaginal substrate for tumorigenesis to occur within (119). Chyle et al. (14) and Hellman et al. (117) also found that previous hysterectomy had more favorable outcome; however, this result did not hold up on multivariate analysis.

GENERAL MANAGEMENT: TREATMENT OPTIONS AND OUTCOME BY FIGO STAGES

Owing to its rarity, data concerning the natural history, prognostic factors, and treatment of vaginal carcinoma derive from small, single institutions, retrospective studies. Most of the currently available literature in terms of radiotherapeutic and surgical techniques refers to primary SCC of the vagina. It is important to recognize the complexity of the management of patients with carcinoma of the vagina and the need for an individualized approach after careful assessment by the gynecologic oncologist and radiation oncologist. With adequate therapy, the survival rates of patients with carcinoma of the vagina are comparable with those reported for carcinoma of the cervix, which range from 20% to 80% at 5 years, depending on stage of the disease (15,20,33,47,123,131). Perez et al. (4) noted a somewhat higher incidence of pelvic failures in patients with carcinoma of the vagina compared with 1,054 patients with invasive cervical carcinoma, although the differences are not statistically significant. Creasman et al. (5), in the NCDB report based on 4,885 patients with primary vaginal cancer, found the survival rate at 5 years to be 96% for stage 0, 73% for stage I, 58% for stage II, and 36% for stages III and IV. In addition, survival was better in the younger patients (90% vs. 30% in the older patients).

In most patients, the primary treatment modality is RT, as reported by the Society of Gynecologist Oncologists in practice guidelines published in 1998 (5). However, several surgical series have reported acceptable to excellent outcomes in well-selected patients, with survival rates after radical surgery for stage I disease ranging from 75% to 100% (5,13,24,33,39), although few studies directly compare the 2 treatment modalities. The SEER analysis by Shah et al. (121) showed that among women with stage I disease, those treated with RT only or RT and limited surgery or no treatment, had worse outcome than those treated with surgery alone (generally involving radical or exenterative procedures). However, only women with stage I disease who received no treatment had a statistically significant increased risk of mortality (HR 2.23; 95% CI, 1.01–5.03).

Local excision and partial and complete vaginectomy have given way to a more individualized approach that takes into consideration the patient's age, the extent of the lesion, and whether it is localized or multicentric. There is evidence that patients with CIS-VAIN and early stage I, primarily with a lesion located in the apex and upper third of the posterior and lateral walls of the vagina or distal third of the vagina, and highly selected women with stage II vaginal cancers can be successfully treated with surgery alone (13,21,24,39,132,133). These patients could be approached with radical hysterectomy, upper or partial vaginectomy, and pelvic lymphadenectomy, provided that adequate margins are obtained (13,15,21,24,33). If the margins are found to be close or positive after resection, adjuvant RT is recommended. In addition, surgery could be considered in younger patients with a desire to preserve ovarian function (134) and/or a functional vagina (21), patients with verrucous carcinoma (135), those with nonepithelial tumors, and patients with localized pelvic failures after radiation.

For the most part, surgical resection often requires a radical approach, resulting in urinary and fecal diversion in order to secure adequate margins (13,33). For those patients, definitive RT

has largely replaced surgery as primary therapeutic modality, in order to maximize cure and improve quality of life, with isolated central failures offered exenteration (33). Even in patients with early stage I invasive tumors involving the middle or upper third of the vagina, surgical treatment requires radical vaginectomy and pelvic lymph node dissection. Frequently the patient has undergone previous hysterectomy, but if the uterus is still present, concurrent hysterectomy may be necessary to achieve adequate margins. Lindeque (305) pointed out that most tumors require removal of the full length of the vagina, although in localized lesions a partial colectomy may be performed. Although radical surgery in the past precluded vaginal function, this has improved significantly by the use of split-thickness grafts and myocutaneous flap (136). Gracilis myocutaneous flaps and rectus abdominis myocutaneous flaps have been commonly used for neovaginal reconstruction following radical pelvic surgery, with superior results noted in those undergoing rectus abdominis reconstruction (136).

Given the potentially devastating functional results often associated with radical surgery, definitive RT has largely replaced surgery as the primary therapeutic modality in patients with vaginal cancer, in order to maximize cure and improve quality of life. Furthermore, most patients are elderly, and a radical surgical approach is often not feasible. Despite the acceptance of RT as the treatment of choice for this disease, the optimal approach for each stage is not well defined in the literature. A combination of limited surgery and RT has been suggested to improve outcome, although the complication rates may increase (137). Frank et al. (48) suggest that radiation treatment be individualized with the optimal treatment approach selected according to the tumor size, tumor site, extent of disease, and response to initial RT. Intracavitary and interstitial irradiation is used in small superficial stage I disease. External beam RT (EBRT) in combination with intracavitary (ICB), and/or interstitial (ITB) brachytherapy is generally used for more extensive stage I-II disease. Data regarding the use of cytotoxic therapy in vaginal carcinomas are based on underpowered phase II trials of various monotherapies or extrapolated from SCC of the cervix, which has a similar biology.

FIGO Stage 0: Vaginal Intraepithelial Neoplasia—Carcinoma *In Situ*

VAIN has been approached both surgically and medically by multiple investigators. Treatment options range from partial or complete vaginectomy to more conservative approaches such as local excision, electrocoagulation, laser vaporization, topical 5% fluorouracil (5-FU) administration, or ICB. For patients in whom invasive disease cannot be ruled out, as well as for those who fail conservative therapy, surgical resection remains the treatment of choice. Overall, the reported control rates are very similar among the different approaches, ranging from 48% to 100% for laser (138–140), 52% to 100% for colectomy (5,132,133,141), 75% to 100% for topical 5-FU (142–145), and 83% to 100% for RT (14,16,131), (Table 20.3) (5,14,16,35,131–133,140–145). The degree of VAIN and the age and general health of the patient are important treatment considerations. A therapy appropriate for CIS in a woman with good performance status and many anticipated years of life expectancy may not be appropriate for a woman with multiple comorbidities who may succumb to one of her other illnesses before the CIS would be expected to progress to invasive carcinoma.

The anatomic constraints posed by the location of the vagina with the close proximity of the bladder and rectum led to the use of the CO₂ laser as a relatively noninvasive surgical approach (139,140). Data published by Hoffman et al. (133), who performed upper colectomy in 32 patients, of whom 31 had

Table 20.3 VAIN—Carcinoma *In Situ*: Treatment Approach and Results

Treatment Modality, Author(s)	No. of Patients	Comments	Outcome Local Control
Laser Therapy			
Julian et al. (140)	10	Used to effect colpectomy	80%
Hoffman et al. (139)	26	3 of 11 failures had invasive disease Recommended excision. Not ideal	58%
Topical 5-FU			
Woodruff et al. (145)	9	1%–2% 5-FU q month	88%
Piver et al. (144)	8	20% 5-FU bid × 5 d Could use 5% or 10%	75%
Petrilli et al. (143)	15	5% 5-FU bid × 5 d Repeat in 12 wk	80%
Krebs (142)	31	One-third applicator q wk × 10 wk	81%
Surgical Excision			
Creasman et al. (NCDB) (5)	23		96%
Fanning et al. (132)	15	Used LEEP, 1 patient had cancer	100%
Robinson et al. (141)	46	CUSA—29 primaries CUSA—17 recurrent	66% 52%
Hoffman et al. (133)	32	28% invasive cancer out of 23 with VAIN	83%
Irradiation			
Chyle et al. (14)	37		83%
Kirkbride et al. (16)	14		100%
Perez et al. (131)	20		94%

5-FU, 5-fluorouracil; bid, twice a day; CUSA, Cavitron ultrasonic aspirator; LEEP, loop electrosurgical excision procedure; NCDB, National Cancer Data Base.

undergone prior hysterectomy and 14 prior therapy for VAIN, and found a 28% risk of invasive disease, in addition to reports of invasive disease in the laser failures, and in patients who had undergone upper colpectomy for presumed VAIN, prompted some to begin to use the laser to effect colpectomy (140). Later series have used novel approaches with the Cavitron ultrasonic aspirator (CUSA) (141) to effect partial colpectomy with satisfactory results, at least in the reporting investigator's hands. In a series of 52 patients reported by Diakomanolis et al., in which 28 underwent laser and 24 had partial colpectomy, results were found to be operator dependent, but they favored partial colpectomy for unifocal disease and laser ablation for multifocal disease (138). Overall, the control rates following laser vaporization range from 58% to 100% (139,140). Patients most likely to fail after vaporization are those with anatomic distortion caused by scarring (133). In general, patient acceptance is high and scarring is minimal (146).

Even though partial colpectomy has many advocates for focal VAIN without any prior history of pelvic RT, patients who had received prior pelvic RT for other gynecologic malignancies, wherein partial colpectomy would have high risk of fistula formation, may benefit from a medical approach with topical application of 5-FU. This creates a desquamation of the vaginal squamous epithelium, which later reepithelializes with presumably normal cells. Multiple schedules have been suggested since the first use of 5-FU, including monthly, daily, twice a

day, and weekly administrations, with control rates ranging from 75% to 88% (142,144,145,147). However, we prefer the schedule suggested by Krebs et al. of one-third applicator weekly for 10 weeks (142). It is important that the perineal skin be protected with a topical ointment such as zinc oxide to prevent painful vulvar erosions regardless of which 5-FU application schedule is chosen. More recently, investigators have demonstrated the feasibility and likely efficacy of Imiquimod (Aldara®) in the treatment of VAIN, although large series remain to be performed (148). In the study by Haidopoulos et al., 6 out of 7 patients with high-grade dysplasia (VIN 2–3) regressed to either no evidence of dysplasia or VIN 1 following Imiquimod treatment (148). Application of 0.25 g of Imiquimod 5% intravaginally once weekly for 3 weeks was effective and well tolerated. Larger studies are required, but this regimen appears to be promising, with a simpler dosing regimen, and lower toxicity when compared to 5-FU (148).

Partial or total vaginectomy has been considered by many to be an acceptable treatment for VAIN (127). However, one of its main drawbacks is shortening or stenosis of the vagina, frequently with poor functional results. Hoffman et al. (133) reported a 17% recurrence rate in a series of 32 patients with CIS of the vagina who underwent upper vaginectomy. In this series, 44% had received prior therapy, including laser vaporization, or topical 5-FU and local excision. Nine patients (28%) were found to have invasive cancer upon final pathologic examination. Four

of 9 patients with invasive carcinoma showing more than 3.5-mm infiltration were treated subsequently with RT, 3 of these patients remained free of disease. Of the 5 patients with less than 2 mm invasion, 1 received RT for local recurrence, and the remaining 4 patients were without disease after surgery alone. Overall, 5 of 9 patients with microinvasive carcinoma required RT in addition to surgery, and only 72% of all patients treated with surgery remained free of disease at last follow-up. Of 23 patients with VAIN 3, 19 (83%) remained without evidence of recurrence at a mean follow-up of 38 months. Hoffman et al. (133) advocated upper vaginectomy with 1 cm margins when there were concerns about possible invasion, and when the lesion was confined to the upper one-third or one-half of the vagina. To minimize postoperative stenosis, they (133) recommend not closing the mucosa, using a dilator with estrogenic vaginal cream, and consideration of a skin graft. Prior RT is probably a contraindication to vaginectomy owing to significantly increased morbidity. Control rates of 66% to 100% following partial colectomy effected with a traditional surgical approach (133,149), with CUSA (141), or with the loop electrosurgical excision procedure (LEEP) (132) have been achieved.

Radiation therapy has a long history of documented efficacy with control rates ranging between 80% and 100%, and a significantly better therapeutic ratio than other modalities (14,16,18,35,47,150). Using conventional low-dose-rate (LDR) ICB techniques, the entire vaginal mucosa should receive between 50 and 60 Gy, given the high incidence of multicentricity; the area of involvement should receive 70 to 80 Gy, in 1 or 2 implants, prescribed to the mucosal surface (131). Higher doses may cause significant vaginal fibrosis and stenosis. Perez et al. reported only 1 distal local failure in the 20 patients treated for CIS (131). Pelvic recurrences or distant failures have not been observed in the absence of invasive component, after ICB (44,131,151).

There have been some reports in the literature regarding the use of high-dose-rate (HDR) ICB for patients with VAIN 3. Ogino et al. (152) reported 6 patients treated with HDR to a mean dose of 23.3 Gy (range, 15 to 30 Gy), none of whom developed recurrent disease. Limited rectal bleeding and moderate to severe vaginal mucosa reactions were noted in patients treated to the entire length of the vagina. MacLeod et al. (153) reported on 14 patients with VAIN 3 treated with HDR-ICB to a dose of 34 to 45 Gy in 4.5- to 8.5-Gy fractions. With a median duration of follow-up of 46 months, 1 patient had persistent tumor and another showed progression of tumor with an overall local control of 78.5%; 2 patients developed grade 3 vaginal toxicity. Mock et al. (154) reported 100% recurrence-free survival in 6 patients with CIS treated with HDR-ICB. At the present time, no definite conclusions can be drawn from the limited data published in the literature regarding the use of HDR-ICB. Based on the excellent local control and functional results obtained with LDR-ICB, this remains, in our opinion, the treatment of choice when definitive RT is used.

Estrogen therapy should be considered in women who are postmenopausal or have undergone RT, provided the possibility of invasive disease has been eliminated. The effect of irradiation on ovarian function, as well as occasional fibrosis of the vaginal vault, makes this treatment currently unacceptable except in cases resistant to conservative therapy.

Invasive SCC

Surgical Approach and Outcomes

In general, SCC of the vagina has been treated with RT. However, several surgical series have reported acceptable to excellent outcomes in well-selected patients, with survival rates

after radical surgery for stage I disease ranging from 75% to 100% (5,14,21,24,33,39). Cases in which surgery may be the preferred treatment include selected stage I-II patients, with lesions at the apex and upper third of the posterior or lateral vagina that could be approached with radical hysterectomy, upper vaginectomy, and pelvic lymphadenectomy providing adequate margins (10,12,18,21) and very superficial lesions that may be removed with wide local excision. Lesions in the lower third of the vagina would require vulvovaginectomy in addition to dissection of inguinofemoral nodes or even exenteration to achieve negative margins (13,15,21,33). If the margins are found to be close or positive after resection, adjuvant RT is recommended. However, for lesions at other sites, and those cases requiring more extensive resection, definitive RT is the treatment of choice since it offers excellent results (4), with isolated central failures postirradiation being offered exenteration (33).

Creasman et al., in a review of the NCDB for cancers of the vagina, noted superior survival in those patients undergoing surgery (5). However, they and Tjalma et al. (39) recognized that there may be bias in surgical series, such that younger, healthier patients with better performance status are more likely to be offered radical surgery, whereas older patients with multiple comorbid medical conditions are offered RT.

Ball and Berman's series (13) included 58 patients: 27 stage I and 18 stage II disease. Twenty-seven patients were managed primarily with surgery, with an overall 78% 5-year survival rate, 84% in patients with stage I, and a 63% rate in those with stage II disease, which is comparable to the results reported by Perez et al. in their RT series (4,35). Rubin et al. (33) reported 75 cases of vaginal cancer: 14 patients with stage I and 35 patients with stage II. RT was the primary modality used in this series; however, 8 patients (5 with stage I and 3 with stage II) underwent primary surgery with curative intent. Six of these 8 patients survived 5 years, and the local control rate for stage I patients was 80%. However, only 1 patient with stage II was a long-term survivor. This surgical outcome compares unfavorably with the remaining patients in whom RT was the primary modality. In general, patients with lesions that could be encompassed by radical vulvovaginectomy with or without hysterectomy did better than those requiring exenteration. Rubin et al. (33) advocated that exenteration should be reserved for those with central failure after RT, or as primary therapy in those with disease not fixed to the bone. Davis et al. (24) reported on 52 patients with cancer of the vagina treated with surgery alone in a series that included 89 cases. In this nonrandomized series, an 85% 5-year survival rate was achieved in stage I patients compared to 65% in those treated with RT (24). Of 45 patients with stage II disease, 49% survived after surgery, 50% after RT, and 69% after surgery and RT.

The Peters et al. series (110) included 86 vaginal carcinomas, with an overall survival rate of 56%. Most were treated with RT. However, 12 highly selected patients had surgery, with a 75% survival rate. The investigators suggested that vaginectomy with radical hysterectomy, if the uterus was still in place, should be limited to those with superficial disease because the closeness of the bladder and rectum limited the true radicality of surgical approaches. Gallup et al. (15) reported 28 cases, of which 57% were stage I to II lesions (only 3 patients had stage II), and of these, 83% survived. Most patients in this series received RT; however, all 3 patients with stage I disease who were treated with surgery survived. Extent of surgery and median follow-up were not stated.

In the largest single-institution series reported to date by Stock et al. (21), of 100 patients with carcinoma of the vagina (including 85 with SCC), a 47% 5-year survival rate was achieved. In this series, 40 patients were treated with surgery alone, 47 with radiation alone, and 13 with combination

therapy. Overall, 5-year survival was 47%. Survival for stage I patients was 56% when treated with surgery versus 80% for those who received RT, whereas for stage II patients, the survival rates were 68% and 31% after surgery and RT, respectively (21). The investigators acknowledged that the apparent surgical superiority for stage II patients may have been due to selection bias in that those treated with RT alone were more likely to have had stage IIB disease with extensive paracolpos involvement, and those with lesser involvement were preferentially offered surgery. Stock advocated RT for stage II patients with extensive paracolpos. Stock et al. concluded that for upper-third vault lesions, radical hysterectomy and pelvic lymphadenectomy with upper vaginectomy should be offered to those with stage I lesions, with a consideration for wide local excisions, and postoperative RT for patients with small lesions. If there was extension to the paracolpos, RT should be recommended; however, in very well-selected patients, there might be a role for surgery (21).

Tjalma et al. reported on 55 cases of SCC of the vagina, including 27 cases with stage I and 12 with stage II disease, with a median follow-up of 45 months (39). Of the 27 cases with stage I disease, 26 underwent surgery, and 4 of them received some form of postoperative RT. A 91% 5-year survival rate was achieved for stage I disease. Surgery was a part of the primary management for 6 of the 12 patients with stage II disease. In the multivariate analysis, age and lesion size were the only prognostic factors. Tjalma et al. concluded that surgery should be considered part of the therapeutic approach for stage I and minimal stage II disease (39). However, as Stock et al. suggested (21), and later Creasman et al. (5) and Tjalma et al. (39) concurred, such apparent improvement in small surgical series may be secondary to a selection bias such as patients with better performance status and smaller lesions are selected for surgery, whereas older patients with more comorbid medical conditions and larger stage I to II lesions undergo RT.

While several series have reported on primary surgical approaches, including exenteration for patients with advanced stage III–IV SCC, achieving control rates as high as 50% for highly selected patients (13,15,21,33), the number of patients treated in any single series is so small that in modern practice, primary exenteration for advanced disease would not be recommended as the preferred approach (137). Therefore, advanced-stage patients should receive definitive RT, probably in combination with concurrent chemotherapy, although the role of combined modality therapy is unknown.

With regard to the surgical technique, if a complete vaginectomy is to be undertaken, most experts have suggested a combined abdominoperineal approach, with the perineal incision in the pubocervicovesical fascia made beneath the urethra and above the rectum so as to avoid the hemorrhoidal plexus. Some have suggested that the perineal incision can be made before or after the abdominal incision to perform the radical abdominal resection. However, we would favor performing the abdominal incision, first mobilizing the bladder, urethra, and rectum down to the perineum, and dividing the paracolpos at the side wall, mobilizing the ureters, and harvesting the nodes such that if unresectable disease is found, the patient would be spared a perineal incision. Given the large defect that is left after surgical resection, placement of a gracilis myocutaneous flap allows not only coverage of the defect, but may serve as a neovagina in the sexually active woman (155,156). Alternatively, 2 new techniques have been described with excellent results. Vaginal reconstruction can be performed with the use of vicryl mesh combined with a pedicle omental grafter with a deep inferior epigastric perforator flap. Both techniques have been shown to be effective, and when performed at the time of pelvic exenteration, carry the additional benefit of avoiding an additional surgical incision, as required for creation of a

gracilis flap. Long-term follow-up has been favorable for the former, while only preliminary data is available for the latter (157,158).

Radiation Approach: Outcomes

Stage I. In patients with stage I lesions, usually 0.5 to 1 cm thick, that may involve 1 or more vaginal walls, it is important to individualize radiation therapy techniques to obtain optimal functional results. Most investigators emphasize that brachytherapy alone is adequate for superficial stage I patients with 95% to 100% local control rates when using low-dose-rate (LDR) ICB and ITB techniques (4,18,110,123).

Superficial lesions with less than 3 mm invasion can be adequately treated with ICB alone, using afterloading vaginal cylinders. The entire length of the vagina is generally treated to a mucosal dose of 60 Gy, and an additional mucosal dose of 20 to 30 Gy is delivered to the area of tumor involvement (131). Mucosal doses of 80 to 100 Gy are typically delivered, depending on the diameter of the cylinders, when prescribing 65 to 70 Gy to the tumor area, at 0.5 cm depth beyond the vaginal surface (131). For lesions thicker than 0.5 cm at the time of implantation, it is advisable to combine ICB and ITB with a single-plane implant to increase the depth dose and limit excessive irradiation to the vaginal mucosa. With LDR-ICB a dose of 60 to 65 Gy is delivered to the entire vaginal mucosa; the dose to 0.5 cm depth from the ICB should be calculated; an additional 15 to 20 Gy at a depth of 0.5 cm beyond the plane of the implant will be delivered with the ITB such that the base of the tumor receives between 65 and 70 Gy, with the involved vaginal mucosa receiving an estimated 80 to 100 Gy. The proximal and distal vaginal mucosal doses should be limited to 140 and 98 Gy, respectively (131).

There are no well-established criteria regarding the use of external beam RT (EBRT) in patients with stage I disease. Perez et al. (4,35) did not find a significant correlation between the technique of irradiation used and the probability of local or pelvic recurrence, probably since the treatment technique varied based on tumor-related factors. There is general consensus that EBRT is advisable for larger, more infiltrating or poorly differentiated tumors that may have a higher risk of lymph node metastasis. The whole pelvis is treated with 10 to 20 Gy; an additional parametrial dose should be delivered with a midline block (5 half-value layer [HVL]) to give a total of 45 to 50 Gy to the parametria and pelvic side walls (4,35). Chyle et al. (14) recommended EBRT in addition to brachytherapy for stage I disease to cover at least the paravaginal nodes, and, in larger lesions, to cover the external and internal iliac nodes. Ninety-five percent to 100% local control has been achieved with intracavitary and interstitial techniques, with 5-year survival for patients with stage I disease treated with RT alone ranging from 70% to 95% (Table 20.4) (4,18,21,23,48,123).

Stage II. Patients with stage IIA tumors have more advanced paravaginal disease without extensive parametrial infiltration. These patients are uniformly treated with EBRT followed by ICB and/or ITB. Perez et al. (35) showed that in stage IIA, the local tumor control was 70% (37/53) in patients receiving brachytherapy combined with EBRT, compared with 40% (4/10) in patients treated with either brachytherapy or EBRT alone. Generally, the whole pelvis receives 45 Gy followed by an additional boost using a combination of LDR-ICB or LDR-ITB in order to deliver a minimum of 30 to 35 Gy 0.5 cm beyond the deep margin of the tumor (in addition to the whole pelvis dose, to a total tumor dose of 75 to 80 Gy). Double-plane or volume implants may be necessary for more extensive disease. The superiority of the combination of EBRT and brachytherapy over EBRT or brachytherapy alone has been shown as well in other series (14,21,122).

Table 20.4 FIGO Stage I–II Vaginal Cancer: Treatment Approach and Results

Treatment Modality, Authors	No. of Patients	Outcome—Survival
Irradiation ± Surgery		
Chyle et al. (14)	59 St I	10 yr, 76%
	104 St II	10 yr, 69%
Creasman et al. (NCDB) (5)	169 St I	5-yr survival: 73%; 79% S+RT (47), 63% RT (122)
	175 St II	5-yr survival: 58%; 58% S+RT (39), 57% RT (136)
Davis et al. (24)	19 St I	5-yr survival: 100% S+RT (5), 65% RT (14)
	18 St II	5-yr survival: 69% S+RT (9), 50% RT (9)
Kirkbride et al. (16)	40 St I	5 yr, 72%
	38 St II	5 yr, 70%
Kucera and Vavra (123)	16 St I	5 yr, 81%
	23 St II	5 yr, 43.5%
Perez et al. (35)	59 St I	10 yr, 80%
	63 St IIA	10 yr, 55%
	34 St IIB	10 yr, 35%
Stock et al. (21)	8 St I	5 yr: 100% S+RT, 80% RT
	35 St II	5 yr: 69% S+RT, 31% RT
Urbanski et al. (23)	33 St I	5 yr, 73%
	37 St II	5 yr, 54%
Frank et al. (48)	50 St I	5-yr DSS, 85%
	97 St II	5-yr DSS, 78% 5-yr survival
Radical Surgery		
Ball and Berman (13)	19 St I	84%
	8 St II	63%
Creasman et al. (NCDB) (5)	76 St I	90%
	34 St II	70%
Davis et al. (24)	25 St I	85%
	27 St II	49%
Rubin et al. (33)	5 St I	80%
	3 St II	33%
Stock et al. (21)	17 St I	56%
	23 St II	68%
Tjalma et al. (39)	26 ^a	91%

DSS, disease-specific survival; NCDB, National Cancer Data Base; RT, radiotherapy; S, surgery; St, stage.

^aFour patients received adjuvant irradiation.

Patients with stage IIB, with more extensive parametrial infiltration, will receive 40 to 50 Gy whole pelvis and 55 to 60 Gy total parametrial dose (with midline shielding). An additional boost of 30 to 35 Gy will be given with LDR interstitial and intracavitary brachytherapy, to deliver a total tumor dose of 75 to 80 Gy to the vaginal tumor (14,23,35,122). In patients with parametrial infiltration, a “boost” with EBRT and/or an interstitial implant is advisable to deliver a minimum tumor dose of 70 to 75 Gy and 55 to 60 Gy to the pelvic side wall. The pelvic side wall dose should be kept below 60 Gy (including the contributions of EBRT and brachytherapy) (35). Patients with lesions limited to the upper third of the vagina can be treated with an intrauterine tandem and vaginal ovoids or cylinders. The local-regional control in patients with stage IIB in the Perez et al. series (35) was also superior with combined EBRT and brachytherapy (61% vs. 50%, respectively).

The 5-year survival for patients with stage II disease treated with RT alone ranges between 35% and 70% for stage IIA, and 35% and 60% for stage IIB (14,21,35). The results of several series published in the literature using different treatment approaches for stage I and II vaginal cancer are shown in Table 20.4 (5,13,14,16,21–24,33,35,39,48,117,119,120,123,159–162).

Stage III–IVA. Generally, patients with stage III and IVA disease will receive 45 to 50 Gy EBRT to the pelvis, and in some cases, additional parametrial dose with midline shielding to deliver up to 60 Gy to the pelvic side walls. Ideally, ITB brachytherapy boost is performed, if technically feasible, to deliver a minimum tumor dose of 75 to 80 Gy. If brachytherapy is not feasible, a shrinking-field technique can be used, with fields defined using the 3-dimensional treatment planning capabilities to deliver a tumor dose around 65 to 70 Gy. An alternative approach is intensity modulated RT (IMRT) using multiple beams of varying intensity that conform the high-dose region to the shape of the target tissues, with more adequate sparing of the surrounding normal tissues, primarily the bladder, rectum, and small bowel (163,164).

Boronow et al. (137) proposed an alternative to exenterative procedure for locally advanced vulvovaginal carcinoma, using RT to treat the pelvic disease and a radical vulvectomy with bilateral inguinal node dissection to treat the vulvar extension of the tumor. External irradiation to the pelvis and inguinal nodes consisted of 45 to 50 Gy, combined with LDR intracavitary insertions to deliver maximal doses of 80 to 85 Gy to the vaginal mucosa with both modalities. The overall cure rate for patients with stage III disease is 30% to 50%.

Stage IVA includes patients with rectal or bladder mucosa involvement, or in most series, positive inguinal nodes. Although some patients with stage IVA disease are curable, many patients are treated palliatively with EBRT only. Pelvic exenteration can also be curative in highly selected stage IV patients with small-volume central disease. Table 20.5 (5,13,14,16,21,23,33,35,48,119,120,123,159,161,162) shows the treatment results with different therapeutic modalities, including 4 series that reported the use of primary surgery in highly selected patients with advanced disease. However, each of these series reported a far greater number of patients with similar stage disease treated with RT, which represents the preferred approach in contemporary practice (4,47).

Radiation Therapy Techniques

External Beam Radiotherapy

EBRT is advisable in patients with deeply infiltrating or poorly differentiated stage I lesions and in all patients with stages II to IVA disease. The treatment is generally delivered using opposed anterior and posterior fields (AP/PA). The pelvis receives between 20 and 45 Gy, depending on the stage of the disease.

Table 20.5 FIGO Stage III–IV Vaginal Cancer Outcome with Radiation Therapy with/without Surgery

Treatment Modality, Authors	No. of Patients	Outcome—Survival
Irradiation ± Surgery		
Chyle et al. (14)	55 St III	10 yr, 47%
	16 St IV	10 yr, 27%
Creasman et al. (NCDB) (5)	180 St III–IV	5-yr survival: 36%; 60% S+RT (36), 35% RT (144)
Kirkbride et al. (16)	42 ^a St III–IV	5 yr, 53%
Kucera and Vavra (123)	46 St III	5 yr, 35%
	19 St IVA	5 yr, 32%
Perez et al. (35)	20 St III	10 yr, 38%
	15 St IV	0%
Stock et al. (21)	9 St III	5 yr, 0%
	8 St IV	0%
Urbanski et al. (23)	40 St III	5 yr, 22.5%
	15 St IVA	0%
Frank et al. (48)	46 St III–IVA	5-yr DSS, 58% 5-yr survival
Radical Surgery		
Ball and Berman (13)	2 St III	50%
Creasman et al. (NCDB) (5)	20 St III–IV	47%
Rubin et al. (33)	2 St III	50%

DSS, disease-specific survival; NCDB, National Cancer Data Base; RT, radiotherapy; S, surgery; St, stage; Yr, year.

^aTwenty patients with St III–IV were treated with chemotherapy (5-FU ± mitomycin C) and radiotherapy.

This will be followed, in some cases, by bilateral pelvic sidewall boosts from 50 to 55 Gy. High-energy photons (≥ 10 MV) are usually preferred. CT simulation is highly encouraged since it allows a more accurate delineation of the regional lymph node areas, rather than relying on pelvic bony anatomy (165). Treatment portals cover at least the true pelvis with 1.5- to 2.0-cm margin beyond the pelvic rim. Superiorly, the field extends to either L4–5 or L5–S1 to cover the pelvic lymph nodes up to the common iliacs, and extends distally to the introitus to include the entire vagina. The distal margin of the tumor should be identified with a radiopaque marker or bead at the time of the simulation. Lateral fields, if used, should extend anteriorly to adequately include the external iliac nodes, anterior to the pubic symphysis, and at least to the junction of S2–3 posteriorly to adequately cover the presacral nodes (Fig. 20.6).

In patients with tumors involving the middle and lower vagina with clinically negative groins, the bilateral inguinofemoral lymph node regions should be treated electively to 45 to 50 Gy (35). Planning CT is recommended to adequately determine the depth of the inguinofemoral nodes. In patients with distal vaginal lesions it is often necessary to treat the vulva in order to achieve adequate tumor coverage, in which case the patient should be placed in open-leg position to reduce the vulvar skin reaction (48).

A number of techniques have been used to treat the areas at risk without overtreating the femoral necks. Some of the most commonly used techniques include the use of unequal loading (2:1, AP/PA), a combination of low- and high-energy photons (4 to 6 MV, AP; and 15 to 18 MV, PA), or equally weighted beams with a transmission block in the central AP field, utilizing small AP photon or electron beams to deliver a daily boost to the inguinofemoral nodes (166). A technique has been developed and implemented at Indiana University that uses a narrow PA field to treat the pelvis and a wider AP field encompassing the pelvis and inguinofemoral nodes, with daily AP photon boost to the inguinal nodes being delivered using the asymmetric collimator jaws (167). Advantages of this technique include simplicity of setup and treatment (single isocenter, no need for transmission block), dose homogeneity, reduced dose to the femoral necks, low potential risk of nodal underdose, and elimination of dosimetric difficulties inherent in electron boosts (Fig. 20.7).

The above technique was initially set up and planned using a conventional simulator. With the advent of more modern CT based simulation and 3D treatment planning software, the technique described above is being replaced by a similar technique described by Moran et al. (168) with some modifications. In their technique called modified segmental boost technique (MSBT), Moran et al. (168) use CT simulation and 3D treatment planning software that incorporate multileaf collimators (MLC's) to shape the desired fields. Relevant anatomic areas such as femoral vessels, involved nodes etc. are outlined on the CT scan to help create the appropriate field borders. The field arrangements are similar to the Indiana University technique including a wide AP photon field, a narrow PA pelvic field, and a bilateral (or unilateral) inguinal boost field(s). The inguinal fields are angled slightly to align with the divergence of the PA field and are shaped using MLC's. They found this technique significantly improved homogeneity throughout the treatment volume in comparison to other traditional techniques (168).

In patients with clinically palpable inguinal nodes, additional doses of 15 to 20 Gy (calculated at a depth determined by CT scan) are necessary with reduced portals. This is generally achieved by using low-energy photons or electron beam (12–18 MeV). For patients with positive pelvic nodes, or those patients with advanced disease not amenable to interstitial implant, additional boost to the areas of gross disease, as defined by CT scan, should be given using conformal therapy to deliver a total dose between 65 to 70 Gy, when feasible, with high-energy photons.

Intensity modulated radiation therapy (IMRT) is another potential therapeutic option in pelvic tumors that require the treatment of the inguinofemoral region as well as delivering higher doses to the gross disease while reducing the dose to the bladder and rectum (Fig. 20.8) (163,164,168–172). It is postulated that the use of IMRT may reduce acute and long-term toxicity by minimizing the dose to organs at risk (OAR). This is a topic of current investigation in a phase II RTOG trial (05–29), in which IMRT to the pelvic and inguinal nodes is being combined with chemotherapy for anal cancer in a multi-institutional setting. Moran et al. (168) performed a dosimetric comparison of the MSBT technique to IMRT for treatment of pelvic/inguinal nodes in variety of patients, including those with the diagnoses of primary vaginal cancers (168). The doses to the bladder, rectum, small bowel, and bone marrow were higher using the MSBT technique compared to IMRT plan; however, the treatment planning process (including contouring) was 40 minutes for the MSBT plan compared to approximately 6 hours for the IMRT plan (168). At this time there is not sufficient data on outcomes to routinely recommend the use of IMRT for the treatment of primary vaginal cancer when the inguinofemoral nodes must be irradiated. Certain clinical scenarios may warrant the use of IMRT, such as those patients who require doses greater than 50 Gy to the pelvis or inguinofemoral region or

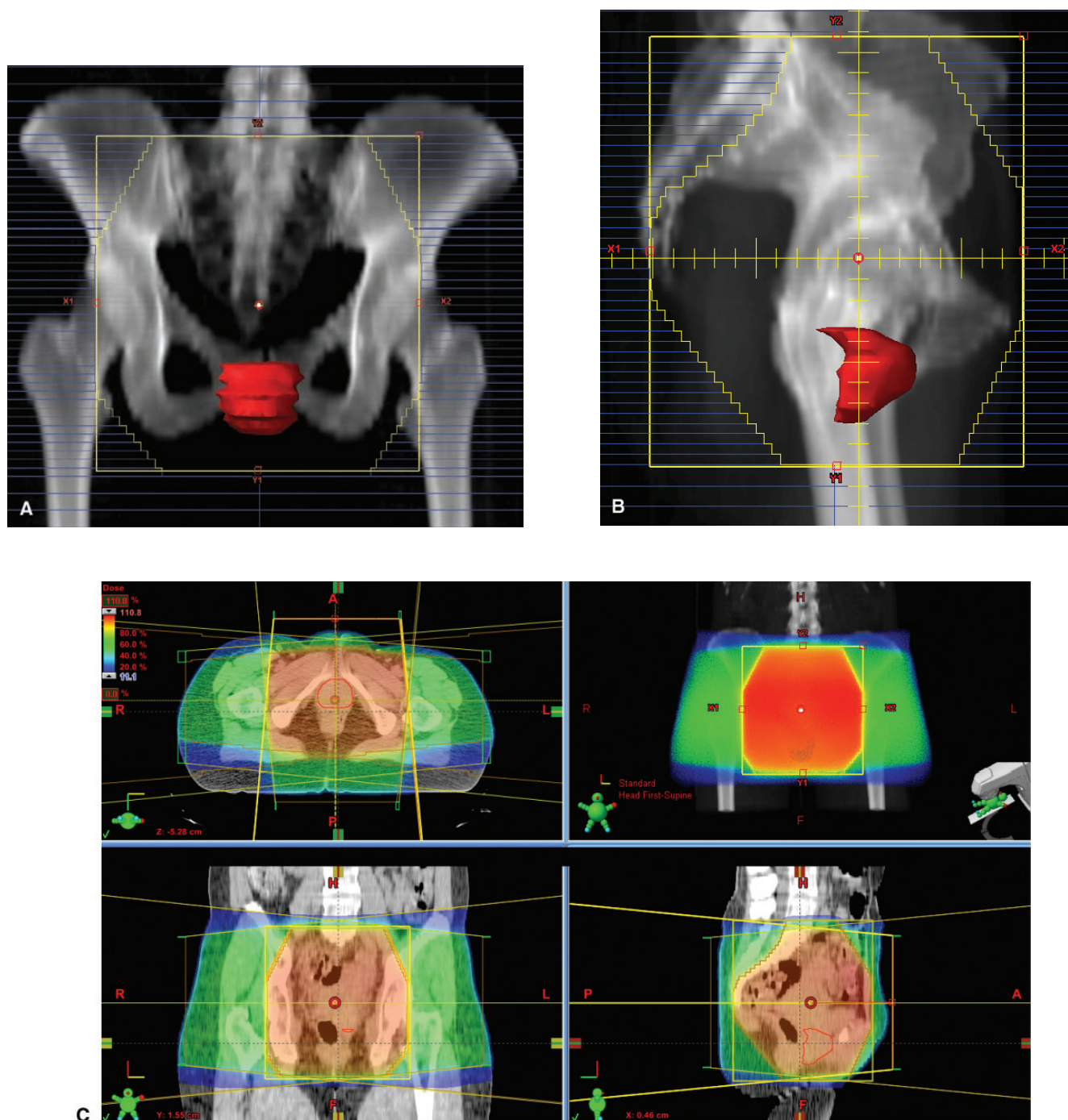


FIGURE 20.6. Proximal third vaginal cancer; invasive squamous cell carcinoma, with mid-third of the vagina squamous cell carcinoma *in situ*, without involvement of inguino-femoral nodes. Digital Reconstructed Radiographs (DRRs). **A:** AP/PA whole pelvis fields. **B:** Right/Left lateral whole pelvis fields, intended to treat the entire length of the vagina. **C:** Axial, sagittal, and coronal isodose distributions.

when radiation must be delivered to an area that has previously been irradiated.

Independently of the technique to be used, it is important to keep in mind that the overall treatment time (7 to 9 weeks) has been found to be a significant treatment factor predicting tumor control (130,150), although this has not been universally recognized (35).

Low-Dose-Rate Intracavitary Brachytherapy

VAIN and small T1 lesions with less than a 0.5-cm depth can be adequately treated with intracavitary brachytherapy (ICB)

alone. Low-dose-rate (LDR)-ICB is performed using vaginal cylinders such as Burnett, Bloedorn, Delclos (173), or MIRALVA (Nucletron Veenendaal, the Netherlands) (174) loaded with cesium 137 (^{137}Cs) radioactive sources. Choo et al. (175) evaluated the depth distribution of lymphatics lying beneath the mucosal surface of the vagina in 31 patients who underwent full-thickness vaginal biopsy or resection for benign or malignant lesions. In their series, 95% of vaginal lymphatic channels were located within a 3 mm depth from the vaginal surface, confirming the adequacy of prescribing the dose to a depth of 5 mm for superficially invasive lesions (173).

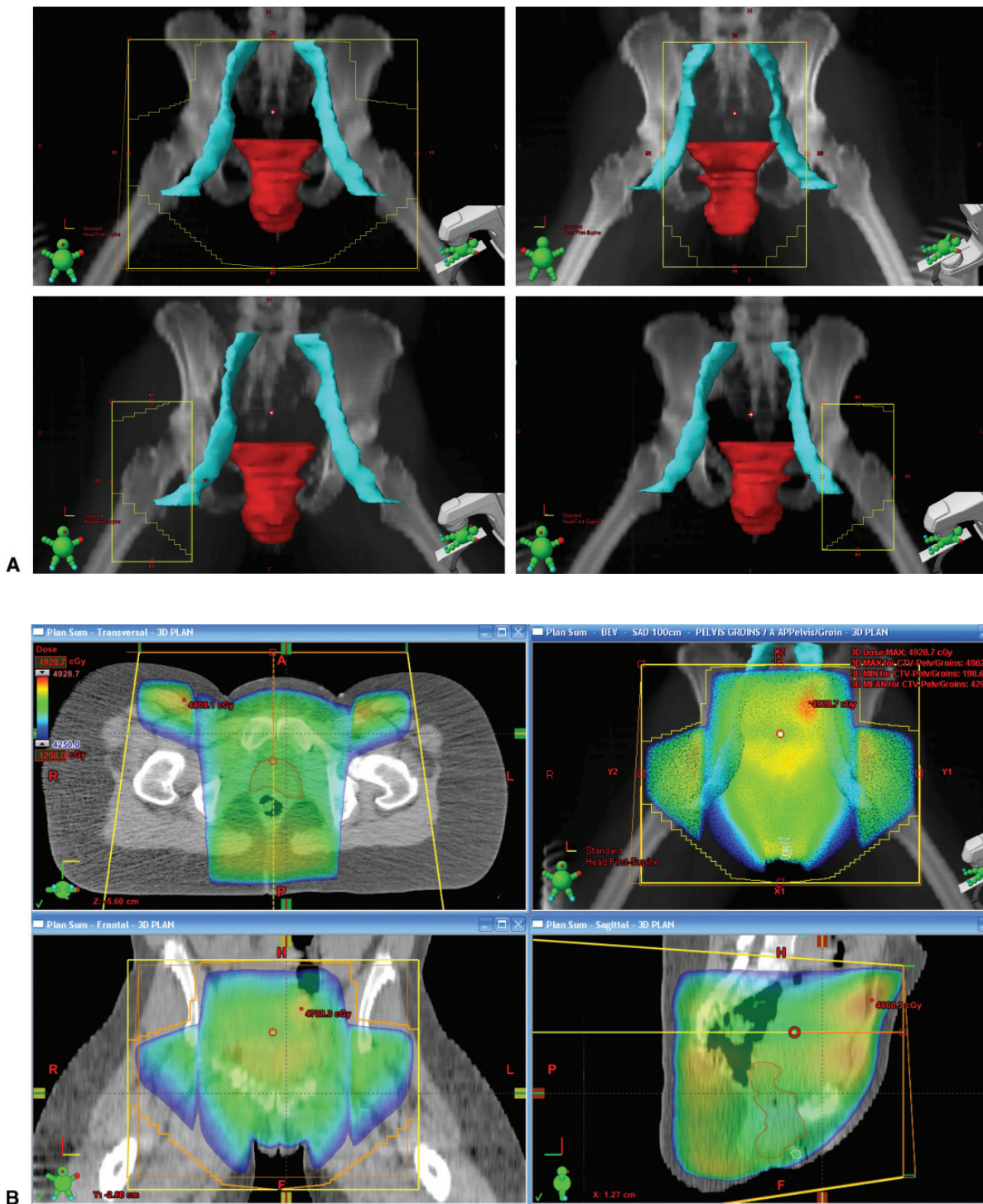


FIGURE 20.7. Vaginal cancer with distal third vaginal involvement, squamous cell carcinoma. Technique for pelvic and inguinofemoral nodal irradiation. **A:** Digital reconstructed radiographs. AP field intended to treat pelvis and groins; PA field intended to treat the pelvis only, in order to decrease the dose to the femoral heads; small AP photon field for additional daily boost to the inguinofemoral nodes. **B:** Axial, sagittal, and coronal isodose distributions.

Delclos afterloading vaginal cylinders have a central hollow metallic cylinder in which the sources are placed, and plastic rings of varying diameter (2.5 to 4 cm), 2.5 cm in length, which are inserted over the cylinder. Domed cylinders are used to irradiate the vaginal cuff homogeneously, when indicated. Delclos recommended a short ^{137}Cs source to be used at the top to obtain a uniform dose around the dome, because a lower dose occurs at the end of the linear cesium source (173). Some cylinders have a lead shielding to protect selected portions of the vagina,

the bladder, and/or the rectum. It is recommended that the largest possible diameter that can be comfortably accommodated by the patient should be used to improve the ratio of mucosa to tumor dose, and to eliminate vaginal rugations. The cylinders can be mounted in the vaginal component of an intrauterine tandem, or along the stem of a dome cylinder. Before the cylinders are mounted over the vaginal component of an intrauterine tandem, this is inserted into the uterus (when present) and the cylinders are fitted along the protruding tandem. To minimize

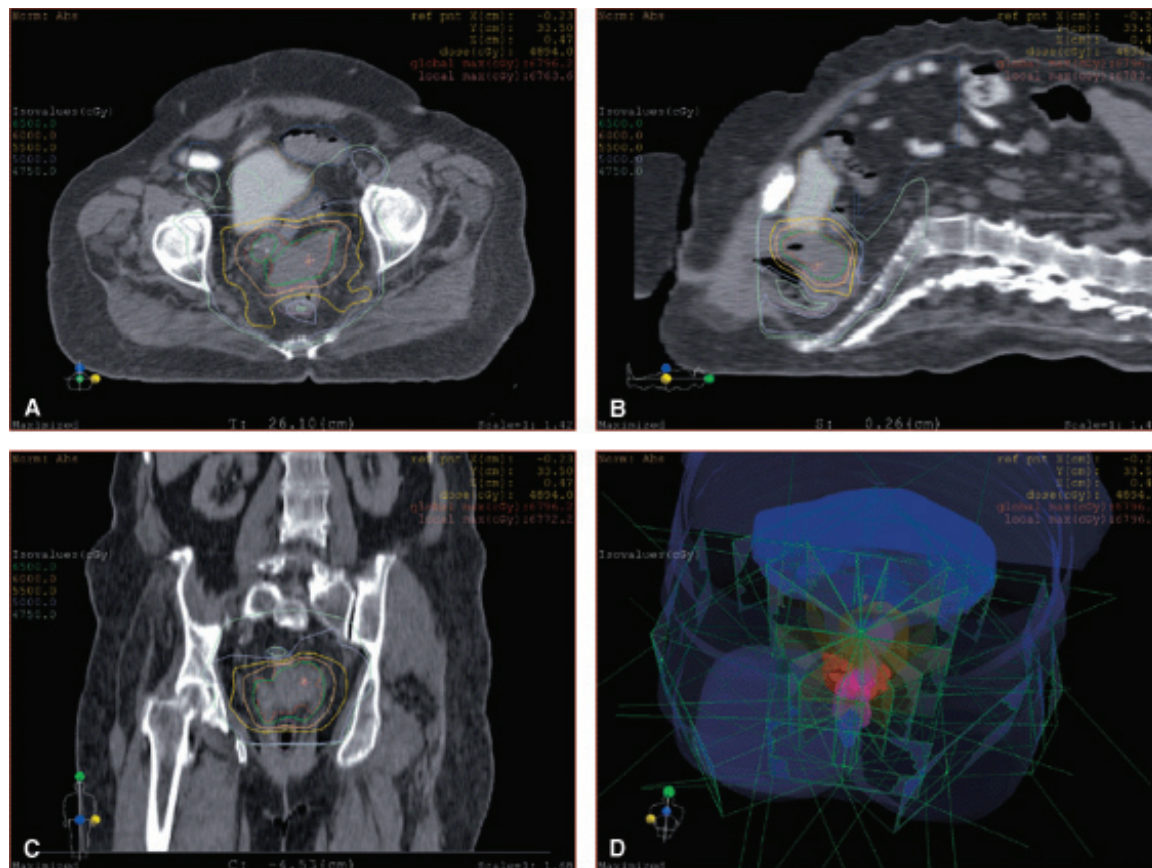


FIGURE 20.8. **A:** Axial dose distribution intensity-modulated radiation therapy plan for vaginal cancer. **B:** Sagittal dose distribution IMRT plan for vaginal cancer. **C:** Coronal dose distribution IMRT plan for vaginal cancer. **D:** Beam arrangement IMRT plan for vaginal cancer.

the rotation of the tandem, a flat, round flange with keel is placed below the last cylinder and is kept in position with some packing if required. In general, the vulva is sutured-closed with praline or silk for the duration of the implant in order to secure the position of the applicators (Fig. 20.9). In general, the vulva is sutured closed for the duration of the implant in order to secure the position of the applicators.

In patients with upper vagina lesions with less than a 0.5 cm depth of invasion, vaginal colpostats alone (after hysterectomy) or in combination with intrauterine tandem, loaded with ^{137}Cs sources similar to that used in treatment of cervical cancer, can be used to treat the proximal vagina to a minimum dose of 65 to 70 Gy, estimated to 0.5 cm depth, including the contribution of EBRT if given. When indicated, the remainder of the vagina can be treated by performing a subsequent implant using vaginal cylinders (generally 50 to 60 Gy prescribed to the vaginal surface). It is important to avoid the placement of a protruding source over the vulva, with the subsequent increased risk of complications. When appropriate dose specification points are chosen, a very uniform dose distribution over the entire length of the vagina can be obtained. Perez et al. and Slessinger et al. (174) designed and constructed a vaginal applicator, MIRALVA, which incorporates 2 ovoid sources and a central tandem that can be used to treat the entire vagina (alone or in combination with the uterine cervix). The applicator has vaginal apex caps and additional cylinder sleeves to allow for increased dimensions. A tandem in the uterus can be used if clinically indicated, using standard loadings, depending on the depth of the uterus. The vaginal cylinder or uterine tandem never carries an active source at the level of the ovoids to prevent excessive doses to the bladder or rectum. The use of LDR remote control afterloading

technology allows the reduction of radiation exposure to hospital personnel and optimization of the isodose distribution.

High-Dose-Rate Intracavitary Brachytherapy

The International Commission of Radiation Units (ICRU) defines HDR brachytherapy as exceeding 12 Gy/hour (35). High-dose-rate intracavitary brachytherapy (HDR-ICB) is typically performed with a 10 Ci single iridium-192 (^{192}Ir) source (Micro-Selectron HDR, Nucletron). The applicators are similar to those described for LDR.

Limited information regarding HDR-ICB in the treatment of primary carcinoma of the vagina is available (22,154,176–180). Fewer patients have been treated compared with LDR-ICB, follow-up for most series is short, publication bias is likely, and there is no agreement on treatment regimen. With HDR there is a need to adjust the total dose and additional fractionation is necessary, compared with LDR brachytherapy, because of the biologically equivalent dose considerations. Generally, the number of insertions ranges from 1 to 6 (median, 3), with the dose per fraction ranging from 300 to 800 cGy (median, 700 cGy).

HDR-ITB has also been reported by Kushner et al. (177); in this report, the Syed Template Applicators were used. Newer HDR compatible interstitial systems are available including the M.A.C. (Mick-Alektiar-Cohen) HDR-GYN Contour Template, compatible with ultrasound stabilizing devices, and the Miami Multi-Channel Vaginal Applicator (Mick Radio-Nuclear Instruments Inc., Mount Vernon, NY) (Fig. 20.10).

Stock et al. (22) described results in 15 patients with carcinoma of the vagina treated with HDR brachytherapy; dose per fraction ranged from 3 to 8 Gy, with a median dose of

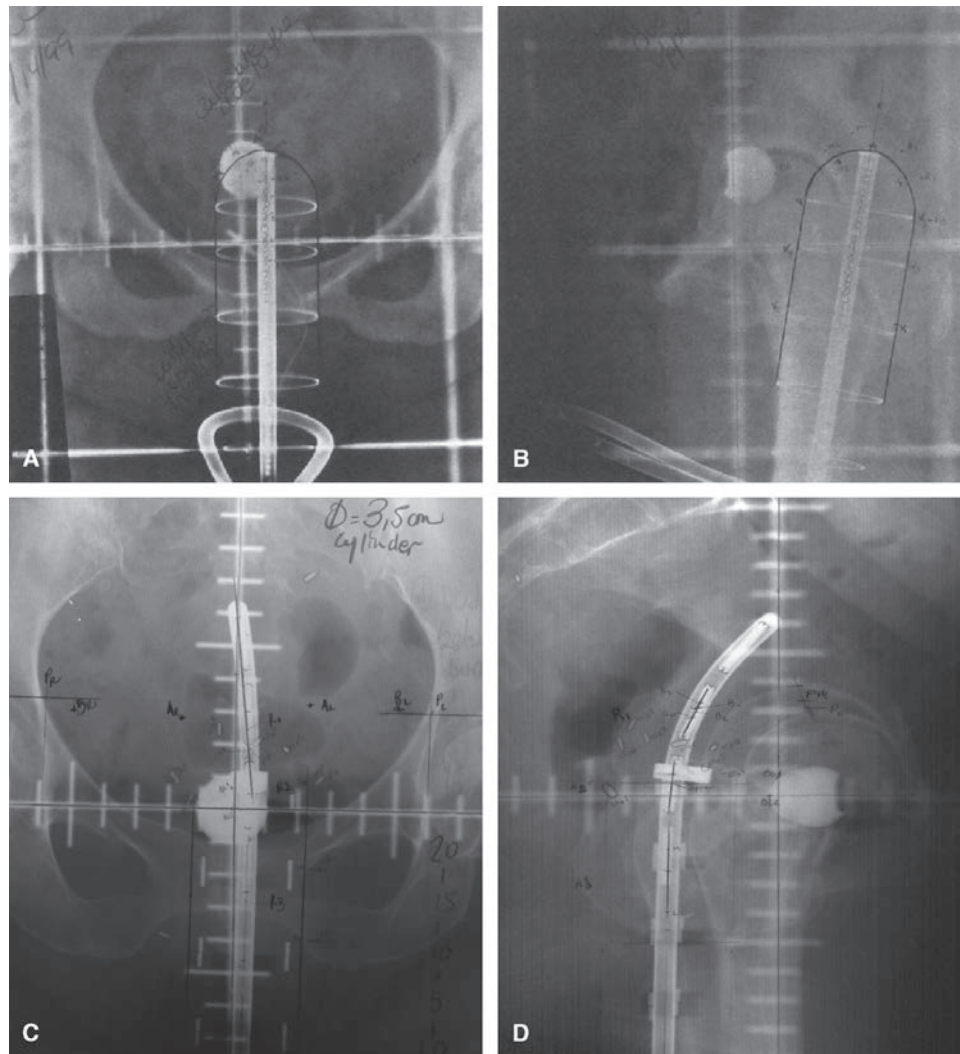


FIGURE 20.9. AP (A) and lateral views (B) of vaginal cylinders only. AP (C) and lateral views (D) of intrauterine tandem and vaginal cylinders.

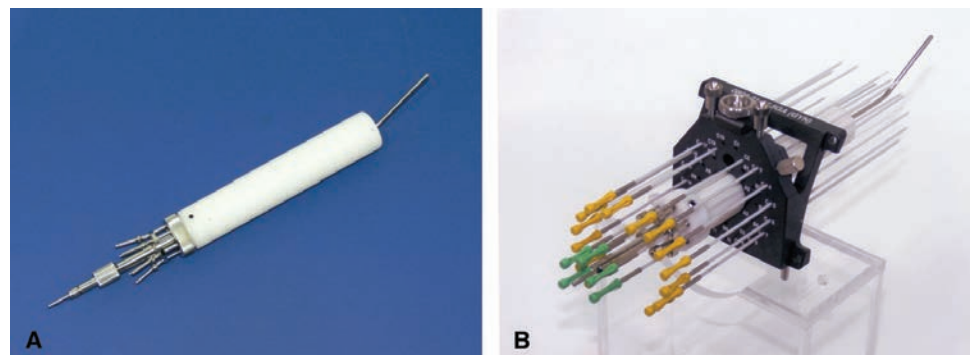
7 Gy, for a total median dose of 21 Gy. The median interval between fractions was 2 weeks. Brachytherapy was combined with EBRT (30 to 63 Gy, with a median dose of 42 Gy, 1.8 to 2.92 Gy per fraction). The median total tumor dose from both components was 63 Gy. The 5-year actuarial survival rate was 50% with brachytherapy, compared with 9% in the EBRT-alone patients ($p < 0.001$), although a larger percentage of stage IV lesions (36%) were in the EBRT-alone group than in the brachytherapy group (5%). Local tumor control rates were 50% for

stage I, 47% for stage II, and 40% for stage III. Survival closely paralleled tumor control. There was no significant difference in outcome in the LDR or HDR groups. Acceptable morbidity of therapy was noted for all 49 patients, but no comment was made comparing LDR with HDR (22).

Nanavati et al. (178) reported 13 patients with primary vaginal cancer (5 St I, 4 St IIA and 4 St IIB) treated with external beam RT (45 Gy) and HDR-ICB (20–28 Gy in 3–4 fractions, calculated at 0.5 cm from the surface of the applicator). All

FIGURE 20.10. A: M.A.C. HDR-GYN Contour Template. B: HDR CT Miami Multi-Channel Vaginal Applicator.

Source: Reprinted with permission from Mick Radio-Nuclear Instruments, Inc.



13 patients had a complete response, and local control was achieved in 92% of the patients with a median follow-up of only 2.6 years (range 0.7 to 5.2 years). Originally the planned dose was 2100 cGy in 3 fractions, 700 cGy/fraction, but because of reports of decreased complications with increased fractionation, the planned dose was changed to 2000 cGy in 4 equal fractions. The investigators did not observe any acute or chronic intestinal or bladder grade 3 or 4 toxicity. However, moderate to severe vaginal stenosis occurred in 46% of the patients. They recognize that “late-occurring toxicity could be missed at a medium follow-up of 2.6 years” (178).

Kucera et al. (176) reported on 190 patients with invasive carcinoma of the vagina. Eighty were treated with intracavitary HDR-ICB with or without EBRT. These patients are compared with a historical group of 110 patients treated with intracavitary LDR brachytherapy with or without EBRT. No significant differences were found for stages, tumor grade, or location between the 2 groups. The crude 5-year survival rates for all patients were 41% in the LDR group, 81% in stage I, and 43% in stage II. Overall actuarial 3-year survival and disease-specific survival rates for all patients in the HDR series were 51% and 66%, respectively. Disease-specific 3-year survival rates were 83% in stage I and 66% in stage II. There were no significant differences in local and distant recurrences between the treatment modalities. Complications analysis showed no significant differences between the HDR and LDR series. Similar results were published by Mock et al. (154) in 86 patients treated with HDR-ICB alone or in combination with EBRT with fairly good toxicity profile. However, Kushner et al. (177) reported on 19 patients with vaginal cancer treated with different combinations of EBRT and intracavitary and interstitial HDR brachytherapy, with a low (39.3%), 2-year progression-free survival and 15.8% serious late complications including ureteral stenosis, painful vaginal necrosis, and small bowel obstruction.

Many aspects remain unknown or not well understood in the use of HDR-ICB in vaginal cancer treatment. These include the radiobiological equivalency of HDR to LDR, fractionation schedule, total dose, specification of dose prescription, and how to combine HDR with EBRT and/or LDR brachytherapy. In addition, optimization approaches and methods of dose calculation, such as the inclusion of anisotropic corrections, are not well described in the sparse literature available to date (181,182). Li et al. (182) have shown that when optimized dose distribution at a distance from the cylinder surface is calculated using an accurate dose calculation model, the vaginal mucosa dose becomes significantly higher than calculated, and therefore should be carefully monitored. These factors could result in an increased incidence of severe complications, such as vaginal necrosis and rectovaginal or vesicovaginal fistulas (177,183,184). In our opinion, until further data are available with longer follow-up, as well as a better understanding of the physical and radiobiological principles involved in HDR-ICB, its use should be cautiously considered in the radiotherapeutic management of primary vaginal carcinoma.

Interstitial Brachytherapy

Interstitial brachytherapy (ITB) is an important component in the treatment of more advanced primary vaginal carcinomas, typically in combination with EBRT and/or ICB. In the first place, a careful definition of the “target volume,” which is the gross tumor volume (based on clinical, radiologic, and operative findings) and a margin of adjoining normal tissue, is required. Other considerations include whether a permanent (^{198}Au or ^{125}I) or temporary implant (^{192}Ir) is optimal, the geometry of the implant (e.g., single or double plane or volume implant), source distribution, dose rate, and total dose, based upon tumor size, location, local extent, and proximity of normal structures (185). The principal advantages of temporary

implants are readily controlled distribution of the radioactive sources and easier modification of the dose distribution. The main advantages of a permanent seed implant include relative safety/simplicity, easy applicability, cost-effectiveness, and ability, in most cases, to be performed using local anesthesia. As a general rule, temporary implants are more commonly used in the curative treatment of larger gynecologic malignancies, whereas permanent implants are usually performed for smaller volume disease.

The number and strength of the radioactive sources and their intended distribution within the target volume are determined preoperatively, making use of available guidelines such as nomograms, tables, and computer-assisted optimization techniques. Following this it is necessary to specify an approximate dose rate to the target volume, which requires careful localization of the sources and computer calculation of the 3-dimensional radiation dose distribution. Finally, a dose prescription, based upon the treatment volume, tumor sensitivity, dose rate, prior treatments and tolerance of normal surrounding tissues is required (152).

When performing an interstitial procedure, freehand implants or template systems designed to assist in preplanning and to guide and secure the position of the needles in the target volume can be employed. Popular commercially available templates include the Syed-Neblett device (SNIT) (Alpha Omega Services, Bellflower, California, USA) (186), the modified Syed-Neblett (187), and the “MUPIT” (Martinez Universal Perineal Interstitial Template) (188). All rely on pelvic examination to help guide the location and depth of needle placement. These templates generally consist of a perineal template, vaginal obturator, and 17-Gy hollow guides of various lengths that can be afterloaded with ^{192}Ir sources. The vaginal obturator is centrally drilled so that it can allow the placement of a tandem to be loaded with ^{137}Cs sources. This makes it possible to combine an interstitial and intracavitary application simultaneously (Fig. 20.11). The major advantage of these systems is greater control of the placement of the sources relative to tumor volume and critical structures due to the fixed geometry provided by the template and central cylinder. In addition, improved dose-rate distributions are obtained by means of computer-assisted optimization of the source placement and strength during the planning and loading phase (Fig. 20.12).

Owing to the inaccuracies of pelvic examination and close proximity of the rectum and bladder to the target volume, there exists a serious risk of either underdosing the target volume or causing bladder and rectal morbidity. In order to improve the accuracy of target localization and needle placement, several investigators have explored performing ITB under transrectal

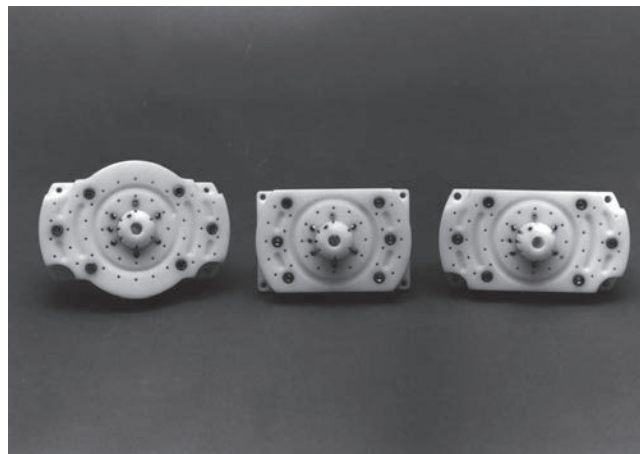


FIGURE 20.11. Syed-Neblett and modified templates.

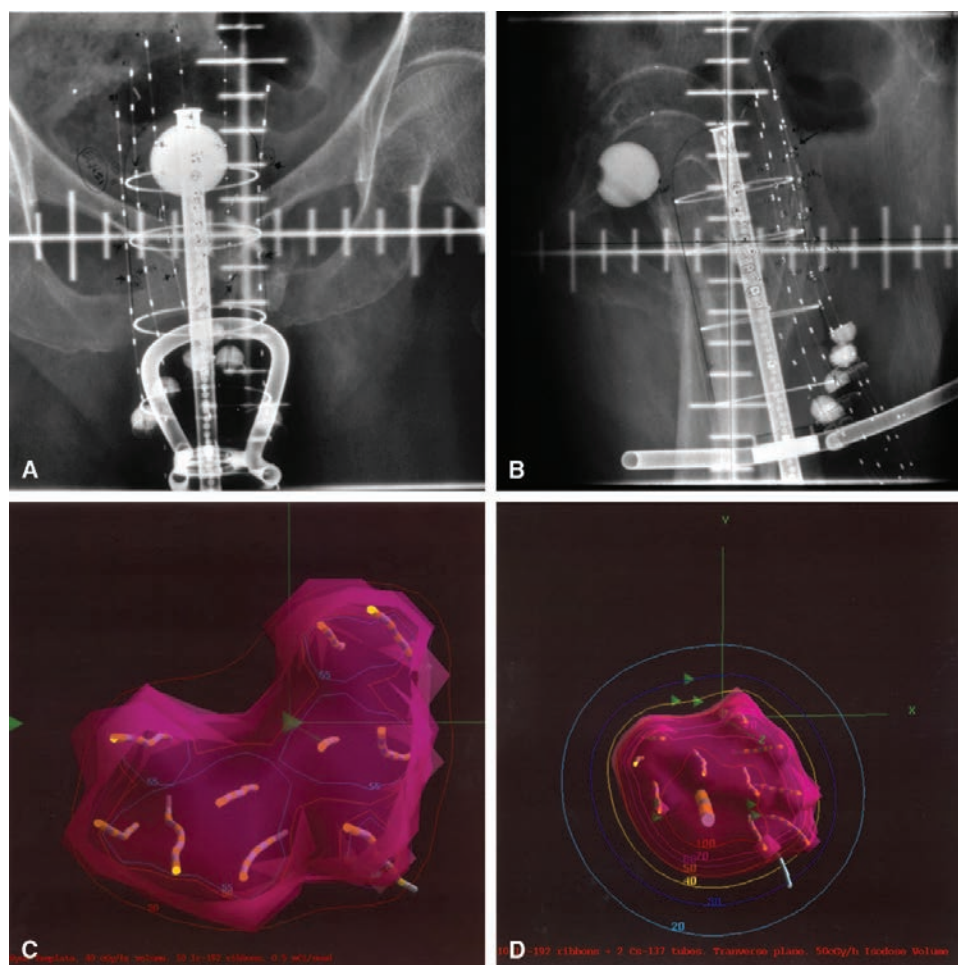


FIGURE 20.12. **A:** AP and **B:** lateral radiographs of an interstitial and intracavitary implant in carcinoma of the vagina using the modified Syed-Neblett template. **C:** Three-dimensional isodose distribution, Ir¹⁹² only; **D:** Ir¹⁹² plus Cs¹³⁷.

ultrasound (TRUS) (189), CT and/or MRI-planned implants with endorectal coil (204), laparotomy, and laparoscopic guidance (187–193). While laparotomy facilitates the displacement of bowel during the procedure by using slings or tissue expanders and/or lysis of adherent bowel there is some degree of associated morbidity, such as ileus, bleeding, and increased operative time. Laparoscopy is a shorter and less invasive procedure. An open retropubic approach allows direct visualization of the bladder and urethra during interstitial implantation of anterior vaginal malignancies and facilitates negotiation of the pubic arch. Paley et al. (193) described a technique using an open retropubic approach for Syed template interstitial implants in anterior vaginal tumors under direct visualization. Real time TRUS-guided Syed-Neblett template implantation technique was reported by Stock et al. (189). TRUS allows the ultrasound (US) probe to be in closer proximity to the pelvic structures (cervix, parametria, and vagina) than trans-abdominal US and can more accurately guide needle placement into tumor and avoid needle insertion into critical surrounding normal tissues. Transverse US imaging is used to assure that the needles cover the target area and do not enter the bladder, rectum or small bowel. The longitudinal mode of the US probe is equally important in the implant procedure due to its ability to guide the optimum depth of needle insertion. With this technique, invasive laparotomy and/or laparoscopy can often be avoided, providing an interactive, noninvasive technique allowing for highly accurate needle placement (189).

Shah et al. (194) reported on toxicity after needle puncture of visceral organs during interstitial brachytherapy without assistance of image guidance during the placement (194). They imaged 36 patients after needle placement with a postoperative CT scan and found bowel puncture in 26 patients and bladder puncture in 19 patients; however, they found no relationship between visceral puncture and the incidence of acute or late gastrointestinal or urinary toxicity. They did note that needles that perforated the bowel or bladder were not loaded or the dwell times were minimized in these areas and conclude that toxicity may be related to the dose received by the normal structures rather than the occurrence of visceral puncture (194).

Tewari et al. (195) described results in 71 patients who underwent ITB with (61 patients) or without (10 patients) EBRT. Patients included those with stage I (10 patients), Perez modification stage IIA (14 patients), Perez modification stage IIB (25 patients), stage III (15 patients), and stage IV (7 patients) disease. Each implant delivered a total tumor dose reaching 80 Gy integrated with EBRT. Local control was achieved in 53 patients (75%). With a median follow-up of 66 months the 5- and 10-year actuarial disease-free survival rates were both 58%. By stage, 5-year disease-free survival rates included stage I, 100%; stage IIA, 60%; stage IIB, 61%; stage III, 30%; and stage IV, 0%. Stage and primary lesion size independently influenced the survival rates. Significant complications occurred in 9 patients (13%) including necrosis (n = 4), fistulas (n = 4), and small bowel obstruction (n = 1) (195).

Stryker (196) treated 40 patients with vaginal carcinoma; 14 had a history of prior hysterectomy. There were 4 treatment groups: EBRT and intracavitary brachytherapy (group WPIC, $n = 15$), EBRT and interstitial brachytherapy (group WPIS, $n = 10$), EBRT alone (group WP, $n = 7$), and brachytherapy alone (group BA, $n = 2$). The 5-year disease-specific survival rates were 68% for 28 patients with SCC and 50% for 6 patients with adenocarcinoma. The 5-year survival rates were 78% for stage I disease, 63% for stage II, 33% for stage III, and 50% for stage IV ($p = 0.2$). Local failure occurred in 2 patients (13%) in the WPIC group, 2 (20%) in WPIS, 3 (43%) in WP, and 1 (50%) in BA. Nine patients (26%) had late small/large intestine or bladder morbidity. Vaginal morbidity occurred in 15 patients (44%) (196).

Role of Chemotherapy and Radiation

The control rate in the pelvis for stage III to IV patients is relatively low, and about 70% to 80% of the patients have persistent disease or recurrent disease in the pelvis in spite of high doses of EBRT and brachytherapy. Failure in distant sites does occur in about 25% to 30% of the patients with locally advanced tumors, which is much less than pelvic recurrences. Therefore, there is a need for better approaches to the management of advanced disease such as the use of concomitant chemoradiotherapy. Agents such as 5-FU, mitomycin-C, and cisplatin have shown promise when combined with RT, with complete response rates as high as 60% to 85% (197,198), but long-term results of such therapy have been variable. In these small studies, many of the patients had advanced (stage III) disease at the initiation of combined-modality therapy, perhaps explaining the lack of long-term disease control.

Evans et al. (197) found no local recurrences, however, among patients achieving a complete response with RT and 5-FU plus mitomycin C (12 of 25 patients), with a median follow-up period of 28 months, suggesting that local control may be improved with combined-modality therapy since local failure is common with radiation alone in large-volume pelvic disease. The survival for the entire population was 56% (66% for patients with primary vaginal cancer). Only 2 patients had severe complications, although the investigators recognize that longer follow-up is probably required to assess the true incidence of late effects.

More sobering are the data from Roberts et al. (198), who reported 67 patients with advanced cancers of the vagina, cervix, and vulva treated with concurrent 5-FU, cisplatin, and RT. Although 85% experienced a complete response, 61% of the cancers recurred, with a median time to recurrence of only 6 months and an overall survival at 5 years of 22%. Further, 9 of 67 patients (13%) developed severe late complications, of which 8 required surgeries. Kersh et al. (199) reported that 5 of 8 vaginal cancer patients achieved local control with combined modality therapy.

Dalrymple et al. (200) published a small study including 14 patients, primarily stages I and II SCC of the vagina, treated with reduced doses of RT (median 63 Gy) concurrently with different 5-FU-based chemotherapeutic regimens. They reported a 93% control rate (4 patients died of intercurrent disease with no evidence of tumor), probably reflecting a more favorable stage distribution. Interestingly, none of the patients required interstitial implants and no patients developed fistulas. The authors indicate that this approach, similar to the one used in the management of anal and vulvar cancer, would allow reducing the RT dose with the subsequent improvement in organ function and late toxicity.

Samant et al. (201) reviewed institutional data on 12 patients (50% FIGO St III or IVA) treated with concurrent radiation and weekly cis-platinum chemotherapy (40 mg/m² for 5 weeks). At

a median follow-up of 50 months, the 5-year overall, progression-free, and local relapse-free survival rates were 66%, 75%, and 92% respectively. Sinha et al. (120) reported on 11 of 45 patients that received concurrent cisplatin with radiation that failed to show a benefit in disease control with the addition of chemotherapy; however these patients had more advanced FIGO stages which has shown to be a major determinant of failure and survival.

In a study by Panici et al. (202), 11 patients received neoadjuvant chemotherapy with paclitaxel and cisplatin for 3 courses followed by radical surgery for patients with FIGO stage II vaginal cancer. They found complete clinical responses in 3 (27%) patients, partial clinical responses in 7 (64%) patients, and 1 patient with stable disease (9%). At a median follow-up of 75 months, 91% are alive and 73% are disease-free.

Studies of primary chemoradiation in primary vaginal cancer are small or heterogeneous populations, including cervical and vulvar cancers, making it difficult to truly assess the role of combined-modality therapy in the management of locally advanced disease. No randomized trials comparing radiation with or without chemotherapy have been reported. Further investigation is needed to determine the therapeutic efficacy of the concurrent chemoradiotherapeutic and the optimal chemotherapeutic regimen.

Published data on cervical cancer have demonstrated an advantage in locoregional control, overall survival, and disease-free survival for patients receiving cisplatin-based chemotherapy concurrently with RT (203–206). The only drug common to all the studies was cisplatin, suggesting it may be the only agent needed to improve radiation sensitivity. Based on these data, as well as data on locoregionally advanced vulvar cancer (136,207) consideration should be given to a similar approach in patients with advanced vaginal cancer. In a recent SEER analysis for vaginal cancer, using the year 2000 as a surrogate for the introduction of chemoradiation in cervical cancer, a trend toward lower risk of death after 2000 in their multivariate model was found, as compared with women diagnosed between 1990 and 1994 (HR 0.83, $p = 0.07$) (121). Randomized trials comparing radiation therapy alone to chemoradiation therapy, however, are unlikely due to small patient numbers.

PATTERNS OF FAILURE IN SCC

At least 85% of patients who recur will have a component of locoregional failure, and the vast majority of these recurrences will be confined to the pelvis and vagina. The rate of locoregional recurrence in stage I is approximately 10% to 20% versus 30% to 40% in stage II. The pelvic control rate for patients with stage III and stage IV is relatively low and about 50% to 70% of the patients have recurrences or persistence in spite of well-designed RT. The median time to recurrence is 6 to 12 months. Tumor recurrence is associated with a dismal prognosis, with only a few long-term survivors after salvage therapy (159). Failure in distant sites alone or associated with locoregional failure does occur in about 25% to 40% of patients with locally advanced tumors (Table 20.6) (48,159,208–213). It is important to recognize that analysis of RT doses and techniques and their impact on local/pelvic tumor control are fraught with difficulty since the available data are retrospective and not the result of prospective randomized or dose escalation studies. Andersen (12) has shown that the combination of EBRT and brachytherapy and tumor dose over 70 Gy were associated with improved local control. In the Stanford experience (20), earlier stage and higher RT dose had a positive influence on survival. Nine of 16 patients receiving lesser than or equal to 75 Gy had recurrent disease versus 3 of 22 receiving greater than 75 Gy. Larger series have

Table 20.6 Patterns of Failure: SCC Vagina

Authors	No. of Patients	Percent of Recurrence	Local-regional Recurrence	Distant Recurrence	Local + Distant
Chyle et al. (14)	301	35%	21%	11%	3%
Davis et al. (24)	89	Stage I (23%)	18%	5%	Not shown
		Stage II (36%)	16%	20%	
Kirkbride et al. (16)	153	42%	32%	7%	3%
Kucera and Vavra (123)	110	24.5%	21%	4%	0.5%
Perez et al. (35)	212	Stage 0 (5%)	5%	0	0
		Stage I (22%)	8%	8%	5%
		Stage IIA (47%)	17%	13%	17%
		Stage IIB (71%)	15%	26%	29%
		Stage III (55%)	5%	20%	30%
		Stage IVA (73%)	27%	0	47%
		Total: 42%	13%	12%	17%
Tabata et al. (159)	51	Stage 0–II (36%)	36%	0%	Not shown
		Stage III–IV (92%)	50%	42%	
Urbanski et al. (23)	125	53%	41%	8%	4%
Frank et al. (48)	193	25%	12%	7%	13%

not found a significant impact of the RT dose and recurrence rate, probably because larger tumors received higher EBRT and brachytherapy doses (14,35). The M. D. Anderson series (48) did not find dose lower than or greater than 75 Gy to be associated with improved pelvic control or disease-specific survival, the only 2 statistically significant factors being the stage of the disease and the size of the tumor over 4 cm.

Perez et al. (4,35) observed increased tumor control in patients with stages IIA to IVA with EBRT and brachytherapy compared to patients receiving brachytherapy alone. In patients with stage I disease, no correlation was found between the technique of RT used and the incidence of local or pelvic recurrences. In addition, they suggested that doses in the range of 70 to 75 Gy to the primary tumor volume and 55 and 65 Gy to the medial parametria for patients with more advanced disease are necessary to optimize tumor and pelvic control. Furthermore, of 100 patients with primary tumors involving the upper and middle third of the vagina who received no elective irradiation to the groins, none developed metastatic inguinofemoral lymph nodes, which is in contrast to 3 of 29 (10%) patients with lower-third primaries and 1 of 20 patients with tumors involving the entire length of the vagina. Of 7 patients with initially palpable inguinal lymph nodes treated with doses to around 60 Gy, only 1 developed a nodal recurrence. The investigators recommended that elective RT of the inguinal lymph nodes should be carried out only in patients with primary tumors involving the lower third of the vagina. Similar results were published by Stock et al. (21) and Stryker (196). Lee et al. (150) identified overall treatment time as the most significant treatment factor predicting pelvic tumor control in 65 patients with carcinomas of the vagina treated with definitive RT. If the entire course of RT, including EBRT and brachytherapy, was completed within 9 weeks, pelvic tumor control was 97% in contrast to only 57% when treatment time extended beyond 9 weeks ($p < 0.01$). Conversely, Perez et al. (35) did not find a significant impact of prolongation

of treatment time on pelvic tumor control. Nevertheless, these investigators advocate completion of treatment within 7 weeks to 9 weeks.

TREATMENT COMPLICATIONS AND THEIR MANAGEMENT

Clearly, the knowledge of common acute and late complications with standard RT and consideration of risk factors may improve the therapeutic ratio of RT for gynecological malignancies in general and for vaginal cancer in particular (228). The anatomic location of the vagina places the lower gastrointestinal and genitourinary tracts at greatest risk for complications after surgery or RT. Although in most of the retrospective series, the investigators comment on the nature of the complications encountered, little information is typically given regarding their prevention or management (13,15,21,33,110,133). In modern oncology, survival rate is the primary endpoint in treatment evaluation, but the analysis of treatment complications and quality of life is of crucial importance.

The acute and chronic pathophysiology of vaginal RT has been well described by Grigsby et al. (215). As an immediate response to high-dose RT, there is loss of most or all of the vaginal epithelium, especially in areas in proximity to brachytherapy sources. Clinically, the severity of the acute effects (edema, erythema, moist desquamation, and confluent mucositis with or without ulceration) varies in intensity and duration depending upon patient age, hormonal status, tumor size, stage, RT dose, and personal hygiene. These effects usually resolve within 2 to 3 months after completion of therapy. In some patients, there is progressive vascular damage with subsequent ulcer formation and mucosal necrosis, which may require up to 8 months for healing. Chemotherapy concurrently with RT enhances the

acute mucosal response to both EBRT and brachytherapy. The effects of chemotherapy on the incidence of late complications, if any, are unclear. Over time, most patients will develop some degree of vaginal atrophy, fibrosis, and stenosis. Telangiectasis is commonly seen in the vagina. Vaginal narrowing or shortening, paravaginal fibrosis, loss of elasticity, and reduced lubrication often result in dyspareunia. More severe complications include necrosis with ulceration that can progress to fistula formation (rectovaginal, vesicovaginal, urethrovaginal). MRI may be useful in evaluating complications of the disease and treatment, such as vesicovaginal or rectovaginal fistulas (216).

The RT tolerance limits of the entire vagina are ill defined given the variety of techniques employed for the treatment of vaginal cancers. An irradiation tolerance level of the proximal vagina was suggested by Hintz et al. (217) based on a study of 16 patients who received a maximum surface dose of 140 Gy, without concurrent chemotherapy, none of whom developed severe complications or necrosis of the upper vagina. Based on their previous observation of a patient who developed a vesicovaginal fistula after receiving a 150-Gy mucosal dose to the anterior vaginal wall, they recommended a tolerance dose level of 150 Gy (direct summation of EBRT dose and ICB) to the anterior upper vaginal mucosa. They advocated dose rates of less than 0.8 Gy/hour. These authors cautioned against placing radioactive needles on the surface of the vaginal cylinder because this may increase the frequency of vaginal necrosis. They also recommended keeping the total dose to the distal vagina less than 98 Gy. In addition, it was also observed that the posterior wall of the vagina is more prone to radiation injury than the anterior or lateral walls, and that the dose should be kept below 80 Gy in order to minimize the risk of rectovaginal fistula (217). More conservative doses are recommended when combining RT with concurrent chemotherapy.

Rubin and Casarett (218) suggested that the tolerance of the vaginal mucosa (Tolerance dose 5/5: 5% necrosis within 5 years) is approximately 90 Gy for ulceration and more than 100 Gy for fistula formation. This tolerance limit has been specified as a direct summation of dosage given by LDR-ICB and EBRT in the treatment of cervical cancer. Within the low-dose-rate range, whether a correction for the brachytherapy dose rate is necessary remains controversial. In a series from Washington University, the traditional LDR tolerance dose of 150 Gy to the mucosa of the proximal vagina was shown to yield a nominal 11% and 4% grade 1, 2, and 3 sequelae, respectively (219).

The incidence of grade 2 or higher complications has been reported to be 15% to 25%, (21,23,33,35,48,120,198,220) with the average of severe complications (those requiring surgery for correction or necessitating hospitalization) being approximately 8% to 17% (48,120). Table 20.7 (47,48,208–210,212,213,221,222) shows the incidence of complications greater than grade 2 in several large series of vaginal cancer patients.

In a series by de Crevoisier et al. (118), anterior tumor location was associated with increased bladder toxicity ($p = 0.01$) and decreased rectal toxicity ($p = 0.08$). Vaginal toxicity was associated with the extent of vaginal involvement ($p = 0.02$) and FIGO stage ($p = 0.03$); the total reference air kerma was significantly higher in the group of patients who experienced grade 2 to 3 urinary or intestinal toxicity ($p = 0.03$).

Host factors that may increase the risk of complications include prior pelvic surgery, pelvic inflammatory disease, immunosuppression status, collagen vascular disease, low body weight, patient age, significant smoking history, and comorbid illness (e.g., diabetes, hypertension, and cardiovascular disease) (4,35,48). In Frank et al. (48) series, major complications at 5 years were found in 25% of current smokers compared to 18% in patients who claimed to quit more than 6 months prior to radiation therapy, compared to only 5% in patients who had

Table 20.7 Complications of Therapy (Grade 2)

Authors	No. of Patients	Percent of Complications (Grade 2)
Chyle et al. (14)	310	19% actuarial at 20 years
Kirkbride et al. (16)	153	10%
Kucera and Vavra (123)	110	5.5%
Perez et al. (35)	212	13%
Peters et al. (110)	86	7 (8%)
Rubin et al. (33)	75	15 (23%)
Stock et al. (21)	100	16% actuarial at 10 years
Urbanski et al. (23)	125	13%
Frank et al. (48)	193	5 years, actuarial Stage I, 4% Stage II, 9% Stage III–IVA, 21%

no smoking history ($p < 0.01$). Other factors, such as diabetes and hypertension, were not found to be significant in their series (48).

Perez et al. (4) reported an increase in the rate of severe complications with higher clinical stage, probably reflecting the higher doses delivered with EBRT and brachytherapy. They observed grade 2 to 3 complications in approximately 5% of patients treated for stage 0 and I disease and in approximately 15% of patients with stage II lesions. No complications were reported in stage III and IV disease, probably because few patients lived long enough to manifest complications of treatment. The most common major complications were proctitis (2), rectovesicovaginal fistula (3), and vesicovaginal fistula (2). The most common minor complications were fibrosis of the vagina and small areas of mucosal necrosis, which were noted in approximately 10% of patients.

Lee et al. (150) showed that the total dose to the primary site was the most significant factor predicting the development of a severe complication (9% in patients receiving ≤ 80 Gy as compared with 25% in those receiving higher doses). Perez et al. (19) reported an increase in the rate of severe complications with higher clinical stage, probably reflecting the higher doses delivered with EBRT and brachytherapy.

Ball and Berman (13) reported on 58 patients with carcinoma of the vagina, including 30 who underwent surgery. There were 4 rectovaginal fistulae (1 following RT and 3 after exenterative surgeries) and 2 vesicovaginal fistulae (1 following radical vaginectomy and the other following a recurrence, being managed with cystectomy and diversion). The single ureterovaginal fistula occurred after radical vaginectomy and partial cystectomy and was managed with ureteroneocystostomy.

In the Peters et al. report (110) of 86 vaginal primaries, there were 2 fistulae in the 57 patients who received primary RT. However, there was a 44% rate of fistula formation in the 9 patients who underwent reirradiation after having previously received RT for an earlier cancer. Rubin et al. (33) reported a 23% incidence of complications after RT, including a 13% rate of fistula formation and a 10% rate of cystitis/proctitis. Although 2 patients developed fistulae following combination therapy, the investigators did not think that the rate of complications following combination therapy was greater than that seen following RT alone.

In the Stock et al. series (21) of 100 patients with vaginal carcinoma, there was a 16% actuarial complication rate at 10 years. All patients undergoing vaginectomy or exenteration lost vaginal function. None of the patients was offered vaginal reconstruction in this series. The investigators emphasized that therapeutic options need to be individualized such that surgery is offered only to those most likely to benefit and least likely to suffer complications.

Chyle et al. (14) in 301 patients noted that 39 (13%) had 48 grade 2 or greater sequelae, including rectal ulceration or proctitis in 10 (3 requiring colostomy), small bowel obstruction in 7, rectovaginal fistula in 6, vesicovaginal fistula in 4, vaginoperitoneal/cutaneous fistula in 2, and vaginal ulceration or necrosis in 8 patients. Fewer complications developed in patients with stage 0 or I tumors (8% to 9%) than with more advanced stages (14% to 40%). Vaginal ulceration occurred in 8 of 206 patients (4%) treated with brachytherapy, but in none of 95 patients who received no brachytherapy ($p = 0.06$).

Frank et al. (48) reported 10% and 17% 5- and 10-year cumulative rates of major (greater than grade 2) complications in a series of 193 patients treated with definitive RT with or without chemotherapy. They found FIGO stage and history of smoking to be the 2 factors significantly correlated with subsequent complications. Other clinical, dosimetric factors or the addition of chemotherapy did not correlate with the likelihood of complications. However, 73% of patients with major complications had tumors involving the posterior vaginal wall.

Treatment options for acute radiation vaginitis include daily vaginal douching with a diluted hydrogen peroxide/water mixture (215). This should continue for 2 to 3 months or until the mucosal reactions have subsided. Patients are then advised to continue douching once or twice per week for several months. Regular vaginal dilation is recommended as a way for patients to maintain vaginal health and good sexual function, although the compliance rate is low. The lack of resolution of vaginal ulceration or necrosis after several months of adequate therapy must be appropriately evaluated, considering the possibility of recurrent tumor. The use of topical estrogens following completion of RT appears to stimulate epithelial regeneration more than systemic estrogens. Some patients with severe radiation sequelae, such as fistula formation, will respond to conservative treatment with antibiotics and periodic limited debridement of necrotic tissue. Delanian et al. (223) published a randomized trial demonstrating the effectiveness of the combination of pentoxifyllin and vitamin E in the regression of radiation-induced fibrosis.

Patients with more severe gastrointestinal or urinary late effects will require urinary or fecal diversion with possible delayed reanastomosis. Occasionally, repair of the fistula may be attempted by employing a myocutaneous graft in which the skin, subcutaneous fat, and muscle are mobilized using a vascular pedicle to maintain the blood supply to the pedicled graft (Martius flap), or by excision of the necrotic tissue with reestablishment of organ continuity (such as in the treatment of high rectovaginal fistula). A detailed review of the pathogenesis and management of potential late effects of treatment is not within the scope of this chapter, and may be found in the chapter on management of complications of gynecologic cancer treatment (see Chapter 30).

It is likely that improvements in modern practice such as advancements in surgical techniques (such as more generous use of myocutaneous flaps) (131,224), improved supportive care during the immediate postoperative stay, the use of more sophisticated RT field setting (3-dimensional conformal therapy and IMRT) and treatment delivery, more accurate brachytherapy techniques, and dose calculations have the potential to lessen complication rates post therapy, regardless of which modality is used.

CLEAR CELL CARCINOMA OF THE VAGINA

Since Herbst and Scully's first report (225) of 7 adenocarcinomas arising in the vagina of adolescent females after *in utero* exposure to DES, there have been several reports limited to DES-related vaginal CCA (27–29,41). In 1979, Herbst et al. (306) reported 142 cases of stage I CCA of the vagina. An 8% risk of recurrence was seen after radical surgery ($n = 117$), and an 87% survival was achieved. There was a 36% risk of recurrence after RT for stage I lesions; however, the investigators acknowledged that, in general, RT was reserved for large stage I lesions that involved more of the vault and were less amenable to surgical resection. Surgery for stage I CCA may have the advantage of ovarian preservation and, after skin graft, better vaginal function. As the majority of CCAs occur in the upper third of the vault, the largest series addressing the surgical approach to these lesions have advocated radical hysterectomy, pelvic and para-aortic lymphadenectomy, and sufficient colpectomy to achieve negative margins. Senekjian et al. have also reported a series of exenterations done for CCA (226). However, there have also been efforts to attempt fertility-sparing radical resections (227) or more limited wide local excisions followed by some form of RT (103). Wharton et al. (228) advocate intracavitary or transvaginal irradiation for the treatment of small tumors because this may yield excellent tumor control with a functional vagina and preservation of ovarian function.

Senekjian et al. (103) reported a series of 219 stage I CCA cases of which 176 had conventional therapy and 43 underwent local therapy. The 2 groups appear to be similar with respect to symptoms, stage, location of the lesion in the vagina, greatest tumor diameter, depth of invasion, predominant histologic pattern, grade, and number of mitoses. Actuarial survival rates at 5 and 10 years for the local therapy group (92% and 88%, respectively) were essentially equivalent to those for the conventional therapy group (92% and 90%, respectively). However, the recurrence experience after local therapy was less favorable; at 10 years, the actuarial recurrence rate for the local excision subgroup was 45%, in comparison with only 13% for patients treated with more radical surgery. Local therapy consisted of vaginectomy in 9 cases, local excision alone in 17 cases, and local irradiation (with or without local excision) in 17 cases. The subgroup of patients receiving local irradiation had a recurrence rate of 27%, similar to that of the conventional therapy group and more favorable than that of either the subgroup treated with vaginectomy or local excision alone. Recurrences were more frequently noted in patients with tumors greater than 2 cm, with invasion of ≥ 3 mm, and with a predominant histologic pattern other than tubulocystic. Pelvic lymph node metastases were noted at death in 12% of patients. They advocated a combination of wide local excision and extraperitoneal node dissection followed by brachytherapy for patients desirous of fertility preservation (103).

In a subsequent report, Senekjian et al. (229) reviewed the experience with 76 cases with stage II CCA from the Registry for Research on Hormonal Transplacental Carcinogenesis. The overall 5- and 10-year survival rates were 83% and 65%, respectively. Of the 76 patients, 22 received surgery exclusively (either radical hysterectomy with vaginectomy, 13 patients, or exenterative type procedure, 9 patients), 38 received RT alone, 12 received combination therapy, and 4 underwent other approaches. Patients treated with primary RT achieved an 87% 5-year survival rate versus 80% for those treated with surgery and 85% for those receiving both treatments. The investigators concluded that most patients with stage II vaginal CCA should be treated with combination EBRT and brachytherapy; however, small, easily resectable lesions in the upper fornix might

undergo resection, allowing better preservation of coital and ovarian function (229).

In 1989, Senekjian et al. (226) reported their experience of 20 pelvic exenterations for CCA of the vagina, including 13 for primary lesions and 7 for recurrent disease. The 9 patients with stage II disease treated with primary exenteration were compared with the 67 who had other modalities of therapy; no significant difference in the survival experience was noted between the 2 groups. They reported a 72% success rate if the exenterations were done as part of primary therapy. They advocated reserving exenterative approaches for those who have failed RT in order to maximize quality of life for the greatest number of patients (226).

There are few published reports regarding the use of systemic therapy for CCA. Fowler et al. (230) reported 1 complete and 1 partial response after treatment with melphalan (1 mg/kg qd $\times$ 5 days). Robboy et al. (37) reported responses in recurrent disease to both 5-FU and vinblastine.

NONEPITHELIAL TUMORS OF THE VAGINA

Melanoma of the Vagina

Vaginal melanoma is an exceedingly rare entity. Therefore, the number of patients with vaginal melanoma is too small to permit prospective controlled trials. Melanoma of the vagina, with its propensity to develop distant metastases and its lack of a recognized precursor lesion, has presented therapeutic challenges for surgeons. Investigators have reported small series with generally disappointing results irrespective of treatment modality (245–250). Because of the reputation of melanoma as a radioresistant tumor, it is not surprising that radical surgery has been considered to be the treatment of choice in operable patients. However, limited data are available that validate its efficacy. Although 75% 2-year survival has been achieved after radical excision in small series (236), most series report 5-year survival rates of 5% to 30% regardless of radicality of surgery (38,245–250).

Levitan et al. (235), in their review of the literature, indicated that although the 2-year survival following radical surgery was better (20% to 40%) than with any other therapy, the 5-year survival rates were equally poor (average 8%) regardless of type of therapy. Furthermore, the incidence of distant recurrence was not influenced by the extent of surgical resection. Geisler et al. (233) published the Indiana University experience using pelvic exenteration for malignant melanomas of the vagina or urethra with more than 3 mm of invasion. None of the 4 patients included in this study had recurrences, and 3 patients remained alive with a minimum follow-up of 31 months. Conversely, Bonner et al. (231) reported 9 cases of vaginal melanoma: Three received wide local excisions and 6 underwent radical surgery (including exenterations and radical vaginectomies with or without hysterectomies), with a 29% actuarial 5-year survival rate. All 9 patients suffered locoregional recurrence. The investigators advocated that surgery alone was ineffective in obtaining local control, and that preoperative RT should be considered (231).

Reid et al. (31) reported an overall 17% 5-year survival rate in a report of 15 patients, including 13 who underwent surgery. In addition, they reviewed the literature, summarizing the results achieved in 115 patients with vaginal melanoma, and compared outcomes for the 55 patients who underwent some form of surgery, including the 24 treated conservatively with wide local excision or partial vaginectomy, to the 31 treated with more radical excisions. No difference in survival or disease-free

survival was found among the different surgical procedures (31). In a meta-analysis of essentially the same patient population ($n = 119$ patients), Van Nostrand et al. (236), after adding 8 of their own cases, reached different conclusions. They stated that radical surgery is recommended for patients with primary vaginal melanomas of less than 10 cm². In the Van Nostrand et al. series of their own 8 patients with vaginal melanoma, including 4 treated conservatively and 4 undergoing radical surgery, the only long-term survivor was in the radical surgery group. In their review of the literature, comprising a total of 119 patients, there was 48% 2-year survival rate if treated with radical surgery (50 patients) versus only 20% if treated conservatively (69 patients) ($p < 0.005$). Therefore, Van Nostrand et al. advocated radical excision for those vaginal melanomas less than 10 cm² in area (236).

Not all authors support a radical resection approach. Buchanan et al. (232) performed a literature review of 66 cases reported since the publication of Reid et al. (31). Survival was influenced by tumor size, with a median survival time of 41 months of those with lesions lesser than 3 cm and 21 months in those with larger lesions. However, there was no statistically significant difference in median survival or 2- and 5-year survival among the various surgical strategies. Hence, many investigators have adopted the suggestion of Irvin et al. (234) that if distant failure and death are expected, quality of life should be optimized by wide excision followed by RT to affect local control, while obviating the need for disfiguring radical surgery (182). In the Irvin et al. series (234), all patients treated with wide local excision or brachytherapy alone developed recurrent disease locally, whereas those patients treated with radical surgical resection or with wide local excision followed by high-dose-per-fraction EBRT maintained locoregional control until death.

Recent retrospective data suggest that vaginal melanoma is reasonably radioresponsive and possibly radiocurable (234,237). Volumes and doses of irradiation are similar to those used for epithelial tumors, ranging from 50 Gy for subclinical disease to 75 Gy for gross tumors. Retrospective analysis suggested a dose-response curve of melanoma to external beam irradiation as the dose per fraction is increased and fractions of 3.5 Gy 3 times weekly to 5 Gy twice weekly have been used to treat melanoma because of a large D_{50} observed in *in vitro* studies (238,239). However, the Radiation Therapy Oncology Group conducted a prospective randomized study (RTOG 83–05) (240) evaluating the effectiveness of high-dose-per-fraction irradiation in the treatment of melanoma. Patients with measurable lesions were randomized to 4 $\times$ 8.0 Gy in 21 days once weekly to 20 $\times$ 2.5 Gy in 26 to 28 days, 5 days a week. One hundred thirty-seven patients were randomized and 126 patients were evaluable; stratification was performed on lesions lesser than 5 cm or $\geq$ 5 cm. There was no difference between the 2 arms in terms of response rate (complete responses 24.2% and 23.4% in the 4 $\times$ 8.0 Gy and in the 20 $\times$ 2.5 Gy arms, respectively) (240).

Harwood and Cummings (241) described a complete response in 4 patients with vaginal melanoma treated with irradiation, although 2 subsequently relapsed; complete response to irradiation was seen in 1 patient who was alive and well 10 months after treatment. Harrison et al. (242) reported that 1 of 3 patients with vaginal melanoma treated with irradiation survived 7.5 years; the other 2 died with distant metastases but had local tumor control. Rogo et al. (243) reported on 22 cases of vulvovaginal melanoma treated with conservation surgery or irradiation, or both. Eight patients (36%) were alive 5 years after treatment, and 4 were alive 10 years after treatment. Inguinal lymph node recurrences and distant metastases were the most common modes of failure. Results were comparable with those obtained with radical surgery.

In the Petru et al. series (237) of 14 patients, the 3 long-term survivors received either primary RT after biopsy only,

or adjuvantly after local excision. Tumor size was found to be prognostically important, with 43% of patients with tumors ≤ 3 cm surviving longer than 5 years, compared with 0% of patients with tumors greater than 3 cm. The median overall survival was 10 months, and the 5-year DFS and overall survival rates were 14% and 21%, respectively. The authors concluded that prolonged local control could be obtained with RT as an adjunct to more limited surgery, or even with RT alone, primarily in patients with lesions ≤ 3 cm in diameter.

In summary, given that the high incidence of distant metastasis remains a major factor in limiting curability, a more conservative treatment approach might be more reasonable in selected patients. Patients with vaginal melanoma should probably be managed in a manner similar to that recommended for cutaneous lesions (244). Wide local excision with 1- to 2-cm margins should be the surgical treatment of choice for most primary vaginal melanomas since radical surgery has failed to improve long-term survival. The role of adjuvant RT is unclear, but it appears to improve survival in some series. The use of systemic chemotherapy and/or immunotherapy has been very disappointing in the limited published data (245).

Sarcomas of the Vagina

Sarcomas represent 3% of vaginal primaries (5), with leiomyosarcoma representing 50% to 65% of vaginal sarcomas. Unfortunately, most of the sarcomas are diagnosed at an advanced stage. Histopathologic grade appears to be the most important predictor of outcome. Most vaginal leiomyosarcomas arise from the posterior wall of the vagina. Radical surgical resection, such as posterior pelvic exenteration, offers the best chance for cure for vaginal leiomyosarcomas (5,246). The largest series on vaginal sarcomas reported to date included 17 cases, of which 35% had received prior RT. This series, which included ten leiomyosarcomas, 4 malignant mixed müllerian tumors (MMMTs), and 3 other sarcoma types, noted that all were resistant to chemotherapy, and all of the failures were first noted as pelvic recurrences. There were only 3 survivors seen, and all had undergone exenterative surgery. The 5-year survival rate was 36% in patients with leiomyosarcoma and 17% in those with MMMT (247).

Vaginal MMMTs occur more commonly in postmenopausal women. In approximately half of the cases there is a history of prior pelvic RT (247,248). Despite surgery and adjuvant RT, patients usually do poorly, with a high incidence of local and distant recurrences. The treatment of choice is complete surgical resection, followed by EBRT and ICB in an attempt to decrease the local recurrence rate.

The roles of adjuvant chemotherapy and RT in vaginal sarcomas have not been clearly defined, primarily owing to limited patient numbers and even fewer data where chemotherapy was used as the primary treatment rather than as salvage therapy at recurrence. Adjuvant RT seems to be indicated in patients with high-grade tumors and locally recurrent low-grade sarcomas. According to Peters et al. (247), the most common site of failure is the pelvis. In 50% of patients with recurrence, it is the only site of failure. Extrapolating data from the Gynecologic Oncology Group (249) for uterine sarcomas and considering patterns of failure, patients with localized MMMTs would be appropriately treated with pelvic exenteration, or with more limited surgical resection followed by postoperative RT, unless the patient has received prior pelvic RT. Since patterns of failure suggest that local therapies only reduce the local recurrence rate and do not improve survival, consideration should be given to adjuvant treatments with agents that are active in similar tumors arising in the uterus. Agents found to be active in MMMT of the uterus include ifosfamide, cisplatin, and paclitaxel, although it remains unclear whether any combination of these agents is better than

ifosfamide alone, which has produced the highest response rate among these agents (250,251). Doxorubicin remains the standard therapy for leiomyosarcoma (252).

Embryonal rhabdomyosarcoma (RMS) of the vagina, the most common pediatric vaginal tumor, is such a rare lesion that no single institution has sufficient experience to identify superior therapeutic strategies. Rather, cooperative efforts through the Intergroup Rhabdomyosarcoma Study Group (IRSG) through numerous clinical trials have demonstrated that the use of multimodality therapy with wide local excision and cytotoxic chemotherapy with or without RT makes it possible to avoid exenterative surgery and optimize quality of life for these young patients (251–255). Prior to the modern era of multimodality therapy, Hilgers reported that only 20% to 30% 5-year survival rates were achieved with the use of exenterative-type surgery alone (256). Later, several small series noted that 70% survival could be achieved if RT and combination cytotoxic chemotherapy including vincristine, actinomycin D, and cyclophosphamide (VAC) were given in addition to radical surgery (256–258). After complete resection, irradiation of the entire pelvis is not required, thus avoiding its adverse effects.

In a series of reports from the IRSG, survival rates in excess of 85% have been achieved utilizing VAC chemotherapy and wide excision with or without adjuvant RT, sparing the great majority of patients from exenterative surgery (253–255,259,260). In a subsequent report, Andrassy et al. (261) from the IRSG summarized the outcome of 72 patients with embryonal RMS of the vagina treated on 4 IRSG trials. Over the course of the 4 IRSG trials, the need for radical resection decreased from 100% to 13%, with continued improvement in disease-free survival (261). Andrassy et al. suggested that after biopsy to document RMS, multiagent induction chemotherapy with doxorubicin, cisplatin, vincristine, actinomycin D, and cyclophosphamide should be utilized, then local resection undertaken, with radical resection being reserved for those with persistent or recurrent disease (261). In addition, several non-IRSG series have shown that combination chemotherapy with or without RT leads to sufficient tumor shrinkage, and that less radical resections can become feasible (259,260), allowing preservation of anatomy and function.

Flamant et al. (259) reported 11 cases of vaginal RMS (8 stage I, 2 stage II, 1 stage III) in whom 100% survival was achieved with multimodality therapy. Eight patients received neoadjuvant chemotherapy, generally a VAC regimen, and all patients underwent brachytherapy (doses of 26 to 75 Gy), followed by maintenance chemotherapy and VAC alternating with VAD (vincristine, doxorubicin, dacarbazine). Seven patients underwent ovarian transposition in an attempt to preserve function. The investigators noted partial ovarian insufficiency in 1 patient without ovarian transposition. They recommended brachytherapy at a total dose of approximately 50 to 60 Gy (259).

Lymphomas and the Vagina

Lymphomatous involvement of the vagina most often represents metastatic spread from another primary site. Although surgery (including radical hysterectomy, pelvic lymphadenectomy, vaginectomy, and exenteration) has been performed in the past, more recent reports suggest that combination RT and chemotherapy can achieve excellent results. Radical surgery in such patients then should be avoided, as lymphoma represents a systemic disease. Following biopsy, patients with lymphoma should be managed with chemotherapy alone or combined chemoradiation. Extrapolation from patients with similar tumors arising in extranodal sites would suggest that RT has its primary role in preventing local recurrence in patients who present with bulky disease. In some patients who have a rapid and complete response to multiagent chemotherapy, RT may not be indicated

since the combination of both modalities increases the risk of second malignancies. Harris and Scully noted in a clinicopathologic series of 25 lower genital tract lymphomas, including 4 vaginal lymphomas, that definitive local therapy prevented relapse (262). Prevot et al. (263) and Perren et al. (264) also advocated the use of less extensive surgery, with RT plus cytotoxic multiagent chemotherapy such as CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], prednisone) or BACOP (bleomycin, Adriamycin [doxorubicin], cyclophosphamide, Oncovin [vincristine], prednisone) for 4 to 6 cycles to affect local control with better preservation of fertility in patients with stage IE and nonbulky tumors of low and intermediate grade.

Yolk Sac (Endodermal Sinus) Tumors of the Vagina

Prior to the use of multiagent cytotoxic chemotherapy, less than 25% of patients with yolk sac tumor (YST), or endodermal sinus tumor (EST), of the vagina survived. However, Young and Scully noted 100% survival in a small series of 6 patients who had received chemotherapy (265). The VAC regimen in conjunction with surgery or RT was advocated by Copeland et al. (257). Collins et al. (266) reported on the use of combination bleomycin, vinblastine, and platinum (BVP) for patients with EST of the vagina. Aartsen et al. (267) reported a successful pregnancy following surgery and chemotherapy. Most recently, Hwang et al. have reported 2 cases, one of which did well with partial vaginectomy followed by 2 years of VAC; however, the second patient developed a central persistence following wide local excision and VAC, but was salvaged with bleomycin, etoposide, and platinum (BEP) (268). Given the excellent results that 3 to 4 cycles of BEP have achieved in malignant germ cell neoplasms of the ovary (269), it is likely that BEP will become the preferred regimen for EST of the vagina used in conjunction with partial vaginectomy, as it requires less prolonged administration and is less oophorotoxic than VAC. It appears that routine use of combination chemotherapy in the management of endodermal sinus tumor allows conservative surgery with preservation of sexual function in young patients, with excellent prospects for long-term survival.

The role of radiation in this disease is limited because of the younger age at presentation, and preservation of ovarian function is desired; in addition, RT would potentially increase the risk for secondary malignancies (270,271), which may be even more significant with the use of IMRT as the volume of irradiation receiving lower doses is generally larger (272). Brachytherapy may occasionally be used, and in one instance, preservation of hormonal function and subsequent pregnancy were reported (267).

OTHER UNCOMMON VAGINAL CANCERS

SCC of the Neovagina

In situ and invasive carcinomas arising in the neovagina are rare, and this type of malignancy seems to be related to the transplanted tissue. A few cases of SCC have been described after split-thickness skin graft vaginoplasty in patients with vaginal agenesis (273–275), as well as after radical vulvovaginal resection for known malignancy (276). Mucinous adenocarcinoma has been described arising in the sigmoid colon used for the reconstruction of the neovagina (277). Neovaginal malignant melanoma following surgery and radiation therapy for vulvovaginal malignancies, although extremely rare, has been reported (278),

suggesting the potential role of radiation-induced melanoma in non-sun-exposed areas such as the genital tract.

Malignant transformation occurs in the neovaginal epithelium, in relation with local carcinogenic environmental factors as well as possible viral infection, with the subsequent risk of malignancy. Therefore, it is important to emphasize the need for regular follow-up visits with Pap smears. The elapsed time between the construction of the neovagina and the development of malignancy ranges between 10 and 30 years. The optimal treatment is not well defined. Radical surgery resection when possible should be the treatment of choice, since definitive RT seems to be associated with higher failure rates (227). Adjuvant RT could be considered in patients with positive margins or positive nodes (277).

Carcinoma in Episiotomy Scar

Episiotomy scar tumor implantation from a cervical or vulvar carcinoma is a very rare event. Van Dam et al. (279) reported on 3 cases of primary or metastatic carcinoma in an episiotomy scar. One patient had a primary SCC of the vulva in an episiotomy scar; a second patient was diagnosed with cervical carcinoma 6 months postpartum and was found to have a metastatic deposit in the episiotomy scar during the staging of her disease; the third patient developed adenocarcinoma metastatic from an endocervical primary in an episiotomy scar that presented as a small nodule at the introitus. These cases exemplify the need for careful inspection and biopsy of any nodular lesions in episiotomy scars as part of the initial assessment and follow-up of patients with premalignant or malignant lesions of the lower genital tract. Early initial stage, small size lesion, and early therapy appear to improve prognosis. Treatment needs to be individualized given the rarity of this entity. Patients with limited recurrent disease at the episiotomy site without any other evidence of locoregional recurrence could be treated with surgical resection followed by tailored radiation therapy. Patients with more advanced disease may be offered radiation with or without chemotherapy followed by surgical resection when feasible (280,281).

SALVAGE THERAPY

In general, the patient with recurrent cancer of the lower female genital tract presents a difficult clinical dilemma. Optimal therapy for patients with recurrent gynecologic cancer after potentially curative therapy has not been completely defined, partly owing to the difficulty of conducting prospective, randomized trials in this heterogeneous population. It must be determined if the disease is amenable to curative salvage therapy, implying some reasonable chance of cure, or whether palliation is the primary goal. Treatment selection factors include primary therapy, extent of the disease at presentation, site of recurrence, extent of the recurrence, disease-free interval, evidence of metastatic disease, patient age, performance status, and coexisting medical conditions.

The presence of distant metastasis portends a poor prognosis, and although chemotherapy may result in objective responses and improvements in short-term survival, the current lack of curative systemic treatments focuses therapeutic attempts on symptom palliation and quality of life. In most cases, only patients with small volume local recurrences and no metastatic disease are curable. Therefore, careful workup to establish extent of disease is crucial. When salvage therapies are contemplated, local recurrences should be confirmed by biopsy, and, when possible, parametrial recurrences should be documented pathologically. Pelvic sidewall involvement can almost always be diagnosed in the presence of a symptom triad of sciatic pain,

leg edema, and hydronephrosis. It is important to evaluate for regional and/or distant metastasis by physical examination and imaging studies such as CT or MRI scans. More recently, the positron emission tomography (PET) scan has been used to document the extent of recurrent disease (282), but both false-positive and false-negative results have been reported.

Generally, patients with isolated pelvic or regional recurrences after definitive surgery who have not received prior RT are managed with EBRT, often in conjunction with brachytherapy (16,21,24). Concurrent cisplatin-based chemotherapy may also be recommended (23). Salvage options for patients with central recurrence after definitive or adjuvant RT are limited to radical surgery, usually exenterative (16,21,23,24). In selected patients with small volume disease, reirradiation using interstitial radiation implants or highly conformal 3-dimensional EBRT may be feasible. Response rates with chemotherapy are low and the impact on survival is limited. Further, response to chemotherapy in central pelvic recurrences following RT tends to be less common than response at distant sites. Additionally, prior high-dose radiation therapy compromises bone marrow tolerance of many agents that are active in this tumor (e.g., ifosfamide and doxorubicin). However, chemotherapy-responsive patients can obtain meaningful palliation in many cases.

Surgical Considerations

Despite thorough clinical evaluation of patients considered being excellent candidates for salvage surgery, this will be aborted in over 25% of the cases because of advanced disease found at the time of the exploratory laparotomy (283). Pelvic exenteration results in long-term functional and psychological changes that have not been adequately studied (284). Surgical refinements have done much to improve body image changes associated with pelvic exenteration. The purposes of vaginal and perineal reconstruction following radical pelvic surgery for recurrent gynecologic cancer are primarily twofold: to restore or create vulvovaginal function, and thereby minimize the effects of surgical treatment on body image and normal sexual activity, and to minimize postoperative complications by transferring to the pelvic defect healthy tissue with a good blood supply (155,156). A detailed review of urinary diversion and pelvic reconstruction techniques is not within the scope of this chapter.

Radiation Therapy Considerations

Those patients who have not received prior RT should receive whole-pelvis EBRT followed, when feasible, by brachytherapy. Generally, the whole pelvis receives a dose of 40 to 50 Gy. Inguinofemoral lymph node regions should be included in patients with involvement of the distal third of the vagina or with vulvar recurrences. The gross tumor volume in the vagina, paravaginal tissues, and/or parametrium should receive an additional boost, preferably with an interstitial implant, to bring the total tumor dose to 75 to 80 Gy. The role of combined chemoradiotherapy in the management of patients with recurrent disease is unknown. Given the rarity of vaginal carcinoma and the heterogeneity within the population with recurrent disease, large randomized studies intended to answer this question will probably never be conducted. However, by extrapolation from the available data for locally advanced cervical and vulvar cancer (136,203–207), it seems that a combined modality approach may improve the locoregional control and survival in patients with isolated pelvic recurrences.

Reirradiation in previously irradiated patients must be undertaken with extreme caution. However, selected patients who are medically inoperable, technically unresectable, or refuse to undergo exenterative surgery are appropriately considered for reirradiation to limited volumes. A variety of techniques is available,

and the choice is based on patient and tumor-related factors, as well as the experience of the radiation oncologist. When using EBRT, multiple-beam arrangements utilizing 3-dimensional treatment planning are favored. Only limited doses are possible, and the physician might consider a hyperfractionated regimen in an attempt to decrease the incidence of late toxicity.

In patients with small, well-defined vulvovaginal or pelvic recurrences, reirradiation using primarily interstitial techniques has been attempted with control rates between 50% and 75% and grade 3 or higher complication rates between 7% and 15% (285–389). The rationale, logistics, and selection of implant technique when performing an ITI were reviewed earlier in the chapter. Permanent radioactive seed implants (e.g., ¹⁹⁸Gold) in patients with small vaginal recurrences often provide long-lasting tumor control in elderly or medically debilitated patients previously treated with definitive doses of RT (301). In a series by Brabham and Cardenes (307), 19 patients with low volume recurrent gynecologic malignancies (4 vaginal primaries) were treated with permanent interstitial implants using ¹⁹⁸Gold. Complete response was observed in almost 95% of patients and local control was achieved in 63%; however the authors emphasize that these results are in a selected patient population with small volume recurrences no thicker than 1 cm (161).

Other potential treatment options include the use of surgery and intraoperative RT (IORT) with intraoperative electron beam (290,291), laparotomy, or laparoscopically guided placement of HDR catheters (192,291–293), which allows direct visualization of the target volume and displacement and/or shielding of the surrounding normal tissues. However, the published series are generally small, including a wide spectrum of patients with different gynecologic malignancies, varying amounts of residual disease, and disparate initial therapies. The locoregional recurrence and distant metastasis rates after IORT vary between 20% and 60% and 20% and 58%, respectively. The 3- to 5-year actuarial survival is poor, ranging from 8% to 25%. Grade 3 or higher toxicity has been reported in about 35% of patients (290,291). In the Memorial Sloan-Kettering Cancer Center experience using radical surgical resection and HDR-IORT, patients with complete gross resection had a 3-year local control rate of 83% compared to 25% in patients with gross residual disease. Interestingly, most of the failures in the microscopic group were distant, perhaps indicating a potential role for adjuvant chemotherapy (292).

Hockel et al. (293) described a combined operative and radiotherapeutic treatment (CORT) for the treatment of recurrent gynecologic malignancies infiltrating the pelvic side wall. The procedure involves gross complete resection of the tumor and a single plane interstitial implant. In order to improve the therapeutic index, well-vascularized tissue is transposed to the pelvis to protect the hollow organs and reduce the late effects of RT. Reconstruction of pelvic organs is performed as with exenteration. The tumor bed is irradiated postoperatively, days 10 to 14, using HDR brachytherapy. In a total of 48 patients treated with this technique, the overall severe complication rate was 33% at 5 years. The 5-year survival rate was 44%, and the absolute local control rate was 60% for the first 20 patients and 85% for the last 28 treated patients (293).

Stereotactic body radiotherapy (SBRT), also known as extracranial stereotactic radioablation (ESR), is a novel treatment paradigm that delivers a small number of high-dose fractions to extracranial targets using a linear accelerator with highly precise, accurate, and reproducible target localization based on the same principle as that of gamma-knife therapy. By means of better target localization and patient immobilization, smaller margins of normal tissue surrounding the gross tumor volume are required, which allows treatment complications to be minimized. Blomgren et al. (294) reported on 15 patients with 19 extrahepatic abdominal tumors who had a mean survival of 17.7 months. The toxicity was more often self-limited except for

4 patients with gastrointestinal bleeding. They concluded that this treatment, which is noninvasive, painless, rapid, and does not require hospitalization, does not impair the quality of life of the patients when used properly. Additional 3 reports in the literature describe using SBRT for primary or recurrent gynecological malignancies (220,295,296).

Molla et al. (296) used SBRT in place of a brachytherapy boost in 16 patients (14 primary and 2 patients with recurrent disease). SBRT doses of 2 fractions of 7 Gy or 4 fractions of 5 Gy were used and the authors report high rates of local control with only 1 local failure. One patient in their series had late rectal complications with grade 3 rectal bleeding 18 months after reirradiation for a vaginal vault relapse.

Guckenberger et al. (295) reported on 19 patients that were treated with stereotactic body radiotherapy for a local boost in unfavorable locally recurrent gynecological cancers (12 recurrent cervical cancers and 7 recurrent endometrial). The majority of patients were treated with conventionally fractionated EBRT followed by a stereotactic boost because the large volume and/or peripheral location of the recurrence made vaginal brachytherapy inappropriate as a sole boost technique. Three patients received SBRT only. The mean dose delivered with EBRT was 50 Gy and the mean stereotactic dose was 3 fractions of 5 Gy prescribed to the 65% isodose line. The local control rate for these recurrences was 81% after 2 and 3 years. The rate of late toxicity greater than grade 2 was 25%, with 2 patients suffering from intestinovaginal fistula and 1 patient from small bowel ileus.

PALLIATIVE THERAPY

Radiation Therapy

At the present time, there is no curative option for patients who present with stage IVB disease. Many of these patients suffer from severe pelvic pain or bleeding. If vaginal bleeding is the main concern, ICB, if feasible, often offers good symptom control with relatively low morbidity. For patients who have

received prior RT, intracavitary doses in the range of 35 to 40 Gy to point A should be prescribed.

A short course of EBRT using high-dose fractionation schedules has been used, including single doses of 10 Gy per fraction, times 3, with an interval of 4 to 6 weeks between courses, combined with misonidazole (RTOG clinical trial 79-05), resulting in significant palliation in selected patients with advanced gynecologic malignancies. The overall response rate was 41% for patients completing the 3 courses; however, the actuarial 45% incidence of grades 3 and 4 late gastrointestinal toxicity was unacceptable (297).

Spanos et al. (298) reported on a Phase II study (RTOG 85-02) of daily multifraction split-course EBRT in patients with recurrent or metastatic disease. The regimen consisted of 3.7 Gy per fraction given twice daily for 2 consecutive days and repeated at 3- to 6-week intervals for a total of 3 courses (tumor dose 44.4 Gy). Occasionally, this regimen was combined with an intracavitary implant (ICI) (4,500 mgh), with a midline block in the last 14.4 Gy. Complete tumor response was noted in 15 patients (10.5%) and partial response in 32 (22.5%). In patients completing 3 courses of irradiation (59%), the rate of complete or partial response was 45%. Twenty-seven patients survived longer than 1 year. Late complications were significantly fewer, with a projected actuarial rate of 5% at 12 months. In a subsequent Phase III study (299), 136 patients were randomized between rest intervals of 2 versus 4 weeks between the split courses of RT. Decreasing the interval between courses did not result in a significant improvement in tumor response (34% vs. 26%). More patients in the 2-week rest group completed the 3 courses of therapy, and not surprisingly, patients completing all 3 courses had a higher overall response rate than patients completing less than 3 courses (42% vs. 5%) and a higher complete response rate (17% vs. 1%). This schedule offers significant logistic benefits, and has been shown to result in good tumor regression and excellent palliation of symptoms (299). Spanos et al. (300) reported a trend toward increased acute toxicity in patients with shorter rest periods, but late toxicity was not significantly different in the 2 groups (Fig. 20.13).

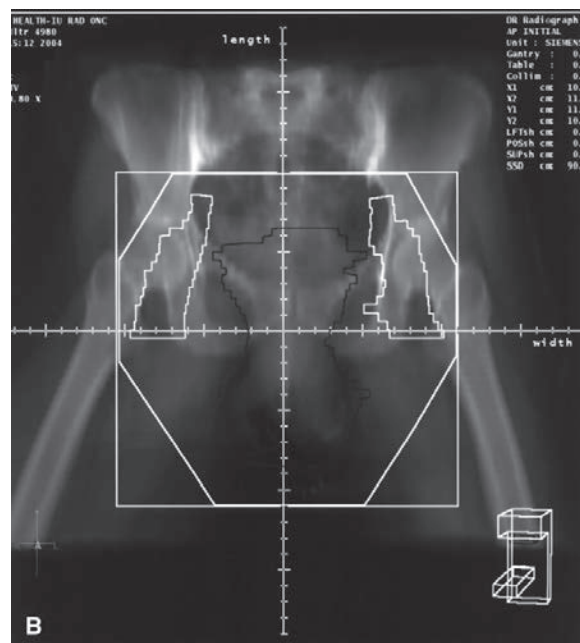
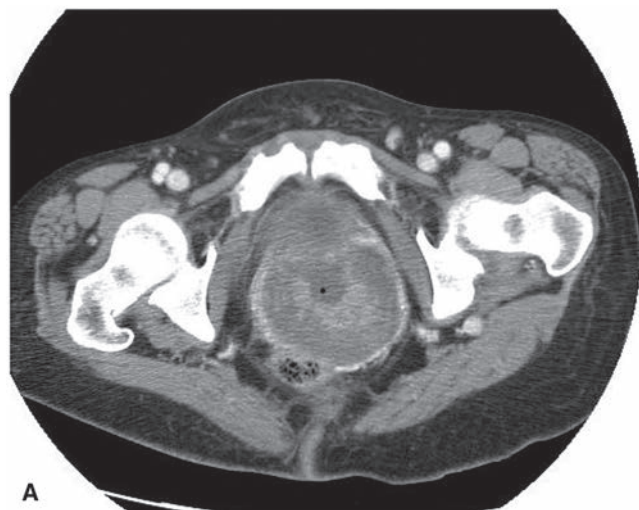


FIGURE 20.13. Palliative course of external beam irradiation using the RTOG 85-02 regimen. CT scan prior to initiation of therapy (A); AP (B) and lateral DRRs (C) of the initial fields; CT scan after 2 split courses of hypofractionated irradiation (2950 cGy) in 1 week (D). AP (E) and lateral DRRs (F) of the cone down fields prior to a brachytherapy boost; AP (G) and lateral radiographs (H) of the brachytherapy implant.

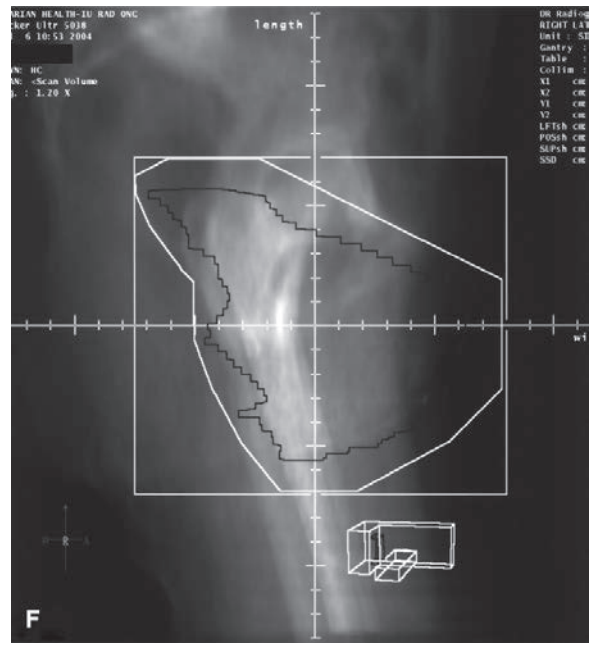
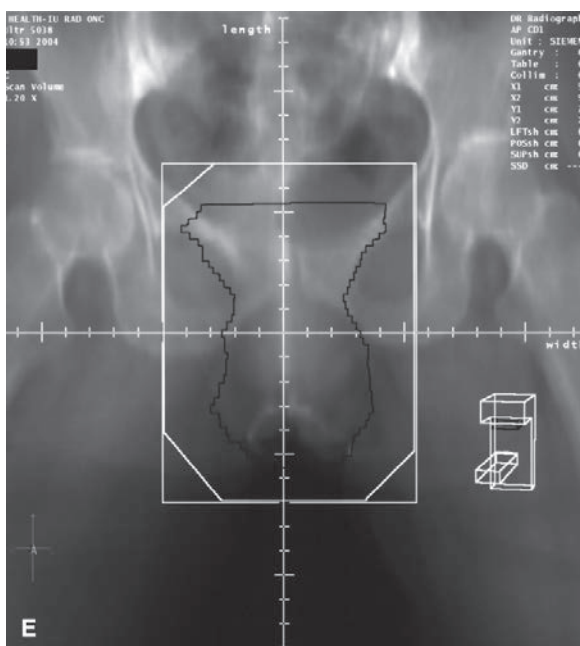
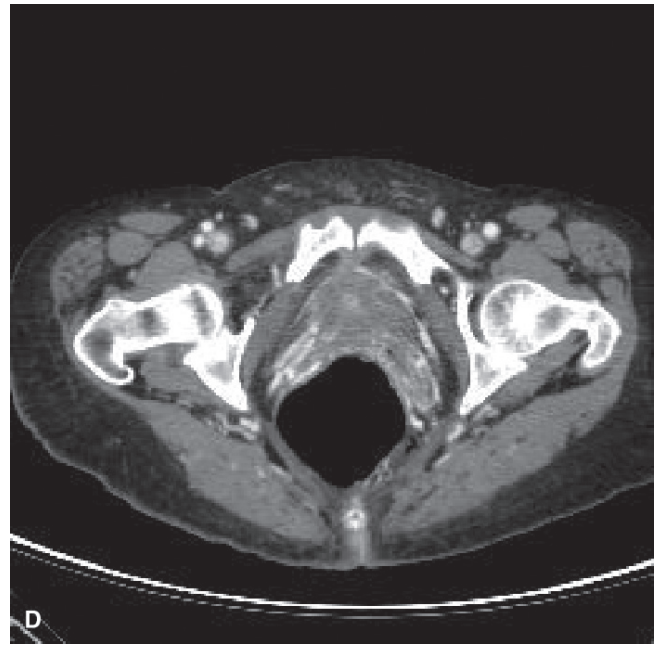
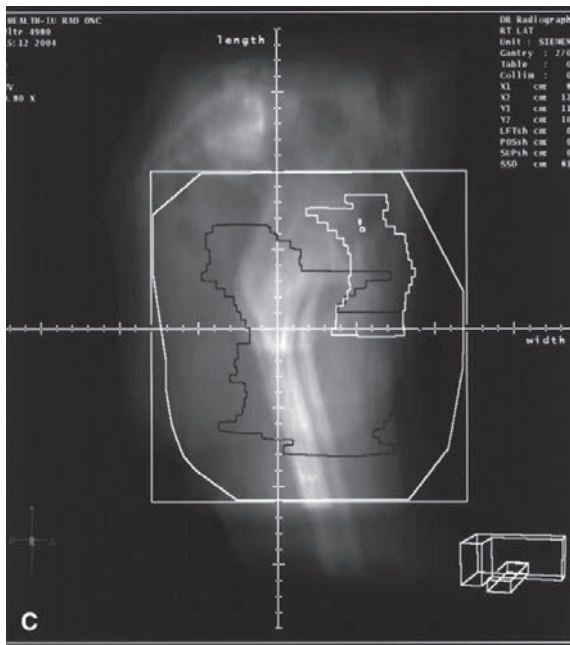


FIGURE 20.13. Continued

Chemotherapy in Advanced and Recurrent Vaginal Cancer

Given its rarity, most chemotherapy reports for treatment of metastatic disease in vaginal cancer are anecdotal or combined with reports of treatment of advanced or recurrent cervical cancer. Concurrent chemoradiation is frequently employed in clinical practice in the treatment of unresectable, locoregionally advanced disease. Various chemotherapeutic agents have been

used with limited success (197,198). Evans et al. (197) reported on 7 patients with vaginal cancers who were treated with a combination of 5-FU 1,000 mg/m²/day for 4 days, mitomycin C 10 mg/m² day 1, and primary irradiation, receiving 2,000 to 6,500 cGy. All of the vaginal cancer patients responded, and 66% were alive with a median follow-up of 28 months. Treatment of recurrent or metastatic disease is confined to a handful of phase 2 clinical trials and anecdotal reports. In general, regimens that are active in cervical cancer are usually active

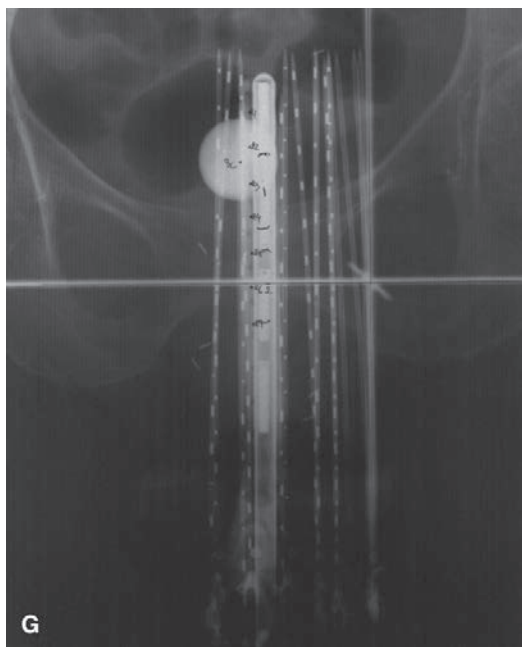
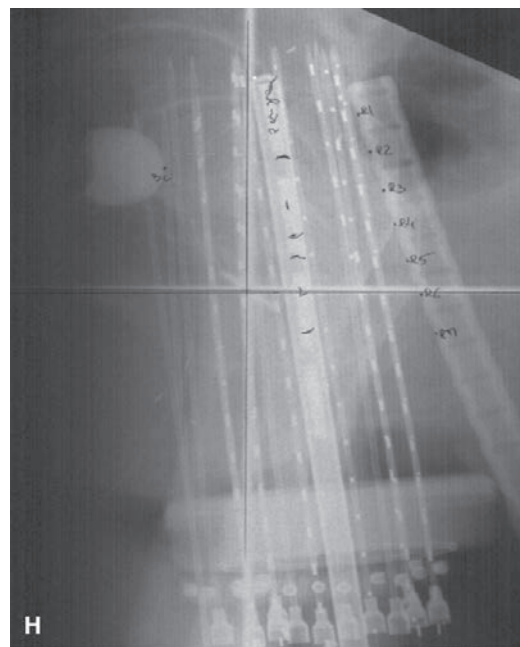


FIGURE 20.13. Continued



in vaginal cancer. Thigpen et al. (251) reported the results of a Phase II trial of cisplatin 50 mg/m² every 3 weeks in 26 patients with advanced or recurrent vaginal cancer. There were 22 evaluable patients, 16 with SCC, 2 adenosquamous carcinoma, 1 CCC, 1 leiomyosarcoma, and 2 unspecified. Of the 16 SCC patients, there was 1 complete response (6.2%). It should be noted that these patients, for the most part, had received prior surgery and RT. Muss et al. (301) reported no responses in 19 evaluable patients who were treated with mitoxantrone 12 mg/m² every 3 weeks. Median survival of patients with vaginal cancer was 2.7 months. Other anecdotal reports of responses in trials that included advanced cervical cancer include a report by Long et al. (302) in which 3 patients with advanced vaginal SCC received treatment with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). All 3 patients achieved a complete response of short duration. Patton et al. (303) reported the results of intra-arterial chemotherapy with mitomycin C, bleomycin, cisplatin, and vincristine, including 6 patients with primary vaginal cancer and 40 patients with cervical cancer. Seventy-six percent responded to intra-arterial chemotherapy and subsequently received primary RT. The report did not give details as to site of relapse, impact on disease-free survival, or overall survival.

At the present time, data on systemic treatment of advanced vaginal cancer outside of a clinical trial is purely anecdotal, although it might be reasonable to extrapolate from the experience reported with SCC of the cervix and vulva (136,203–207). Although published response rates are low, standard therapy should include cisplatin alone or in conjunction with RT in patients with locoregionally advanced vaginal cancer.

SUMMARY AND CONCLUSIONS

The malignant histologies of the vagina are so rare that randomized clinical trials have not been undertaken. It is difficult to establish strong, evidence-based recommendations in such a rare disease as cancer of the vagina. Therefore, future progress will

likely come from reports from single institutions. Most of the available data refer to the treatment of primary invasive SCC of the vagina, since this represents the most common histology. The following management recommendations are made based on the available data.

Vaginal Intraepithelial Neoplasia

In patients with unifocal disease, partial colpectomy has come to be favored over laser vaporization, since there is an approximately 25% risk that there can be underlying invasive disease, and one-quarter to one-third of patients will require a second laser vaporization to effect long-term control. However, for patients who develop VAIN following radiation wherein colpectomy would be associated with a higher risk of fistulae development, there may be a role for laser vaporization and/or topical 5-FU application. Intracavitary brachytherapy alone has provided satisfactory functional and local control results as well.

Invasive SCC

Although RT can control many cases of vaginal cancer, local control remains a problem. The treatment of invasive SCC with RT should include the use of brachytherapy, with particular attention to technique that ensures that the treatment volume is adequately covered. In larger tumors, the dose that is needed to achieve local control may well exceed the tolerance of surrounding normal tissues. Although not specifically proven for patients with vaginal primaries, the addition of chemotherapy (i.e., weekly cisplatin) as a radiosensitizing agent may help to improve these results if the strong evidence in locally advanced cervical cancer can be extrapolated to vaginal cancer. Although there are multiple series that demonstrate excellent results with radical surgery for well-selected early-stage patients, RT will continue to be the primary modality even for early-stage disease and for those elderly patients with multiple comorbid conditions.

Clear Cell Adenocarcinoma

It has been suggested that patients with early-stage disease may be offered fertility-sparing combined modality local therapy with extraperitoneal node dissection and wide local excision followed by brachytherapy with acceptable local failure rates. However, advanced-stage disease would require primary RT. Patients who have completed childbearing would be best served by radical hysterectomy, colectomy, and lymphadenectomy. Exenteration should be reserved for those patients who have isolated central failures following definitive RT.

Melanoma

The risk of distant metastases is high enough that most modern investigators have suggested that ultra-radical surgery, although it might improve 2-year survival rates, has not led to an increase

in long-term survival. Wide excision followed by RT to affect local control may obviate the need of disfiguring surgery in those likely destined to develop distant metastases.

Sarcoma

The trials conducted by the IRSG and others have demonstrated that pediatric embryonal RMS of the vagina is best approached with induction multiagent-combination therapy, such as VAC, followed by local resection with or without brachytherapy, with radical surgery being reserved for those with persistent or recurrent disease. Patients with adult-onset vaginal sarcoma do not respond as well to chemotherapy, and the only long-term survivors are those who have been offered exenterative surgery.

REFERENCES

- Sedlis A, Robboy SJ. Diseases of the vagina. In: Kurman RJ, ed. *Blaustein's Pathology of the Female Genital Tract*. 3rd ed. New York, NY: Springer-Verlag; 1987:98–140.
- Plentl AA, Friedman EA. Lymphatic system of the female genitalia. In: Plentl AA, Friedman EA, eds. *The Morphologic Basis of Oncologic Diagnosis and Therapy*. Vol 2. Philadelphia, PA: WB Saunders; 1971:51–74.
- Frumovitz M, Gayed IW, Jhingran A, et al. Lymphatic mapping and sentinel lymph node detection in women with vaginal cancer. *Gynecol Oncol* 2008;108(3):478–481.
- Perez CA, Camel HM, Galakatos AE, et al. Definitive irradiation in carcinoma of the vagina: long-term evaluation and results. *Int J Radiat Oncol Biol Phys*. 1988;15(1283–1290):1283.
- Creasman WT, Phillips JL, Menck HR. The National Cancer Data Base report on cancer of the vagina. *Cancer*. 1998;83(5):1033–1040.
- Shah CA, Goff BA, Lowe K, et al. Factors affecting risk of mortality in women with vaginal cancer. *Obstet Gynecol*. 2009;113(5):1038–1045.
- Daling JR, Madeleine MM, Schwartz SM, et al. A population-based study of squamous cell vaginal cancer: HPV and cofactors. *Gynecol Oncol*. 2002;84(2):263–270.
- Brinton LA, Nasca PC, Mallin K, et al. Case-control study of *in situ* and invasive carcinoma of the vagina. *Gynecol Oncol*. 1990;38(1):49–54.
- Aho M, Vesterinen E, Meyer B, et al. Natural history of vaginal intraepithelial neoplasia. *Cancer*. 1991;68(1):195–197.
- Weiderpass E, Ye W, Tamimi R, et al. Alcoholism and risk for cancer of the cervix uteri, vagina, and vulva. *Cancer Epidemiol Biomarkers Prev*. 2001;10(8):899–901.
- Iversen T, Tretli S, Johansen A, et al. Squamous cell carcinoma of the penis and of the cervix, vulva and vagina in spouses: is there any relationship? An epidemiological study from Norway, 1960–92. *Br J Cancer*. 1997;76:658–660.
- Andersen ES. Primary carcinoma of the vagina: a study of 29 cases. *Gynecol Oncol*. 1989;33(3):317–320.
- Ball HG, Berman ML. Management of primary vaginal carcinoma. *Gynecol Oncol*. 1982;14(2):154–163.
- Chyle V, Zagars GK, Wheeler JA, et al. Definitive radiotherapy for carcinoma of the vagina: outcome and prognostic factors. *Int J Radiat Oncol Biol Phys*. 1996;35(5):891–905.
- Gallup DG, Talledo OE, Shah KJ, et al. Invasive squamous cell carcinoma of the vagina: a 14-year study. *Obstet Gynecol*. 1987;69(5):782–785.
- Kirkbride P, Fyles A, Rawlings GA, et al. Carcinoma of the vagina—experience at the Princess Margaret Hospital (1974–1989). *Gynecol Oncol*. 1995;56(3):435–443.
- Lenahan PM, Meffe F, Lickrish GM. Vaginal intraepithelial neoplasia: biologic aspects and management. *Obstet Gynecol*. 1986;68(3):333–337.
- Leung S, Sexton M. Radical radiation therapy for carcinoma of the vagina—impact of treatment modalities on outcome: Peter MacCallum Cancer Institute experience 1970–1990. *Int J Radiat Oncol Biol Phys*. 1993;25(3):413–418.
- Perez CA, Camel HM, Galakatos AE, et al. Definitive irradiation in carcinoma of the vagina: long-term evaluation and results. *Int J Radiat Oncol Biol Phys*. 1988;15:1283–1290.
- Spirtos NM, Doshi BP, Kapp DS, et al. Radiation therapy for primary squamous cell carcinoma of the vagina: Stanford University experience. *Gynecol Oncol*. 1989;35(1):20–26.
- Stock RG, Chen AS, Seski J. A 30-year experience in the management of primary carcinoma of the vagina: analysis of prognostic factors and treatment modalities. *Gynecol Oncol*. 1995;56(1):45–52.
- Stock RG, Mychalczak B, Armstrong JG, et al. The importance of brachytherapy technique in the management of primary carcinoma of the vagina. *Int J Radiat Oncol Biol Phys*. 1992;24(4):747–753.
- Urbanski K, Kojs Z, Reinfuss M, et al. Primary invasive vaginal carcinoma treated with radiotherapy: analysis of prognostic factors. *Gynecol Oncol*. 1996;60(1):16–21.
- Davis KP, Stanhope CR, Garton GR, et al. Invasive vaginal carcinoma: analysis of early-stage disease. *Gynecol Oncol*. 1991;42(2):131–136.
- Lee JY, Perez CA, Ettinger N, et al. The risk of second primaries subsequent to irradiation for cervix cancer. *Int J Radiat Oncol Biol Phys*. 1982;8(2):207–211.
- Manetta A, Gutrecht EL, Berman ML, et al. Primary invasive carcinoma of the vagina. *Obstet Gynecol*. 1990;76(4):639–642.
- Bornstein J, Adam E, Adler-Storh K, et al. Development of cervical and vaginal squamous cell neoplasia as a late consequence of *in utero* exposure to diethylstilbestrol. *Obstet Gynecol Surv*. 1988;43(1):15–21.
- Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med*. 1971;284(15):878–881.
- Herbst AL, Anderson D. Clear cell adenocarcinoma of the vagina and cervix secondary to intrauterine exposure to diethylstilbestrol. *Semin Surg Oncol*. 1990;6(6):343–346.
- Palmer JR, Anderson D, Helmrich SP, et al. Risk factors for diethylstilbestrol-associated clear cell adenocarcinoma. *Obstet Gynecol*. 2000;95(6 Pt. 1):814–820.
- Reid GC, Schmidt RW, Roberts JA, et al. Primary melanoma of the vagina: a clinicopathologic analysis. *Obstet Gynecol*. 1989;74(2):190–199.
- Trimble EL. Melanomas of the vulva and vagina. *Oncology (Williston Park)*. 1996;10(7):1017–1023; discussion 1024.
- Rubin SC, Young J, Mikuta JJ. Squamous carcinoma of the vagina: treatment, complications, and long-term follow-up. *Gynecol Oncol*. 1985;20(3):346–353.
- Al-Kurdi M, Monaghan JM. Thirty-two years experience in management of primary tumours of the vagina. *Br J Obstet Gynaecol*. 1981;88(11):1145–1150.
- Perez CA, Grigsby PW, Garipagaoglu M, et al. Factors affecting long-term outcome of irradiation in carcinoma of the vagina. *Int J Radiat Oncol Biol Phys*. 1999;44(1):37–45.

36. Hellman K, Lundell M, Silfversward C, et al. Clinical and histopathologic factors related to prognosis in primary squamous cell carcinoma of the vagina. *International Journal of Gynecological Cancer*. 2006;16(3):1201–1211.
37. Robboy SJ, Herbst AL, Scully RE. Clear-cell adenocarcinoma of the vagina and cervix in young females: analysis of 37 tumors that persisted or recurred after primary therapy. *Cancer*. 1974; 34(3):606–614.
38. Saslow D, Solomon D, Lawson H, et al. American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. [published online ahead of print March 14, 2012]. *CA Cancer J Clin*. 2012;62(3). doi:10.3322/caac.21139.
39. Tjalma WA, Monaghan JM, de Barros Lopes A, et al. The role of surgery in invasive squamous carcinoma of the vagina. *Gynecol Oncol*. 2001; 81(3):360–365.
40. Hanselaar AG, Van Leusen ND, De Wilde PC, et al. Clear cell adenocarcinoma of the vagina and cervix. A report of the Central Netherlands Registry with emphasis on early detection and prognosis. *Cancer*. 1991;67(7):1971–1978.
41. Herbst AL, Robboy SJ, Scully RE, et al. Clear-cell adenocarcinoma of the vagina and cervix in girls: analysis of 170 registry cases. *Am J Obstet Gynecol*. 1974;119(5):713–724.
42. Robboy SJ, Welch WR, Young RH, et al. Topographic relation of cervical ectropion and vaginal adenosis to clear cell adenocarcinoma. *Obstet Gynecol*. 1982;60(5):546–551.
43. FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynaecol Obstet*. 2009;105(1):3–4.
44. American Joint Committee on Cancer (AJCC). Vagina. In: Edge SB, Byrd DR, Compton CC, et al. eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer-Verlag; 2010:469–472.
45. Zaino RJ, Robboy SJ, Kurman RJ. Diseases of the vagina. In: Kurman RJ, ed. *Blaustein's Pathology of the Female Genital Tract*. 5th ed. New York, NY: Springer-Verlag; 2002:151–206.
46. Perez CA. Radiation therapy for cancer of the lung: previous experience and definition of current issues. *Cancer Chemother Rep* 3. 1973; 4(2):145–152.
47. Prempre T, Amornmarn R. Radiation treatment of primary carcinoma of the vagina. Patterns of failures after definitive therapy. *Acta Radiol Oncol*. 1985;24(1):51–56.
48. Frank SJ, Jhingran A, Levenback C, et al. Definitive radiation therapy for squamous cell carcinoma of the vagina. *Int J Radiat Oncol Biol Phys*. 2005;62(1):138–147.
49. Taylor MB, Dugar N, Davidson SE, et al. Magnetic resonance imaging of primary vaginal carcinoma. *Clin Radiol*. 2007;62(6):549–555.
50. Chang YC, Hricak H, Thurnher S, et al. Vagina: evaluation with MR imaging. Part II. Neoplasms. *Radiology*. 1988;169(1):175–179.
51. Lamoreaux WT, Grigsby PW, Dehdashti F, et al. FDG-PET evaluation of vaginal carcinoma. *Int J Radiat Oncol Biol Phys*. 2005;62(3):733–737.
52. van der Aa M, Helmerhorst T, Sieling S, et al. Vaginal and (uncommon) cervical cancers in the Netherlands, 1989–2003. *Int J Gynecol Cancer*. 2010;20:638–645.
53. Zaino R, Nucci M, Kurman R. Diseases of the vagina. In: Kurman R EL, Ronnett B, eds. *Blaustein's Pathology of the Female Genital Tract*. 6th ed. New York, NY: Springer; 2011: 105–154.
54. Balamurugan A, Ahmed F, Saraiya M, et al. Potential role of human papillomavirus in the development of subsequent primary *in situ* and invasive cancers among cervical cancer survivors. *Cancer*. 2008;113(suppl. 10):2919–2925.
55. Kurman R, Ronnett B, Sherman M, et al. *Tumors of the Cervix, Vagina, and Vulva*. Vol 13. Washington, DC: ARP Press; 2010.
56. Brunner A, Grimm C, Polterauer S, et al. The prognostic value of human papillomavirus in patients with vaginal cancer. *Int J Gynecol Cancer*. 2011;21:923–929.
57. De Vuyst H, Clifford G, Nascimento M, et al. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva and anus: a meta-analysis. *Int J Cancer*. 2009;124:1626–1636.
58. Ferreira M, Crespo M, Martins L, et al. HPV DNA detection and genotyping in 21 cases of primary invasive squamous cell carcinoma of the vagina. *Mod Pathol*. 2008;21:968–972.
59. Fuste V, del Pino M, Perez A, et al. Primary squamous cell carcinoma of the vagina: human papillomavirus detection, p16INK4A overexpression and clinicopathological correlations. *Histopathology*. 2010;57:907–916.
60. Srodon M, Stoler MH, Baber GB, et al. The distribution of low and high-risk HPV types in vulvar and vaginal intraepithelial neoplasia (VIN and VaIN). *Am J Surg Pathol*. 2006; 30(12):1513–1518.
61. Goodman A, Schorge J, Greene M. The long-term effects of *in utero* exposures – the DES story. *N Engl J Med*. 2011;364:2083–2084.
62. Verloop J, van Leeuwen F, Helmerhorst T, et al. Cancer risk in DES daughters. *Cancer Causes Control*. 2010:999–1007.
63. Frank S, Deavers M, Jhingran A, et al. Primary adenocarcinoma of the vagina not associated with diethylstilbestrol (DES) exposure. *Gynecol Oncol*. 2007;105(4):470–474.
64. Staats P, Clement P, Young R. Primary endometrioid adenocarcinoma of the vagina: a clinicopathologic study of 18 cases. *Am J Surg Pathol*. 2007;31:1490–1501.
65. McCurdy M, Zouain N. Successful treatment of primary vaginal papillary serous adenocarcinoma using chemoradiation followed by brachytherapy. *Case Rep Oncol*. 2009;2:97–102.
66. Saitoh M, Hayasaka T, Ohmichi M, et al. Primary mucinous adenocarcinoma of the vagina: possibility of differentiating from metastatic adenocarcinomas. *Pathol Int*. 2005;55:372–375.
67. Ditto A, Martinelli F, Carcangiu M, et al. Incidental diagnosis of primary vaginal adenocarcinoma of intestinal type: a case report and review of the literature. *Int J Gynecol Pathol*. 2007;26:490–493.
68. Bague S, Rodriguez IM, Prat J. Malignant mesonephric tumors of the female genital tract: a clinicopathologic study of 9 cases. *Am J Surg Pathol*. 2004;28(5):601–607.
69. Bifulco G, Mandato V, Mignogna C, et al. A case of mesonephric adenocarcinoma of the vagina with a 1-year follow-up. *Int J Gynecol Cancer*. 2008;18:1127–1131.
70. Fader A, Brainard J, Rose PG. Symptomatic vaginal bleeding in a postmenopausal woman: a case report of pancreatic adenocarcinoma metastasizing exclusively to the vagina. *Am J Obstet Gynecol*. 2007;197(5):e8–e9.
71. Sabbagh C, Fuks D, Regimbeau J, et al. Isolated vaginal metastasis from rectal adenocarcinoma: a rare presentation. *Colorectal Dis*. 2011;13:e355–e356.
72. Mahdi H, Thrall M, Agoff N, et al. Pagetoid adenocarcinoma *in situ* of the cervix with pagetoid spread into the vagina. *Obstet Gynecol*. 2011;118:461–463.
73. Nasu K, Hamasaki C, Takai N, et al. Glassy cell carcinoma arising in the vagina. *Acta Obstet Gynecol*. 2008;87:982–984.
74. Woida F, Ribeiro-Silva A. Adenoid cystic carcinoma of the Bartholin gland. *Arch Pathol Lab Med*. 2007;131:796–798.
75. Gardner G, Reidy-Lagunes D, Gehrig P. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. *Gynecol Oncol*. 2011;122:190–198.
76. Weberpals J, Djordjevic B, Khalifa M, et al. A rare case of ectopic adrenocorticotrophic hormone syndrome in small cell carcinoma of the vagina: a case report. *J Lower Gen Tract Dis*. 2008;12(2):140–145.
77. Akl M, Naidu S, McCullough A, et al. Vaginal paraganglioma presenting as a pelvic mass. *Surgery*. 2010;147:169–171.
78. Brustmann H. Paraganglioma of the vagina: report of a case. *Pathol – Res Pract*. 2007;203:189–192.
79. Sebenik M, Yan Z, Khalbuss W, et al. Malignant mixed müllerian tumor of the vagina: case report with review of the literature, immunohistochemical study, and evaluation for human papilloma virus. *Hum Pathol*. 2007;38:1282–1288.
80. Meenakshi M, McCluggage WG. Myoepithelial neoplasms involving the vulva and vagina: a report of 4 cases. *Hum Pathol*. 2009;40:1747–1753.
81. Ghaemmaghami F, Zarchi M, Ghasemi M. Lower genital tract rhabdomyosarcoma: case series and literature review. *Arch Gynecol Obstet*. 2008;278:65–69.
82. Walterhouse D, Meza J, Breneman J, et al. Local control and outcome in children with localized vaginal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Pediatr Blood Cancer*. 2011;57:76–83.
83. Lam MM, Corless CL, Goldblum JR, et al. Extragastrintestinal stromal tumors presenting as vulvovaginal/rectovaginal septal masses: a diagnostic pitfall. *Int J Gynecol Pathol*. 2006;25(3):288–292.
84. McCluggage W. Recent developments in vulvovaginal pathology. *Histopathology*. 2009;54:156–173.
85. Iyengar P, Ismail N, Gerber D, et al. Vaginal solitary fibrous tumor: a case report with recurrence after incomplete excision. *J Lower Genital Tract Dis*. 2007;11(1):50–54.
86. Pelosi G, Luzzatto F, Landoni F, et al. Poorly differentiated snovial sarcoma of the vagina: first reported case with immunohistochemical, molecular, and ultrastructural data. *Histopathology*. 2007;50:794–818.
87. Sumathi V, Fisher C, Williams A, et al. Synovial sarcoma of the vulva and vagina: a clinicopathologic and molecular genetic study of 4 cases. *Int J Gynecol Pathol*. 2010;30:84–91.
88. Mhaskar R, Mhaskar V, Pritilata R. Malignant peripheral nerve sheath tumour of the vagina. *J Obstet Gynaecol*. 2009;29(4):360.
89. Dahiya K, Jain S, Duhan N, et al. Aggressive angiomyxoma of vulva and vagina: a series of three cases and review of literature. *Arch Gynecol Obstet*. 2011;283:1145–1148.
90. Lee H, Jang K, Park H, et al. Angiomyofibroblastoma of the vagina in a breast cancer patient. *Pathology (Phila)*. 2008;40(5):534–536.
91. Magro G, Caltabiano R, Kacerovska D, et al. Vulvovaginal myofibroblastoma: expanding the morphological and immunohistochemical

- spectrum: a clinicopathologic study of 10 cases. *Hum Pathol.* 2012;43:243–253.
92. Rettenmaier M, Zerky N, Chang M, et al. A heavily pigmented vaginal perivascular epithelioid cell neoplasm. *J Obstet Gynaecol.* 2009;29(7):676–677.
 93. Ong L, Hwang W, Wong A, et al. Perivascular epithelioid cell tumor of the vagina in an 8 year old girl. *J Pediatr Surg.* 2007;42:564–566.
 94. Frumovitz M, Etchepareborda M, Sun C, et al. Primary malignant melanoma of the vagina. *Obstet Gynecol.* 2010;116:1358–1365.
 95. Tereziani M, Spreafico F, Collini P, et al. Endodermal sinus tumor of the vagina. *Pediatr Blood Cancer.* 2007;48:577–578.
 96. Gangopadhyay M, Raha K, Sinha S, et al. Endodermal sinus tumor of the vagina in children: a report of two cases. *Indian J Pathol Microbiol.* 2009;52:403–404.
 97. Kao C, Idrees M, Young R, et al. Solid pattern yolk sac tumor: a morphologic and immunohistochemical study of 52 cases. *Am J Surg Pathol.* 2012;36:360–367.
 98. Liu A, Cheng L, Du J, et al. Diagnostic utility of novel stem cell markers SALL4, OCT4, NANOG, SOX2, UTF1, and TCL1 in primary mediastinal germ cell tumors. *Am J Surg Pathol.* 2010;34:697–706.
 99. Zynger D, McCallum J, Luan C, et al. Glypican 3 has a higher sensitivity than alpha-fetoprotein for testicular and ovarian yolk sac tumor: immunohistochemical investigation with analysis of histological growth patterns. *Histopathology.* 2010;56(6):750–757.
 100. McCluggage W, Sumathi V, Nucci M, et al. Ewing family of tumours involving the vulva and vagina: a report of a series of four cases. *J Clin Pathol.* 2007;60:674–680.
 101. Rekhi B, Qureshi S, Basak R, et al. Primary vaginal Ewing's sarcoma or primitive neuroectodermal tumor in a 17-year-old woman: a case report. *J Med Case Reports.* 2010;4:88.
 102. Song J, Kim I, Kim Y, et al. Extrarenal teratoid Wilms' tumor: two cases in unusual locations, one associated with elevated serum AFP. *Pathol Int.* 2010;60:35–41.
 103. Senekjian EK, Frey KW, Anderson D, et al. Local therapy in stage I clear cell adenocarcinoma of the vagina. *Cancer.* 1987;60(6):1319–1324.
 104. Lagoo A, Robboy SJ. Lymphoma of the female genital tract: current status. *Int J Gynecol Pathol.* 2005;25:1–21.
 105. Cohn D, Resnick K, Eaton L, et al. Non-Hodgkin's lymphoma mimicking gynecological malignancies of the vagina and cervix: a report of four cases. *Int J Gynecol Cancer.* 2006;17:254–293.
 106. Hussein I, Said M, Macheta A, et al. Primary non-Hodgkin's lymphoma of the vagina. *J Obstet Gynaecol.* 2007;27(7):752.
 107. Ikuta A, Tanaka Y, Tsuzuki T, et al. Vaginal lymphoma with immune thrombocytopenic purpura: an unusual case report. *Case Rep Oncol.* 2010;8(3):397–405.
 108. Skeete D, Cesar-Rittenberg P, Jong R, et al. Myeloid sarcoma of the vagina: a report of 2 cases. *J Lower Genital Tract Dis.* 2010;14(2):136–141.
 109. Lee RJ, Sause WT. Surgically staged patients with prostatic carcinoma treated with definitive radiotherapy: fifteen-year results. *Urology.* 1994;43(5):640–644.
 110. Peters WA 3rd, Kumar NB, Morley GW. Carcinoma of the vagina. Factors influencing treatment outcome. *Cancer.* 1985;55(4):892–897.
 111. Chu AM, Beechinor R. Survival and recurrence patterns in the radiation treatment of carcinoma of the vagina. *Gynecol Oncol.* 1984;19(3):298–307.
 112. MacNaught R, Symonds RP, Hole D, et al. Improved control of primary vaginal tumours by combined external-beam and interstitial radiotherapy. *Clin Radiol.* 1986;37(1):29–32.
 113. Eddy GL, Marks RD Jr, Miller MC 3rd, et al. Primary invasive vaginal carcinoma. *Am J Obstet Gynecol.* 1991;165(2):292–296; discussion 296–298.
 114. Dixit S, Singhal S, Baboo HA. Squamous cell carcinoma of the vagina: a review of 70 cases. *Gynecol Oncol.* 1993;48(1):80–87.
 115. Delclos L. *Technological Basis of Radiation Therapy—Practical Clinical Applications.* Philadelphia, PA: Lea & Febiger; 1984.
 116. Dancuart F, Delclos L, Wharton JT, et al. Primary squamous cell carcinoma of the vagina treated by radiotherapy: a failures analysis—the M.D. Anderson Hospital experience 1955–1982. *Int J Radiat Oncol Biol Phys.* 1988;14(4):745–749.
 117. Hellman K, Lundell M, Silfversward C, et al. Clinical and histopathologic factors related to prognosis in primary squamous cell carcinoma of the vagina. *Int J Gynecol Cancer: Official J Int Gynecol Cancer Soc.* 2006;16(3):1201–1211.
 118. de Crevoisier R, Sanfilippo N, Gerbaulet A, et al. Exclusive radiotherapy for primary squamous cell carcinoma of the vagina. *Radiation Oncol.* 2007;85(3):362–370.
 119. Tran PT, Su Z, Lee P, et al. Prognostic factors for outcomes and complications for primary squamous cell carcinoma of the vagina treated with radiation. *Gynecol Oncol.* 2007;105(3):641–649.
 120. Sinha B, Stehman F, Schilder J, et al. Indiana University experience in the management of vaginal cancer. *Int J Gynecol Cancer: Official J Int Gynecol Cancer Soc.* 2009;19(4):686–693.
 121. Shah CA, Goff BA, Lowe K, et al. Factors affecting risk of mortality in women with vaginal cancer. *Obstet Gynecol.* 2009;113(5):1038–1045.
 122. Ali MM, Huang DT, Goplerud DR, et al. Radiation alone for carcinoma of the vagina: variation in response related to the location of the primary tumor. *Cancer.* 1996;77(9):1934–1939.
 123. Kucera H, Vavra N. Radiation management of primary carcinoma of the vagina: clinical and histopathological variables associated with survival. *Gynecol Oncol.* 1991;40(1):12–16.
 124. Tarraza MH Jr, Muntz H, Decain M, et al. Patterns of recurrence of primary carcinoma of the vagina. *Eur J Gynaecol Oncol.* 1991;12(2):89–92.
 125. Tjalma W, Weyler J, Pollefliet C, et al. The evaluation of proliferative activity in CIN III and microinvasive cervical cancer and its role in recurrence. *Eur J Obstet Gynecol Reprod Biol.* 2001;94(2):270–275.
 126. Boice JD Jr, Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res.* 1988;116(1):3–55.
 127. Tavassoli FA, Norris HJ. Smooth muscle tumors of the vagina. *Obstet Gynecol.* 1979;53(6):689–693.
 128. Berchuck A, Rodriguez G, Kamel A, et al. Expression of epidermal growth factor receptor and HER-2/neu in normal and neoplastic cervix, vulva, and vagina. *Obstet Gynecol.* 1990;76(3 Pt. 1):381–387.
 129. Waggoner SE, Anderson SM, Luce MC, et al. p53 protein expression and gene analysis in clear cell adenocarcinoma of the vagina and cervix. *Gynecol Oncol.* 1996;60(3):339–344.
 130. Pingley S, Shrivastava SK, Sarin R, et al. Primary carcinoma of the vagina: Tata Memorial Hospital experience. *Int J Radiat Oncol Biol Phys.* 2000;46(1):101–108.
 131. Perez CA, Korba A, Sharma S. Dosimetric considerations in irradiation of carcinoma of the vagina. *Int J Radiat Oncol Biol Phys.* 1977;2(7–8):639–649.
 132. Fanning J, Manahan KJ, McLean SA. Loop electrosurgical excision procedure for partial upper vaginectomy. *Am J Obstet Gynecol.* 1999;181(6):1382–1385.
 133. Hoffman MS, DeCesare SL, Roberts WS, et al. Upper vaginectomy for *in situ* and occult, superficially invasive carcinoma of the vagina. *Am J Obstet Gynecol.* 1992;166(1 Pt. 1):30–33.
 134. Han SS, Kim YH, Lee SH, et al. Underuse of ovarian transposition in reproductive-aged cancer patients treated by primary or adjuvant pelvic irradiation. *J Obstet Gynaecol Res.* 2011;37(7):825–829.
 135. Vayrynen M, Romppanen T, Koskela E, et al. Verrucous squamous cell carcinoma of the female genital tract. Report of three cases and survey of the literature. *Int J Gynaecol Obstet.* 1981;19(5):351–356.
 136. Soper JT, Secord AA, Havrilesky LJ, et al. Comparison of gracilis and rectus abdominis myocutaneous flap neovaginal reconstruction performed during radical pelvic surgery: flap-specific morbidity. *Int J Gynecol Cancer.* 2007;17(1):298–303.
 137. Boronow RC, Hickman BT, Reagan MT, et al. Combined therapy as an alternative to exenteration for locally advanced vulvovaginal cancer. II. Results, complications, and dosimetric and surgical considerations. *Am J Clin Oncol.* 1987;10(2):171–181.
 138. Diakomanolis E, Rodolakis A, Boulgaris Z, et al. Treatment of vaginal intraepithelial neoplasia with laser ablation and upper vaginectomy. *Gynecol Obstet Invest.* 2002;54(1):17–20.
 139. Hoffman MS, Roberts WS, LaPolla JP, et al. Laser vaporization of grade 3 vaginal intraepithelial neoplasia. *Am J Obstet Gynecol.* 1991;163(5 Pt. 1):1342–1344.
 140. Julian TM, O'Connell BJ, Gosewehr JA. Indications, techniques, and advantages of partial laser vaginectomy. *Obstet Gynecol.* 1992;80(1):140–143.
 141. Robinson JB, Sun CC, Bodurka-Beyers D, et al. Cavitation ultrasonic surgical aspiration for the treatment of vaginal intraepithelial neoplasia. *Gynecol Oncol.* 2000;78(2):235–241.
 142. Krebs HB. Treatment of vaginal intraepithelial neoplasia with laser and topical 5-fluorouracil. *Obstet Gynecol.* 1989;73(4):657–660.
 143. Petrilli ES, Townsend DE, Morrow CP, et al. Vaginal intraepithelial neoplasia: biologic aspects and treatment with topical 5-fluorouracil and the carbon dioxide laser. *Am J Obstet Gynecol.* 1980;138(3):321–328.
 144. Piver MS, Barlow JJ, Tsukada Y, et al. Postirradiation squamous cell carcinoma *in situ* of the vagina: treatment by topical 20% 5-fluorouracil cream. *Am J Obstet Gynecol.* 1979;135(3):377–380.
 145. Woodruff JD, Parmley TH, Julian CG. Topical 5-fluorouracil in the treatment of vaginal carcinoma-in-situ. *Gynecol Oncol.* 1975;3(2):124–132.

146. Wright VC, Schieve LA, Reynolds MA, et al. Laser surgery for vaginal disease. In: Wright VC, ed. *Gynecologic Laser Surgery: A Practical Handbook*. Houston, TX: Biomedical Communications; 1986:155–160.
147. Daly JW, Ellis GF. Treatment of vaginal dysplasia and carcinoma *in situ* with topical 5-fluorouracil. *Obstet Gynecol*. 1980;55(3):350–352.
148. Haidopoulos D, Diakomanolis E, Rodolakis A, et al. Can local application of imiquimod cream be an alternative mode of therapy for patients with high-grade intraepithelial lesions of the vagina? *Int J Gynecol Cancer*. 2005;15(5):898–902.
149. Indermaur MD, Martino MA, Fiorica JV, et al. Upper vaginectomy for the treatment of vaginal intraepithelial neoplasia. *Am J Obstet Gynecol*. 2005;193(2):577–580; discussion 580–571.
150. Lee WR, Marcus RB Jr, Sombeck MD, et al. Radiotherapy alone for carcinoma of the vagina: the importance of overall treatment time. *Int J Radiat Oncol Biol Phys*. 1994;29(5):983–988.
151. Perez CA, Camel HM. Long-term follow-up in radiation therapy of carcinoma of the vagina. *Cancer*. 1982;49(6):1308–1315.
152. Ogino I, Kitamura T, Okajima H, et al. High-dose-rate intracavitary brachytherapy in the management of cervical and vaginal intraepithelial neoplasia. *Int J Radiat Oncol Biol Phys*. 1998;40(4):881–887.
153. MacLeod C, Fowler A, Dalrymple C, et al. High-dose-rate brachytherapy in the management of high-grade intraepithelial neoplasia of the vagina. *Gynecol Oncol*. 1997;65(1):74–77.
154. Mock U, Kucera H, Fellner C, et al. High-dose-rate (HDR) brachytherapy with or without external beam radiotherapy in the treatment of primary vaginal carcinoma: long-term results and side effects. *Int J Radiat Oncol Biol Phys*. 2003;56(4):950–957.
155. Burke TW, Morris M, Roh MS, et al. Perineal reconstruction using single gracilis myocutaneous flaps. *Gynecol Oncol*. 1995;57(2):221–225.
156. Magrina JF, Masterson BJ. Vaginal reconstruction in gynecological oncology: a review of techniques. *Obstet Gynecol Surv*. 1981;36(1):1–10.
157. Elaffandi AH, Khalil HH, Aboul Kassem HA, et al. Vaginal reconstruction with a greater omentum-pedicled graft combined with a vicryl mesh after anterior pelvic exenteration. Surgical approach with long-term follow-up. *Int J Gynecol Cancer*. 2007;17(2):536–542.
158. Wang X, Qiao Q, Burd A, et al. A new technique of vaginal reconstruction with the deep inferior epigastric perforator flap: a preliminary report. *Plast Reconstr Surg*. 2007;119(6):1785–1790; discussion 1791.
159. Tabata T, Takeshima N, Nishida H, et al. Treatment failure in vaginal cancer. *Gynecol Oncol*. 2002;84(2):309–314.
160. Otton GR, Nicklin JL, Dickie GJ, et al. Early-stage vaginal carcinoma—an analysis of 70 patients. *Int J Gynecol Cancer*. 2004;14(2):304–310.
161. de Crevoisier R, Sanfilippo N, Gerbaulet A, et al. Exclusive radiotherapy for primary squamous cell carcinoma of the vagina. *Radiother Oncol*. 2007;85(3):362–370.
162. Lian J, Dundas G, Carlone M, et al. Twenty-year review of radiotherapy for vaginal cancer: an institutional experience. *Gynecol Oncol*. 2008;111(2):298–306.
163. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2002;52(5):1330–1337.
164. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys*. 2003;56(5):1354–1360.
165. Taylor A, Rockall AG, Reznick RH, Powell ME. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1604–1612.
166. Digel CA, Lastner GM, Zinreich ES. The use of transmission block in the radiation therapy portal treatment of the inguinal nodes in late stage pelvic malignancies. *Radiol Technol*. 1987;58(3):227–231.
167. Dittmer PH, Randall ME. A technique for inguinal node boost using photon fields defined by asymmetric collimator jaws. *Radiation Oncol*. 2001;59(1):61–64.
168. Moran MS, Castrucci WA, Ahmad M, et al. Clinical utility of the modified segmental boost technique for treatment of the pelvis and inguinal nodes. *Int J Radiat Oncol Biol Phys*. 2010;76(4):1026–1036.
169. Menkarios C, Azria D, Laliberte B, et al. Optimal organ-sparing intensity-modulated radiation therapy (IMRT) regimen for the treatment of locally advanced anal canal carcinoma: a comparison of conventional and IMRT plans. *Radiat Oncol* 2007;2:41.
170. Milano MT, Jani AB, Farrey KJ, et al. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. *Int J Radiat Oncol Biol Phys*. 2005;63(2):354–361.
171. Pepek JM, Willett CG, Wu QJ, et al. Intensity-modulated radiation therapy for anal malignancies: a preliminary toxicity and disease outcomes analysis. *Int J Radiat Oncol Biol Phys*. 2010;78(5):1413–1419.
172. Salama JK, Mell LK, Schomas DA, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. *J Clin Oncol*. 2007;25(29):4581–4586.
173. Delclos L, Fletcher GH, Moore EB, et al. Minicoplasts, dome cylinders, other additions and improvements of the Fletcher-suit afterloadable system: indications and limitations of their use. *Int J Radiat Oncol Biol Phys*. 1980;6(9):1195–1206.
174. Slessinger ED, Perez CA, Grigsby PW, et al. Dosimetry and dose specification for a new gynecological brachytherapy applicator. *Int J Radiat Oncol Biol Phys*. 1992;22(5):1117–1124.
175. Choo JJ, Scudiere J, Bitterman P, et al. Vaginal lymphatic channel location and its implication for intracavitary brachytherapy radiation treatment. *Brachytherapy*. 2005;4(3):236–240.
176. Kucera H, Mock U, Knoke TH, et al. Radiotherapy alone for invasive vaginal cancer: outcome with intracavitary high dose rate brachytherapy versus conventional low dose rate brachytherapy. *Acta Obstet Gynecol Scand*. 2001;80(4):355–360.
177. Kushner DM, Fleming PA, Kennedy AW, et al. High dose rate (192)Ir afterloading brachytherapy for cancer of the vagina. *Br J Radiol*. 2003;76(910):719–725.
178. Nanavati PJ, Fanning J, Hilgers RD, et al. High-dose-rate brachytherapy in primary stage I and II vaginal cancer. *Gynecol Oncol*. 1993;51(1):67–71.
179. Beriwal S, Bhatnagar A, Heron DE, et al. High-dose-rate interstitial brachytherapy for gynecologic malignancies. *Brachytherapy*. 2006;5(4):218–222.
180. Beriwal S, Heron DE, Mogus R, et al. High-dose rate brachytherapy (HDRB) for primary or recurrent cancer in the vagina. *Radiat Oncol*. 2008;3:7.
181. Gore E, Gillin MT, Albano K, et al. Comparison of high dose-rate and low dose-rate dose distributions for vaginal cylinders. *Int J Radiat Oncol Biol Phys*. 1995;31(1):165–170.
182. Li Z, Liu C, Paltal JR. Optimized dose distribution of a high dose rate vaginal cylinder. *Int J Radiat Oncol Biol Phys*. 1998;41(1):239–244.
183. Rutkowski T, Bialas B, Rembielak A, et al. Efficacy and toxicity of MDR versus HDR brachytherapy for primary vaginal cancer. *Neoplasma*. 2002;49(3):197–200.
184. Tyree WC, Cardenas H, Randall M, et al. High-dose-rate brachytherapy for vaginal cancer: learning from treatment complications. *Int J Gynecol Cancer*. 2002;12(1):27–31.
185. Hilaris BS, Nori D, Anderson LL. Brachytherapy treatment planning. *Front Radiat Ther Oncol*. 1987;21:94–106.
186. Syed AMN, Puthawala AA, Neblett D, et al. Transperineal interstitial-intracavitary “Syed-Neblett” applicator in the treatment of carcinoma of the uterine cervix. *Endocuriether Hypertherm Oncol*. 1986;2:1–13.
187. DiSaia PJ, Syed N, Puthawala AA. Malignant neoplasia of the upper vagina. *Endocuriether Hypertherm Oncol*. 1990;6:251–256.
188. Martinez A, Cox RS, Edmundson GK. A multiple-site perineal applicator (MUPIT) for treatment of prostatic, anorectal, and gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 1984;10(2):297–305.
189. Stock RG, Chan K, Terk M, et al. A new technique for performing Syed-Neblett template interstitial implants for gynecologic malignancies using transrectal-ultrasound guidance. *Int J Radiat Oncol Biol Phys*. 1997;37(4):819–825.
190. Corn BW, Lanciano RM, Rosenblum N, et al. Improved treatment planning for the Syed-Neblett template using endorectal-coil magnetic resonance and intraoperative (laparotomy/laparoscopy) guidance: a new integrated technique for hysterectomized women with vaginal tumors. *Gynecol Oncol*. 1995;56(2):255–261.
191. Childers JM, Surwit EA. Current status of operative laparoscopy in gynecologic oncology. *Oncology (Williston Park)*. 1993;7(11):47–51; discussion 53–44, 57.
192. Orr JW Jr, Dosoretz DD, Mahoney D, et al. Surgically (laparotomy/laparoscopy) guided placement of high dose rate interstitial irradiation catheters (LG-HDRT): technique and outcome. *Gynecol Oncol*. 2006;100(1):145–148.
193. Paley PJ, Koh WJ, Stelzer KJ, et al. A new technique for performing Syed template interstitial implants for anterior vaginal tumors using an open retropubic approach. *Gynecol Oncol*. 1999;73(1):121–125.
194. Shah AP, Strauss JB, Gielda BT, et al. Toxicity associated with bowel or bladder puncture during gynecologic interstitial brachytherapy. *Int J Radiat Oncol Biol Phys*. 2010;77(1):171–179.
195. Tewari KS, Cappuccini F, Puthawala AA, et al. Primary invasive carcinoma of the vagina: treatment with interstitial brachytherapy. *Cancer*. 2001;91(4):758–770.
196. Stryker JA. Radiotherapy for vaginal carcinoma: a 23-year review. *Br J Radiol*. 2000;73(875):1200–1205.

197. Evans LS, Kersh CR, Constable WC, et al. Concomitant 5-fluorouracil, mitomycin-C, and radiotherapy for advanced gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 1988;15(4):901-906.
198. Roberts WS, Hoffman MS, Kavanagh JJ, et al. Further experience with radiation therapy and concomitant intravenous chemotherapy in advanced carcinoma of the lower female genital tract. *Gynecol Oncol*. 1991;43(3):233-236.
199. Kersh CR, Constable WC, Spaulding CA, et al. A phase I-II trial of multimodality management of bulky gynecologic malignancy. Combined chemoradiosensitization and radiotherapy. *Cancer*. 1990;66(1):30-34.
200. Dalrymple JL, Russell AH, Lee SW, et al. Chemoradiation for primary invasive squamous carcinoma of the vagina. *Int J Gynecol Cancer*. 2004;14(1):110-117.
201. Samant R, Lau B, E C, et al. Primary vaginal cancer treated with concurrent chemoradiation using Cis-platinum. *Int J Radiat Oncol Biol Phys*. 2007;69(3):746-750.
202. Panici PB, Scambia G, Baiocchi G, et al. Neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer. Prognostic factors for response and survival. *Cancer*. 1991;67(2):372-379.
203. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340(15):1154-1161.
204. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999;340(15):1137-1143.
205. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340(15):1144-1153.
206. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol*. 1999;17(5):1339-1348.
207. Moore DH, Thomas GM, Montana GS, et al. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. *Int J Radiat Oncol Biol Phys*. 1998;42(1):79-85.
208. Antonioli DA, Burke L. Vaginal adenosis. Analysis of 325 biopsy specimens from 100 patients. *Am J Clin Pathol*. 1975;64(5):625-638.
209. Hatch EE, Herbst AL, Hoover RN, et al. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States). *Cancer Causes Control*. 2001;12(9):837-845.
210. Kaminski JM, Anderson PR, Han AC, et al. Primary small cell carcinoma of the vagina. *Gynecol Oncol*. 2003;88(3):451-455.
211. Shah C, Pizer E, Veljovich DS, et al. Clear cell adenocarcinoma of the vagina in a patient with vaginal endometriosis. *Gynecol Oncol*. 2006;103(3):1130-1132.
212. Ulbright TM, Kraus FT. Endometrial stromal tumors of extra-uterine tissue. *Am J Clin Pathol*. 1981;76(4):371-377.
213. Watanabe Y, Ueda H, Nozaki K, et al. Advanced primary clear cell carcinoma of the vagina not associated with diethylstilbestrol. *Acta Cytol*. 2002;46(3):577-581.
214. Cardenes H, Song G, Randall M. Late sequelae of radiation therapy in the management of gynecologic malignancies. Current medical literature. *Gynecol Oncol*. 2001;2:1-10.
215. Grigsby PW, Russell A, Bruner D, et al. Late injury of cancer therapy on the female reproductive tract. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1281-1299.
216. Parikh JH, Barton DP, Ind TE, et al. MR imaging features of vaginal malignancies. *Radiographics*. 2008;28(1):49-63; quiz 322.
217. Hintz BL, Kagan AR, Chan P, et al. Radiation tolerance of the vaginal mucosa. *Int J Radiat Oncol Biol Phys*. 1980;6(6):711-716.
218. Rubin P, Casarett GW. The female genital tract. In: Rubin P CG, ed. *Clinical Radiation Pathology*. Philadelphia, PA: WB Saunders; 1968:396-442.
219. Au SP, Grigsby PW. The irradiation tolerance dose of the proximal vagina. *Radiother Oncol*. 2003;67(1):77-85.
220. Deodato F, Macchia G, Grimaldi L, et al. Stereotactic radiotherapy in recurrent gynecological cancer: a case series. *Oncol Rep*. 2009;22(2):415-419.
221. O'Toole RV, Tuttle SE, Lucas JG, et al. Alveolar soft part sarcoma of the vagina: an immunohistochemical and electron microscopic study. *Int J Gynecol Pathol*. 1985;4(3):258-265.
222. Riva C, Fabbri A, Facco C, et al. Primary serous papillary adenocarcinoma of the vagina: a case report. *Int J Gynecol Pathol*. 1997;16(3):286-290.
223. Delanian S, Porcher R, Balla-Mekias S, et al. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. *J Clin Oncol*. 2003;21(13):2545-2550.
224. Coleman NM, Smith-Zagone MJ, Tanyi J, et al. Primary neuroendocrine carcinoma of the vagina with Merkel cell carcinoma phenotype. *Am J Surg Pathol*. 2006;30(3):405-410.
225. Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence. A report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). *Cancer*. 1970;25(4):745-757.
226. Senekjian EK, Frey K, Herbst AL. Pelvic exenteration in clear cell adenocarcinoma of the vagina and cervix. *Gynecol Oncol*. 1989;34(3):413-416.
227. Hudson CN, Findlay WS, Roberts H. Successful pregnancy after radical surgery for diethylstilboestrol (DES)-related vaginal adenocarcinoma. Case report. *Br J Obstet Gynaecol*. 1988;95(8):818-819.
228. Wharton JT, Rutledge FN, Gallager HS, et al. Treatment of clear cell adenocarcinoma in young females. *Obstet Gynecol*. 1975;45(4):365-368.
229. Senekjian EK, Frey KW, Stone C, et al. An evaluation of stage II vaginal clear cell adenocarcinoma according to substages. *Gynecol Oncol*. 1988;31(1):56-64.
230. Fowler WC Jr, Brantley JC 3rd, Edelman DA. Clear cell adenocarcinoma of the genital tract. *South Med J*. 1979;72(1):15-16.
231. Bonner JA, Perez-Tamayo C, Reid GC, et al. The management of vaginal melanoma. *Cancer*. 1988;62(9):2066-2072.
232. Buchanan DJ, Schlaerth J, Kurosaki T. Primary vaginal melanoma: thirteen-year disease-free survival after wide local excision and review of recent literature. *Am J Obstet Gynecol*. 1998;178(6):1177-1184.
233. Geisler JP, Look KY, Moore DA, et al. Pelvic exenteration for malignant melanomas of the vagina or urethra with over 3 mm of invasion. *Gynecol Oncol*. 1995;59(3):338-341.
234. Irvin WP Jr, Bliss SA, Rice LW, et al. Malignant melanoma of the vagina and locoregional control: radical surgery revisited. *Gynecol Oncol*. 1998;71(3):476-480.
235. Levitan Z, Gordon AN, Kaplan AL, et al. Primary malignant melanoma of the vagina: report of four cases and review of the literature. *Gynecol Oncol*. 1989;33(1):85-90.
236. Van Nostrand KM, Lucci JA 3rd, Schell M, et al. Primary vaginal melanoma: improved survival with radical pelvic surgery. *Gynecol Oncol*. 1994;55(2):234-237.
237. Petru E, Nagele F, Czerwenka K, et al. Primary malignant melanoma of the vagina: long-term remission following radiation therapy. *Gynecol Oncol*. 1998;70(1):23-26.
238. Bentzen SM, Overgaard J, Thames HD, et al. Clinical radiobiology of malignant melanoma. *Radiother Oncol*. 1989;16(3):169-182.
239. Overgaard J, Overgaard M, Hansen PV, et al. Some factors of importance in the radiation treatment of malignant melanoma. *Radiother Oncol*. 1986;5(3):183-192.
240. Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *Int J Radiat Oncol Biol Phys*. 1991;20(3):429-432.
241. Harwood AR, Cummings BJ. Radiotherapy for mucosal melanomas. *Int J Radiat Oncol Biol Phys*. 1982;8(7):1121-1126.
242. Harrison LB, Fogel T, Peschel R. Primary vaginal cancer and vaginal melanoma: a review of therapy with external beam radiation and a simple intracavitary brachytherapy system. *Endocuriether Hypertherm Oncol*. 1987;3:67-72.
243. Rogo KO, Andersson R, Edbom G, et al. Conservative surgery for vulvovaginal melanoma. *Eur J Gynaecol Oncol*. 1991;12(2):113-119.
244. Das Gupta T, D'Urso J. Melanoma of the female genitalia. *Surg Gynecol Obstet*. 1964;119:1074-1078.
245. Brand E, Fu YS, Lagasse LD, et al. Vulvovaginal melanoma: report of seven cases and literature review. *Gynecol Oncol*. 1989;33(1):54-60.
246. Hachi H, Ottmany A, Bougtab A, et al. [Leiomyosarcoma of the vagina: a rare case]. *Bull Cancer*. 1997;84(2):215-217.
247. Peters WA 3rd, Kumar NB, Andersen WA, et al. Primary sarcoma of the adult vagina: a clinicopathologic study. *Obstet Gynecol*. 1985;65(5):699-704.
248. Neesham D, Kerdelmidis P, Scurry J. Primary malignant mixed Mullerian tumor of the vagina. *Gynecol Oncol*. 1998;70(2):303-307.
249. Hornback NB, Omura G, Major FJ. Observations on the use of adjuvant radiation therapy in patients with stage I and II uterine sarcoma. *Int J Radiat Oncol Biol Phys*. 1986;12(12):2127-2130.
250. Sutton GP, Blessing JA, Rosenshein N, et al. Phase II trial of ifosfamide and mesna in mixed mesodermal tumors of the uterus (a Gynecologic Oncology Group study). *Am J Obstet Gynecol*. 1989;161(2):309-312.
251. Thigpen JT, Blessing JA, Homesley HD, et al. Phase II trial of cisplatin in advanced or recurrent cancer of the vagina: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 1986;23(1):101-104.
252. Muss HB, Bundy B, DiSaia PJ, et al. Treatment of recurrent or advanced uterine sarcoma. A

- randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). *Cancer*. 1985;55(8):1648–1653.
253. Andrassy RJ, Hays DM, Raney RB, et al. Conservative surgical management of vaginal and vulvar pediatric rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study III. *J Pediatr Surg*. 1995;30(7):1034–1036; discussion 1036–1037.
 254. Hays DM, Shimada H, Raney RB Jr, et al. Sarcomas of the vagina and uterus: the Intergroup Rhabdomyosarcoma Study. *J Pediatr Surg*. 1985;20(6):718–724.
 255. Raney RB Jr, Gehan EA, Hays DM, et al. Primary chemotherapy with or without radiation therapy and/or surgery for children with localized sarcoma of the bladder, prostate, vagina, uterus, and cervix. A comparison of the results in Intergroup Rhabdomyosarcoma Studies I and II. *Cancer*. 1990;66(10):2072–2081.
 256. Hilgers RD. Pelvic exenteration for vaginal embryonal rhabdomyosarcoma: a review. *Obstet Gynecol*. 1975;45(2):175–180.
 257. Copeland LJ, Gershenson DM, Saul PB, et al. Sarcoma botryoides of the female genital tract. *Obstet Gynecol*. 1985;66(2):262–266.
 258. Grosfeld JL, Smith JP, Clatworthy HW Jr. Pelvic rhabdomyosarcoma in infants and children. *J Urol*. 1972;107(4):673–675.
 259. Flamant F, Gerbaulet A, Nihoul-Fekete C, et al. Long-term sequelae of conservative treatment by surgery, brachytherapy, and chemotherapy for vulvar and vaginal rhabdomyosarcoma in children. *J Clin Oncol*. 1990;8(11):1847–1853.
 260. Friedman M, Peretz BA, Nissenbaum M, et al. Modern treatment of vaginal embryonal rhabdomyosarcoma. *Obstet Gynecol Surv*. 1986;41(10):614–618.
 261. Andrassy RJ, Wiener ES, Raney RB, et al. Progress in the surgical management of vaginal rhabdomyosarcoma: a 25-year review from the Intergroup Rhabdomyosarcoma Study Group. *J Pediatr Surg*. 1999;34(5):731–734; discussion 734–735.
 262. Harris NL, Scully RE. Malignant lymphoma and granulocytic sarcoma of the uterus and vagina. A clinicopathologic analysis of 27 cases. *Cancer*. 1984;53(11):2530–2545.
 263. Prevot S, Hugol D, Audouin J, et al. Primary non-Hodgkin's malignant lymphoma of the vagina. Report of 3 cases with review of the literature. *Pathol Res Pract*. 1992;188(1–2):78–85.
 264. Perren T, Farrant M, McCarthy K, et al. Lymphomas of the cervix and upper vagina: a report of five cases and a review of the literature. *Gynecol Oncol*. 1992;44(1):87–95.
 265. Young RH, Scully RE. Endodermal sinus tumor of the vagina: a report of nine cases and review of the literature. *Gynecol Oncol*. 1984;18(3):380–392.
 266. Collins HS, Burke TW, Heller PB, et al. Endodermal sinus tumor of the infant vagina treated exclusively by chemotherapy. *Obstet Gynecol*. 1989;73(3 Pt. 2):507–509.
 267. Aartsen EJ, Delemarre JF, Gerretsen G. Endodermal sinus tumor of the vagina: radiation therapy and progeny. *Obstet Gynecol*. 1993;81(5 Pt. 2):893–895.
 268. Hwang EH, Han SJ, Lee MK, et al. Clinical experience with conservative surgery for vaginal endodermal sinus tumor. *J Pediatr Surg*. 1996;31(2):219–222.
 269. Williams S, Blessing JA, Liao SY, et al. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. *J Clin Oncol*. 1994;12(4):701–706.
 270. Kleinerman RA, Boice JD Jr, Storm HH, et al. Second primary cancer after treatment for cervical cancer. An international cancer registries study. *Cancer*. 1995;76(3):442–452.
 271. Ohno T, Kakinuma S, Kato S, et al. Risk of second cancers after radiotherapy for cervical cancer. *Expert Rev Anticancer Ther*. 2006;6(1):49–57.
 272. Hall EJ, Wu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys*. 2003;56(1):83–88.
 273. Bobin JY, Zinzindohoue C, Naba T, et al. Primary squamous cell carcinoma in a patient with vaginal agenesis. *Gynecol Oncol*. 1999;74(2):293–297.
 274. Hopkins MP, Morley GW. Squamous cell carcinoma of the neovagina. *Obstet Gynecol*. 1987;69(3 Pt. 2):525–527.
 275. Schult M, Hecker A, Lelle RJ, et al. Recurrent rectovaginal fistula caused by an incidental squamous cell carcinoma of the neovagina in Mayer-Rokitansky-Kuster-Hauser syndrome. *Gynecol Oncol*. 2000;77(1):210–212.
 276. Guven S, Guvendag Guven ES, Ayhan A, et al. Recurrence of high-grade squamous intraepithelial neoplasia in neovagina: case report and review of the literature. *Int J Gynecol Cancer*. 2005;15(6):1179–1182.
 277. Hiroi H, Yasugi T, Matsumoto K, et al. Mucinous adenocarcinoma arising in a neovagina using the sigmoid colon thirty years after operation: a case report. *J Surg Oncol*. 2001;77(1):61–64.
 278. Lara PN Jr, Hearn E, Leigh B. Neovaginal malignant melanoma following surgery and radiation for vulvar squamous cell carcinoma. *Gynecol Oncol*. 1997;65(3):520–522.
 279. Van Dam PA, Irvine L, Lowe DG, et al. Carcinoma in episiotomy scars. *Gynecol Oncol*. 1992;44(1):96–100.
 280. Heron DE, Axtel A, Gerszten K, et al. Vaginal glandular adenocarcinoma of the cervix recurrent in an episiotomy scar: a case report in a 32-year-old female. *Int J Gynecol Cancer*. 2005;15(2):366–371.
 281. Khalil AM, Khatib RA, Mufarrih AA, et al. Squamous cell carcinoma of the cervix implanting in the episiotomy site. *Gynecol Oncol*. 1993;51(3):408–410.
 282. Sun SS, Chen TC, Yen RF, et al. Value of whole body 18F-fluoro-2-deoxyglucose positron emission tomography in the evaluation of recurrent cervical cancer. *Anticancer Res*. 2001;21(4B):2957–2961.
 283. Miller B, Morris M, Rutledge F, et al. Aborted exenterative procedures in recurrent cervical cancer. *Gynecol Oncol*. 1993;50(1):94–99.
 284. Ratliff CR, Gershenson DM, Morris M, et al. Sexual adjustment of patients undergoing gracilis myocutaneous flap vaginal reconstruction in conjunction with pelvic exenteration. *Cancer*. 1996;78(10):2229–2235.
 285. Charra B, Laurent G, Chazot C, et al. Hemodialysis trends in time, 1989 to 1998, independent of dose and outcome. *Am J Kidney Dis*. 1998;32(6 Suppl. 4):S63–S70.
 286. Gupta AK, Vicini FA, Frazier AJ, et al. Iridium-192 transperineal interstitial brachytherapy for locally advanced or recurrent gynecological malignancies. *Int J Radiat Oncol Biol Phys*. 1999;43(5):1055–1060.
 287. Randall ME, Evans L, Greven KM, et al. Interstitial reirradiation for recurrent gynecologic malignancies: results and analysis of prognostic factors. *Gynecol Oncol*. 1993;48(1):23–31.
 288. Russell AH, Koh WJ, Markette K, et al. Radical reirradiation for recurrent or second primary carcinoma of the female reproductive tract. *Gynecol Oncol*. 1987;27(2):226–232.
 289. Xiang EW, Shu-Mo C, Ya-qin D, et al. Treatment of late recurrent vaginal malignancy after initial radiotherapy for carcinoma of the cervix: an analysis of 73 cases. *Gynecol Oncol*. 1998;69(2):125–129.
 290. Garton GR, Gunderson LL, Webb MJ, et al. Intraoperative radiation therapy in gynecologic cancer: update of the experience at a single institution. *Int J Radiat Oncol Biol Phys*. 1997;37(4):839–843.
 291. Haddock MG, Martinez-Monge R, Petersen IA, et al. Locally advanced primary and recurrent gynecologic malignancies EBRT with or without IORT or HDR-IORT. In: Gunderson LLCE, Harrison LB, et al. eds. *Current Clinical Oncology: Intraoperative Irradiation: Techniques and Results*. New Totowa, NJ: Humana Press; 1999:397–419.
 292. Gemignani ML, Alektiar KM, Leitao M, et al. Radical surgical resection and high-dose intraoperative radiation therapy (HDR-IORT) in patients with recurrent gynecologic cancers. *Int J Radiat Oncol Biol Phys*. 2001;50(3):687–694.
 293. Hockel M, Schlenger K, Hamm H, et al. Five-year experience with combined operative and radiotherapeutic treatment of recurrent gynecologic tumors infiltrating the pelvic wall. *Cancer*. 1996;77(9):1918–1933.
 294. Blomgren H, Lax I, Goranson H, et al. Radiosurgery for tumors in the body: clinical experience using a new method. *J Radiosurg*. 1998;1(1):63–74.
 295. Guckenberger M, Bachmann J, Wulf J, et al. Stereotactic body radiotherapy for local boost irradiation in unfavourable locally recurrent gynaecological cancer. *Radiother Oncol*. 2010;94(1):53–59.
 296. Molla M, Escude L, Nouet P, et al. Fractionated stereotactic radiotherapy boost for gynecologic tumors: an alternative to brachytherapy? *Int J Radiat Oncol Biol Phys*. 2005;62(1):118–124.
 297. Spanos WJ Jr, Wasserman T, Meoz R, et al. Palliation of advanced pelvic malignant disease with large fraction pelvic radiation and misomidazole: final report of RTOG phase I/II study. *Int J Radiat Oncol Biol Phys*. 1987;13(10):1479–1482.
 298. Spanos WJ Jr, Guse C, Perez C, et al. Phase II study of multiple daily fractionations in the palliation of advanced pelvic malignancies: preliminary report of RTOG 8502. *Int J Radiat Oncol Biol Phys*. 1989;17(3):659–661.
 299. Spanos WJ Jr, Perez CA, Marcus S, et al. Effect of rest interval on tumor and normal tissue response—a report of phase III study of accelerated split course palliative radiation for advanced pelvic malignancies (RTOG-8502). *Int J Radiat Oncol Biol Phys*. 1993;25(3):399–403.
 300. Spanos WJ Jr, Clery M, Perez CA, et al. Late effect of multiple daily fraction palliation schedule for advanced pelvic malignancies (RTOG 8502). *Int J Radiat Oncol Biol Phys*. 1994;29(5):961–967.
 301. Muss HB, Bundy BN, Christopherson WA. Mitoxantrone in the treatment of advanced vulvar and vaginal carcinoma. A Gynecologic Oncology Group study. *Am J Clin Oncol*. 1989;12(2):142–144.

302. Long HJ 3rd, Cross WG, Wieand HS, et al. Phase II trial of methotrexate, vinblastine, doxorubicin, and cisplatin in advanced/recurrent carcinoma of the uterine cervix and vagina. *Gynecol Oncol.* 1995;57(2):235–239.
303. Patton TJ Jr, Kavanagh JJ, Delclos L, et al. Five-year survival in patients given intra-arterial chemotherapy prior to radiotherapy for advanced squamous carcinoma of the cervix and vagina. *Gynecol Oncol.* 1991;42(1):54–59.
304. Mauer HM, Beltangady M, Gehan EA. The Intergroup RMS Study I.A. Final Report. *Cancer.* 1988;61:209–220.
305. Lindeque BG. The role of surgery in the treatment of carcinoma of the vagina. *Baillieres Clin Obstet Gynaecol.* 1987;1(2):319–29.
306. Herbst AL, Norusis MJ, Rosenow PJ, et al. An analysis of 346 cases of clear cell adenocarcinoma of the vagina and cervix with emphasis on recurrence and survival. *Gynecol Oncol.* 1979;7(2):111–122.
307. Brabham JG, Cardenes HR. Permanent interstitial reirradiation with ¹⁹⁸Au as salvage therapy for low volume recurrent gynecologic malignancies: a single institution experience. *Am J Clin Oncol.* 2009;32(4):417–22.

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EPIDEMIOLOGY, ETIOLOGY, AND RISK FACTORS

Worldwide, cervical cancer is the third most common malignancy and the second most common cancer (after breast cancer) in women. Nearly one-half million new cases occur each year. In 2012, it is estimated that 12,170 women will be diagnosed with invasive cervical cancer in the United States and over a third of them (4,220) will likely succumb to the disease (1). These statistics stand in sharp contrast to those of the developing nations where cervical cancer is the second leading cause of cancer death in women with well over 500,000 new cases annually worldwide and over 250,000 deaths. These are thought to be underestimations of the true numbers and burden of the disease. These disparate statistics and toll are due to paucity of screening programs and lack of access to life-saving treatments for women diagnosed with preinvasive and invasive cervical cancer. The disease burden in the United States is disproportionate among minority and economically burdened populations (1). Over 50% of cervical cancers diagnosed in the United States occur in women with no prior screening and around 10% are in women without any screening in the preceding 5 years.

The incidence and mortality of this disease in North America have declined during the last half century owing to both increased availability of Pap smear screening and a decrease in fertility rate. An extensive discussion of cervical cancer etiology and risk factors appears earlier in the text, particularly in Chapters 1 to 3 and 8. The reader is referred to those chapters for detailed information.

ANATOMY

The uterus, situated in the center of the pelvis, is composed of a muscular layer (myometrium) and mucosal glandular layer (endometrium), which lines a hollow cavity extending from the top of the uterus (fundus) through the lower uterine segment connecting to the endocervical canal. The endometrial cavity is surrounded by the myometrium. The three segments of the uterus include the fundus, body, and isthmus (lower uterine segment). Anteriorly, the lower uterine segment is attached to the bladder peritoneum (vesico-uterine pouch), which requires dissection and separation to expose the cervix. This compartment between the bladder and uterus is the anterior cul-de-sac. Posteriorly the peritoneum lines and separates the lower uterine segment and cervix from the rectum, creating the posterior cul-de-sac (pouch of Douglas). The cervix is an extension of the lower uterine segment and can be divided into vaginal and supravaginal components. The cervix varies in length, averaging 3 to 5 cm.

Centrally located in the vaginal portion is the external cervical os, which connects to the endocervical canal, the internal cervical os, and the endometrial cavity.

The cervix is a fibrous organ lined by squamous and columnar cells. The transition from columnar cells to squamous cells occurs in the region of the cervical os in what is termed the transformation zone. Most dysplastic and malignant cervical lesions arise from this area. The endocervix contains mostly mucinous glandular epithelium with similar morphology to that of the fallopian tube.

The uterus has 5 ligamentous attachments. Specifically these include the round, broad, utero-ovarian, cardinal, and utero-sacral ligaments. The round ligaments run from both sides of the fundus anterolaterally on top of the broad ligaments to the pelvic sidewall, where they are closely related to the inferior epigastric vessels and continue on their path to leave the pelvis through the inguinal ring and canal. They contain a vessel known as Sampson's artery as well as other small vessels and nerves.

The broad ligaments attach to the lateral margin of the uterus on either side and extend underneath the round ligaments from above the cervico-uterine junction and to the pelvic sidewall. These ligaments are covered by peritoneum anteriorly and posteriorly, and are relatively thinner above the cervico-uterine junction. Within the leaves of the broad ligament are extraperitoneal connective tissues known as the parametrium, which surround the lower uterine segment and the cervix.

The utero-ovarian ligaments originate just below the fallopian tubes and directly connect to the ovaries. The cardinal ligaments, also known as Mackenrodt's ligaments, are thickened extensions of the broad ligaments attaching laterally from the lower uterine segment (isthmus) and the cervix. They course to the lateral vaginal wall and rectal pillars and extend to the pelvic sidewalls.

Each cardinal ligament helps create and define 2 important anatomical spaces, the pararectal and paravesical spaces, which are important in the surgical treatment of early cervical cancer. The cardinal ligament covers a portion of the pelvic ureter, which lies underneath the uterine artery and above the uterine vein about 2 cm away from the isthmus. It contains uterine, vaginal, middle rectal, and inferior vesical arteries and veins as well as lymphatic tissue and channels.

Two important anatomical landmarks during radical hysterectomy (RH) for treatment of early cervical cancer are the paravesical and pararectal spaces. The paravesical space is lateral to the bladder and can be opened by dissection underneath the insertion of the round ligament into the pelvic sidewall. This space is opened using blunt dissection underneath the round ligament dissection along the curve of the bony pelvic wall proceeding medially to open the relatively avascular space. The anterior wall is bounded by the superior pubic ramus, the medial wall is the bladder and vagina, the lateral wall is composed of the external iliac vessels and parts of the obturator fossa, and

the posterior wall is formed by the cardinal ligament, separating this space from the pararectal space. This space can be continuous with the space between the bladder and the pubic bone, known as the space of Retzius. The pararectal space is found between the ureter laterally and the origin of the hypogastric artery medially and follows the curve of the sacrum. Anteriorly it is bounded by the cardinal ligament. The lateral wall is formed by the hypogastric vessels. Medially it is bounded by the ureter, and the floor is composed of the curve of the sacrum down to the levator muscles. During a RH, these two spaces allow for direct examination of the parametrium to determine extent of the disease and the resectability of the primary tumor allowing for free surgical margins.

The utero-sacral ligaments connect laterally to the cervix and lower uterine segment medial to the ureters. They run from the posteriolateral segment of the cervix over the top of the antero-lateral portion of the rectum and attach to the rectal wall and the sacrum. The cardinal and utero-sacral ligaments provide the bulk of support for the uterus and cervix.

The blood supply of the uterus is mainly through the uterine artery, originating from the anterior division of the hypogastric artery. An important landmark during a RH, the uterine artery spawns cervical and vaginal branches that supply the cervix, and then extends superiorly to the fundus where its tributaries supply the fundus and the body of the uterus. The uterine artery also descends toward the vagina and gives off a vaginal branch. The ovarian vessels originating from the aorta also contribute to the blood supply of the uterus. There is a rich anastomosis between the uterine and ovarian arteries. Other potential collateral blood supply to the uterus may be from the branches of the posterior division of the hypogastric, the ilio-lumbar artery, or other vessels supplying the pelvis such as middle sacral artery, and pudendal and obturator arteries. The venous drainage follows the arterial supply.

The lymphatic drainage of the cervix is rich and complex. Laterally from the cervix, the lymphatics drain into the paracervical and parametrial lymph nodes and to the internal, external, and common iliac chains. The obturator lymph nodes are the most medial portion of the external iliac nodal region and play a key role as one of the first sites of lymphatic spread of cervical cancer following the parametrial nodal tissues. Other lymphatic drainage routes include the inferior and superior gluteal lymph nodes and the superior rectal, presacral, and paraaortic lymph nodes. The innervations of the cervix are from the sacral roots (S2–4) crossing through the hypogastric plexuses.

NATURAL HISTORY

Preinvasive Disease

Cervical cancer is preceded by an interval of epithelial dysplastic changes, typically in the transformation zone, known as cervical intraepithelial neoplasia (CIN), which may progress to invasive cancer. Low-grade dysplasia (CIN 1) is confined to the basal one-third of the epithelium, whereas high-grade dysplasia (CIN 2 to 3) involves two-thirds or greater of the epithelial thickness. Full thickness involvement is known as carcinoma *in situ* (CIS), which is thought to be the most significant precursor lesion for invasive squamous carcinoma. Cytologic screening has helped in decreasing the incidence of cervical cancer in the United States and other developed nations dramatically. Of approximately 55 million Pap smears performed in the United States annually, 5% to 7% are abnormal, and the majority of these are atypical squamous cells of undetermined significance (ASCUS) (2). The majority of the disease burden is in developing nations where screening and treatment programs are scarce and difficult to implement.

Many studies have evaluated the natural history of cervical dysplasia. Holowaty et al. evaluated cervical dysplasia in about

17,000 women with mild, moderate, and severe dysplasia (3). The reported risk of progression from mild to severe dysplasia was 2% and 6% at years 2 and 5, respectively. However, progression from moderate to severe dysplasia was 16% and 25% at 2 and 5 years, respectively. The relative risks of progression from severe dysplasia to CIS and invasive cancer were 4.2 and 2.5, respectively, 2 years after diagnosis of dysplasia. The majority of mild dysplasias (CIN 1) regressed to normal within 2 years.

In a meta-analysis of 15 studies of 27,929 women, Melnikow et al. found 2-year progression rates to high-grade dysplasia to be 7% and 21% from ASCUS and low-grade dysplasia, respectively (4). The rate of progression to invasive cancer for ASCUS was 0.25%, as compared to low-grade dysplasia (0.15%) and high-grade dysplasia (1.4%). The regression rates to normal for ASCUS, low-grade, and high-grade dysplasias were 68%, 47%, and 35%, respectively.

The incidence of progression from CIS to invasive cancer in patients with persistent abnormal cytology after initial treatment was 24.8 times greater than in those who had normal cytology after initial treatment (5). Overall the reported rate of progression of CIS to invasive cancer ranges from 12% to 22%.

Most low-grade dysplasia will regress to normal in about 24 months. Therefore, only careful follow-up is warranted. However, women with high-grade disease or CIS should be more closely evaluated and treated aggressively as the risk of progression is higher (5). A great deal is being learned about the natural history of this disease; as there are many variations including a subset of CIS lesions that can rapidly present as invasive cancer within a couple of years. Many glandular lesions associated with HPV 18 can also herald a rapid progression to invasive disease proving evasive even in adequately screened populations. Emerging data strongly suggest that despite negative cytology, a woman who tests positive for highly oncogenic HPV 16 has a significantly higher chance of having or developing CIS. These will be discussed in detail in the screening section.

Patterns of Spread

Cervical cancer can spread through direct extension to the endocervix, lower uterine segment, parametrium, vagina, and, less often, to the bladder and/or rectum. It can also spread lymphatically to the parametrial, obturator, and internal, external, and common iliac lymph nodes. Inferior and superior gluteal, superior rectal, presacral, and paraaortic lymph nodes can also become involved. The pattern of spread is usually predictable and orderly, as the rate of paraaortic lymph node metastasis is very rare if the pelvic nodes are spared. The overall risk of pelvic lymph node metastasis in stage IB is about 9% to 17% (6,7). The risk of paraaortic nodal (PANL) metastasis is higher with advanced stage disease, with rates of 16% and 25% for stage II and III, respectively (8). Scalene nodal involvement is reported to be between 10% and 23%, and involvement of higher paraaortic nodes can suggest possible scalene nodal involvement (9).

The most common sites of hematogenous spread include lung, mediastinum, bone, and liver. Other less common sites are spleen, brain, and adrenal gland. Most recurrences occur in the first 24 months, with a median of 17 months.

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

Preclinical Invasive Disease

Screening and Cytology

The effectiveness of screening cytology is related to the ease of obtaining specimens, the sensitivity of the test, and a long

dysplastic phase that can be detected via cytology and effectively treated with high success rates. There are currently 2 primary means of obtaining and diagnosing cervical dysplasia. One is the conventional Pap smear and the other is liquid-based thin layer preparation.

Using classification as low-grade squamous intraepithelial lesion (LSIL) as the threshold, Nanda et al. reported a large variation in the sensitivity of conventional smears, with published data ranging from 30% to 87%; specificity was much higher at 86% to almost 100% (10). Cytologic screening is a continuum in which specificity is increased through sequential testing. The most common reasons for false-negative smears are errors in sampling and preparation. In 1996, liquid-based cytology was introduced in the United States. Cells are obtained by a cytobrush and transferred into a buffered alcohol medium. The suspended cells are then plated in a thin, evenly distributed layer, improving the clarity of the slide for evaluation. Another benefit is that the specimen can be tested for HPV, gonorrhea, and chlamydia. A careful review of data suggests that liquid-based cytology may be superior to conventional cytology in minimizing the number of unsatisfactory smears and increasing detection rates of low- and high-grade abnormalities (11). Sulik et al. reported no difference between the 2 methods in a large systematic review (12). The American Cancer Society (ACS) and U.S. Preventive Services Task Force (USPSTF) have concluded that, although liquid-based technology may be more sensitive than conventional cytology, there was insufficient evidence to recommend universal adoption. The American College of Obstetricians and Gynecologists (ACOG) does not support changing screening intervals based on the method of screening (13).

The changes in recommendations for screening published in 2012 have been sweeping. Screening is not recommended in anyone under the age of 21 regardless of the age of sexual debut. For women aged between 21 and 29, cytology alone is recommended every 3 years. HPV testing is not recommended in this age group, as there is a high prevalence of infection in this population, with many being transient. The rationale is that cotesting with HPV will only increase the number of colposcopies and will result in harm without reducing the risk of CIN 3 or invasive cancer. For patients aged 30 to 65, the recommendations are for cytology alone every 3 years versus cytology and HPV co-testing every 5 years, with the latter being the preferred recommendation.

Screening should stop at age 65 for women with 3 negative consecutive previous cytology results or 2 consecutive negative cytology and HPV testings within the last 10 years, with the most recent being within last 5 years. Once screening is discontinued, it should not be resumed even if the woman has a new sexual partner (14,15). It is important to note that following regression or appropriate clinical treatment of CIN 2 or 3 and AIS, screening should continue for 20 years, even if that exceeds the threshold of 65 years of age. Annual screening results in an over 50% increase in the number of colposcopies when compared to screening every 3 years, without adversely affecting the outcomes.

Women who have undergone hysterectomy for a prior diagnosis of CIN 2 or 3 or a more severe diagnosis should continue screening for 20 years. Those with no prior history of cervical dysplasia should not undergo routine vaginal cytology. Women who have been vaccinated for HPV should follow the age-specific recommendations, since 30% of cervical cancers are caused by etiologies other than HPV 16 and 18.

If HPV is negative and cytology is ASCUS, then rescreening with co-testing in 5 years or with cytology alone in 3 years is reasonable. If HPV is positive and cytology is negative, then a 12-month follow-up with repeat co-testing or subtesting for HPV16 and 18 can be done and, if positive, should herald a referral for colposcopy given the high rate of coexistent CIN 2 or 3 with positive testing for types 16 or 18. If the subtyping is negative, then a 12-month follow-up with co-testing is reasonable.

Detection of adenocarcinoma is much more difficult than detection of squamous lesions. HPV 18 positivity with negative cytology may indicate a significant underlying glandular lesion (16).

To provide a standard terminology for reporting cytologic findings, the Bethesda system set forth guidelines in 1988, with revisions in 2001 (17). This system describes the adequacy of the specimen, a general categorization of whether it falls within normal limits or not, and a description of the dysplastic cytologic abnormalities detected in 3 categories: ASCUS or atypical squamous cells—cannot rule out high-grade squamous intraepithelial lesion (ASC-H), LSIL (the same as CIN 1), and high-grade squamous intraepithelial lesion (HSIL), which is the same as CIN 2 or 3. It can also report squamous cell carcinoma directly. For glandular lesions, categories include atypical glandular cells (AGS), denoting origin if possible (endocervix, endometrial, or not otherwise specified), AGS favoring neoplastic, adenocarcinoma *in situ* (AIS), or frank adenocarcinoma.

It is estimated that approximately 10% to 20% of women with ASCUS or ASC-H have underlying CIN 2 or 3 and that 1 in 1,000 may have underlying invasive cancer. ASC-H is expected to be diagnosed in about 5% to 10% of all ASCUS readings. AGS is associated with a much higher percentage of high-grade disease when compared to ASCUS—as high as 39%.

The ASCUS/LSIL Triage Study (ALTS), a multicenter randomized trial of 3,488 women, compared immediate colposcopy versus triage to colposcopy based on HPV testing, and liquid-based cytology with a threshold of HSIL versus conservative management with triage based on repeat cytology with a threshold of HSIL (18,19). ASCUS was reproducible in repeat liquid-based cytology in only 32% of cases with an overall CIN 2 and 3 diagnosis of 15% when ASCUS cytology was further investigated. HPV testing was able to identify 92% of women who would ultimately have a diagnosis of CIN 3. Only 1.4% of women with negative HPV testing developed CIN 3 over 2 years. If HPV testing was positive with LSIL or ASCUS was the same around 27%. Repeat cytology for ASCUS would have referred almost 67% of women to colposcopy as compared to HPV testing, which referred about half the number of women for colposcopy. The American Society of Colposcopy and Cervical Pathology (ASCCP) endorsed HPV testing as the preferred method of triage for ASCUS smears detected by liquid-based cytology (20).

HPV Testing

HPV DNA testing is a new tool that has gained greater popularity and utility in the last few years. It is especially useful in women over 30 when combined with cytology, because it provides much greater sensitivity for detection of CIN 2–3 disease, although it is less specific (16). Methods of detecting HPV include hybrid capture 2 and polymerase chain reaction. Both tests have similar sensitivity and specificity, but the former is easier to perform technically, especially in a large screening program setting. Sherman et al. studied over 20,000 women, evaluating the role of conventional Pap smear and concurrent HPV testing to determine the risk of developing CIN 3 (21). In this study, 72% of women who developed CIN 3 had baseline abnormal cytology and positive HPV testing with a cumulative incidence of developing CIN 3 or invasive cancer of 4.5% in approximately 45 months of follow-up. This was compared with women with negative smears and HPV testing whose cumulative incidence of developing CIN 3 or invasive cancer was only 0.16%. The combination of negative cytology and HPV testing carries a high-negative predictive value of over 95% for the development of CIN 3 or invasive cancer, providing great reassurance for low-risk women and lengthening the interval of screening in that population.

Clavel et al. studied the role of HPV testing as a primary screening tool in almost 8,000 women (22). They reported 100% sensitivity of HPV testing in detecting histologically proven

high-grade dysplasia compared to conventional smear (68%) and liquid-based cytology (87%). The specificity of HPV testing was 93% in women over 30, compared to conventional and liquid-based technologies with specificities of 86% and 95%, respectively. Overall it was found that HPV testing is much more sensitive in detecting high-grade disease compared to conventional smears, but with a lower specificity rate. This approach requires further study; screening women younger than 30 years may lead to unnecessary testing, as many HPV infections are transient, and most women will not develop dysplasia with HPV infection. In LSIL, more than 85% of cases test positive for HPV. Therefore, HPV testing is not encouraged. CIN 2 and 3 require immediate referral for colposcopic evaluation. The overall 2-year cumulative risk of developing CIN 2 and 3 for LSIL and ASCUS with positive HPV testing was essentially the same (27.6% and 26.7%). The authors suggested that repeat HPV testing 12 months after diagnosis of LSIL and ASCUS with positive HPV yielded the highest sensitivity and lowest rate of referral for colposcopy. Repeat cytology with HPV testing did not significantly increase sensitivity and increased referral for colposcopy. HPV testing appears to be useful in triage of ASCUS smears, possibly reducing colposcopic referrals by almost 50% (17,18). HPV subtyping for 16 and 18 may even be more helpful in further delineating the risk of CIN 3 and subsequent risk of invasive cancer. HPV 16 is found in 55% to 60% of all cervical cancers. A patient with a positive test for HPV 16 has a high risk of CIN 3 or more severe lesion of almost 30% if there is persistent HPV 16 infection for around 2 years. CIN 3 has a roughly 30% chance of progression to invasive cervical cancer over a three-decade period, and treated CIN 3 has less than a 1% risk. CIN 3 is the greatest predictor of development of cervical cancer (16).

A large study (ATHENA) that included 40,901 evaluable patients with positive HPV testing and liquid-based cytology test results was recently reported. Of these, 4,275 women (10%) tested HPV-positive and 2,617 (6%) had abnormal cytology. Four hundred and thirty-one women were diagnosed with CIN 2 or worse, and 274 with CIN 3 or worse. In the subset of women who had colposcopy, the HPV testing was more sensitive than liquid-based cytology for detection of CIN 3 or worse (92% vs. 53.3%). The addition of liquid-based cytology to HPV testing improved sensitivity for CIN 3 or worse to 96.7%; however, this contributed to a greater number of positive screenings (by 35%) compared with HPV testing alone. The rate of positive testing for HRHPV was 6.7%, and 1.5% were positive for types 16 and 18. Overall incidence of CIN 2–3 was 1.2%. The absolute risk of a CIN 2 or worse lesion was 11.4% if positive for HPV 16/18 compared to 6.1% if positive for HRHPV and 0.8% if HPV-negative. These results highlight the importance of types 16 and 18 in the development of CIN 3 and a referral for colposcopy if positive, despite negative cytology (23).

Two commercial tests for HPV DNA have been approved by the U.S. Food and Drug Administration. The hybrid capture II test has been shown to have excellent interlaboratory reliability and reproducibility (24).

Colposcopy

Colposcopy examines the lower genital tract including the vulva, vagina, and epithelium of the cervix and opening of the endocervix. The use of acetic acid and Lugol's solution assists in highlighting abnormal and dysplastic changes. Changes such as aceto-white plaques and vascular abnormalities such as punctations, mosaicism, and abnormal branching may signify high-grade disease. Indications for colposcopy include an abnormal-appearing cervix, persistent postcoital bleeding or discharge, persistent CIN 1, 2, or 3 on cytology, *in utero* exposure to DES, and ASCUS smears with positive high-risk HPV testing (16 and 18). In order to have an adequate colposcopic examination the entire transformation zone must be fully visualized.

Endocervical curettage (ECC) can be helpful if positive; however, its role as a routine procedure is debated. Positive predictive value of colposcopy can be increased by multiquadrant biopsies.

Conization Biopsy

Cervical conization refers to the surgical removal of the squamocolumnar junction. This may be done in the operating suite through a classical cold knife conization technique or as an outpatient procedure using thermal cautery with loop excision. Indications for conization include inadequate colposcopy, positive ECC, persistent CIN 1 (usually >1 year), CIN 2, CIN 3, or CIS, and discrepancy between cytologic, colposcopic, or pathologic findings.

Loop Electrosurgical Excision Procedure

Loop diathermy, an alternative to cold knife conization, is usually performed on an outpatient basis. Trials have demonstrated loop electrosurgical excision procedure (LEEP) to be as effective as cold knife conization, with advantages in terms of cost, anesthesia, and ease of use (25). A disadvantage is that significant thermal artifact can hamper evaluation of margin status, which can be minimized with careful technique avoiding prolonged contact with the tissue.

Clinical Disease

Symptoms and Complaints

The most common presentations of invasive cervical cancer are abnormal vaginal bleeding, postcoital bleeding, and vaginal discharge. However, many women are asymptomatic and are found to have disease upon pelvic examination or cytologic evaluation. As the tumor enlarges, it can cause local symptoms such as pelvic pain and difficulty with urination or defecation. As the disease metastasizes to regional lymph nodes, back pain, leg swelling (especially unilateral), and neuropathic pain may occur.

Physical Findings

The most common finding on physical examination is an abnormal lesion on the cervix, at times necrotic and friable. Possible extension onto the vaginal wall should be assessed. Determination of parametrial, sidewall, and uterosacral ligament involvement must be done through a rectovaginal examination. Other areas of concern are the superficial groin and femoral lymph nodes and the supraclavicular region.

Diagnostic Biopsy

Suspicious lesions on the cervix and surrounding areas should be biopsied with enough depth to assure adequate nonnecrotic tissue to render diagnosis. Biopsy on the margin tends to yield better results.

Staging

Clinical Staging Procedures

The most critical component of staging is a thorough pelvic examination, including a rectovaginal exam. If necessary, an exam under anesthesia allows for a careful visual and digital examination as well as cystoscopy and proctoscopy.

Laboratory Studies

A complete peripheral blood count is indicated to evaluate for anemia, which might warrant correction. Thrombocytosis is

found in up to 30% of patients with locally advanced disease, and has been associated with larger tumor size, parametrial involvement, and poorer survival. Serum chemistries with attention to serum creatinine are essential to evaluate for renal failure or to assess renal function in patients who will receive cisplatin-based chemoradiotherapy. Additional tests should include liver function and urinalysis.

Serum Tumor Markers

Though several tumor markers are thought to be useful as prognostic and predictive markers in response to treatment, risk of relapse, and overall survival (OS) in women with cervical cancer, their role in the initial diagnostic evaluation is limited (26,27). Elevation of the most commonly studied tumor markers, squamous cell carcinoma antigen (SCCA), cytokeratin fragment 19 (CYFRA 21.1), and cancer antigen 125 (CA-125), has been observed in 20% to 88% of women with newly diagnosed cervical cancer (26). These elevated levels have been correlated with tumor stage, tumor size, cervical stromal invasion, lymphovascular space invasion, parametrial involvement, and lymph node status (26). In a retrospective study by Huang et al. (28), pre- and posttreatment levels of SCCA and carcinoembryonic antigen (CEA) were evaluated in 188 women with squamous cell carcinoma (SCC) of the cervix receiving concurrent chemoradiation. Pretreatment marker levels predicting high risk for para-aortic lymph node recurrence (66.5% at 5 years) were SCCA ≥ 40 ng/mL or the combination of CEA ≥ 10 ng/mL and SCCA < 10 ng/mL, for intermediate risk were SCCA 10 to 40 ng/mL, and for low risk were both SCCA and CEA < 10 ng/mL (28). Kotowicz et al. (29) assessed pelvic and paraaortic lymph nodes in 182 untreated patients with cervical cancer (87% SCC and 13% adenocarcinoma) and evaluated levels of the tumor markers SCCA, CYFRA 21.1, CA-125, and CEA, and the cytokines interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF). SCCA, CA-125, and IL-6 were significantly higher in women with lymph node metastases than in those with no lymph node involvement. The simultaneous elevation of SCCA and CA-125 levels or SCCA and IL-6 was statistically significant in women with lymph node metastases.

Sheng et al. (30) evaluated SCCA, CYFRA 21.1, CEA, and a nuclear protein found to play a role in tumor development, growth, and metastases, high mobility group box-1 (HMGB1), in early detection of recurrent SCC of the cervix. In 112 women with recurrent SCC of the cervix, 174 women without evidence of recurrent cervical cancer, and 128 age-matched healthy controls, HMGB1 levels were significantly higher in women with recurrent cervical cancer than in women from the other groups ($p = 0.027$). Measurements with the combined tumor markers HMGB1, SCCA, and CYFRA 21.1 were reported to increase the diagnostic sensitivity and specificity (30). Further studies are required to confirm the use of tumor markers alone or in combination for the early detection of recurrence.

Radiographic Studies

In accordance with the International Federation of Gynecology and Obstetrics (FIGO) system for staging, clinical evaluation is the predominant tool for staging cervical cancer (31–33). Non-invasive radiographic imaging studies such as chest radiography, intravenous pyelography (IVP), cystoscopy, sigmoidoscopy, and barium enema may aid in this process but are not mandatory (31–33). Additionally, radiographic studies such as computed tomography (CT), positron emission tomography (PET), combined PET/CT, and magnetic resonance imaging (MRI) are not considered integral to formal staging, but may aid in determination of extent of disease in the pelvis and lymph nodes, evaluation of prognosis, measurement of response, and assessment of recurrence following initial treatment (34–37).

Given that evaluation of the extent of disease in the pelvis and lymph nodes is important for individualizing treatment, advanced imaging with CT, PET/CT, and MRI should be performed preoperatively when available (37). MRI and CT imaging are the most valuable imaging techniques for evaluation of disease in the pelvis and chest/abdomen, respectively. Due to its superb soft tissue delineation, high-resolution MRI with contrast and diffusion-weighted imaging is useful for the evaluation of disease in the pelvis assessing tumor size, extension into the uterine corpus, depth of stromal invasion, parametrial and pelvic wall extension (34,35). In a randomized, prospective study performed by the American College of Radiology Imaging Network (ACRIN) and the Gynecologic Oncology Group (GOG), MRI more accurately determined tumor diameter, uterine extension, and parametrial involvement than did CT or clinical examination in early invasive cervical cancer (38–41). However, in large, bulky cervical tumors, MRI may overestimate parametrial extension and may less accurately determine upper vagina, bladder, and/or rectum invasion (34).

PET/CT plays a valuable role in the imaging of nodal metastases (36,42–44). Kidd et al. reported a large prospective study to evaluate the role of pretreatment [^{18}F] fluorodeoxyglucose PET imaging for lymph node staging in 560 women with clinical stage IA1–IVB disease (42). The frequency and pattern of lymph node metastases on PET were associated with clinical staging. Although this study did not confirm lymph node status by histopathology, disease-specific survival correlated with PET-positive lymph nodes. Choi et al. published a meta-analysis comparing the diagnostic performance of CT, MRI and PET or PET/CT for detection of nodal metastases in 41 published reports (43). PET or PET/CT showed the highest pooled sensitivity (82%) and specificity (95%), while CT showed 50% and 92%; and MRI, 56% and 91%, respectively (43). Kang et al. performed another meta-analysis assessing the diagnostic value of PET for the evaluation of PALN metastases in 10 published reports (44). Their analyses indicated assessment of PALN metastases by PET or PET/CT is acceptable for higher stage cervical cancer, but for earlier stage disease, PALN dissection is preferable. In summary, PET or PET/CT has a higher diagnostic performance for detecting lymph node metastases than CT or MRI, especially in women with higher-stage cervical cancer.

Future studies combining MRI and PET may provide additional staging information. In a retrospective study by Kim et al., lymph node status was evaluated comparing MRI/PET fusion and PET/CT prior to lymphadenectomy in 79 women with histologically confirmed invasive Stage IB–IVA cervical cancer (45). Review of lymph node status with MRI/PET fused images revealed identification of 6 additional metastatic nodal groups in 3 additional patients as compared to PET/CT images. Sensitivity and specificity of PET/CT was 44.1% and 93.9%, respectively, while for fused MRI/PET was 54.2% and 92.7%, respectively (45).

In conclusion, both MRI and PET/CT imaging modalities are recognized as being very useful in the staging and subsequent treatment planning of this disease. There is further interest in performing dynamic contrast-enhanced MRI to evaluate tumor vascularity and perfusion, and PET/CT to evaluate intratumoral metabolic activity, and using this information to predict response to therapy (46–48). As the technology of these imaging modalities continues to advance, integration of both anatomic and biologic information will permit further individualization of treatment.

FIGO and American Joint Committee on Cancer Staging

The staging system used for cervical cancer is based on the FIGO staging system, updated in 2009 (33). The main change from the 1995 staging system involves stage IIA. Stage IA is microscopic, with IA1 defined as stromal invasion to less than 3 mm in depth and no more than 7 mm wide, and stage IA2 defined as stromal invasion 3 to 5 mm deep with width no greater than 7 mm. The Society

of Gynecologic Oncology (SGO) also considers negative lymphovascular space invasion (LVSI) and margin status as criteria for microinvasive disease (MID). The horizontal spread must be 7 mm or less to be considered MID according to FIGO, but SGO does not include lateral spread in defining MID. The diagnosis of MID must be made on a conization or hysterectomy specimen. Punch biopsies are not adequate. Stage IB involves the cervix only. It is divided into IB1, which includes all lesions greater than IA2 and no more than 4 cm in greatest dimension, and stage IB2 for lesions measuring greater than 4 cm. Stage II invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina. It is divided into A and B. Stage IIA involves the proximal vagina and is now subdivided similarly to stage IB into IIA1, which includes tumors less than 4 cm, and IIA2 for tumors greater than 4 cm involving the proximal vagina and sparing the parametrium. Stage IIB indicates parametrial invasion. In Stage III, the tumor extends to the pelvic wall and/or involves

lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney. Stage IIIA extends to the lower third of the vagina sparing the pelvic sidewall, while IIIB extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney without alternate reason for such findings.

Surgical findings and radiographically guided biopsies of suspected lesions such as lymph nodes or lung metastasis cannot be used to change or modify clinical FIGO staging. In Stage IV, the tumor extends beyond the true pelvis or has involved the mucosa of the bladder or rectum (biopsy proven). Bullous edema alone does not permit a case to be allotted to stage IVA. Stage IVB denotes distant metastasis. A tumor-node-metastasis (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC) corresponds well to the FIGO clinical staging. The current criteria for the various stages are defined in Table 21.1. TNM is mainly used in documenting findings on surgical and pathologic evaluations as the pathologic stage of the disease,

Table 21.1 Definition of TNM

TNM Categories		FIGO Stages
<i>Primary Tumor (T)</i>		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma <i>in situ</i>
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a ^a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion ≤3.0 mm in depth and ≤7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion >3.0 mm and ≤5.0 mm with a horizontal spread ≤7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion >T1a/IA2
T1b1	IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion >4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion >4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
<i>Regional Lymph Nodes (N)</i>		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIB	Regional lymph node metastasis
<i>Distant Metastasis (M)</i>		
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

Note: The definitions of the T categories correspond to the stages accepted by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO). Both systems are included for comparison.

^aAll macroscopically visible lesions—even with superficial invasion—are T1b/IB.

Source: AJCC. Cervix uteri. In: Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010:395–402.

and FIGO is used for clinical staging. All histologic types are included. If there is ambiguity regarding the correct stage, the lower stage is assigned.

Pretreatment Nodal Staging

The presence of paraaortic lymph node metastases has a significantly negative impact on progression-free and overall survival. Pretreatment knowledge of paraaortic spread could potentially direct treatment in a manner that could improve outcomes. Given the limitations of imaging in reliably detecting paraaortic micro-metastases, surgical staging has been used. However, the role of surgical staging for locally advanced cervical cancer remains unclear. The use of PET/CT scans has become widely adopted in Western countries with a relatively low sensitivity rate of 30% to 40%, depending on the study. However, a relatively high negative predictive value of 80% to 90% has been reported in various studies. Ramirez et al. studied 65 patients with stages IB2 to IVA comparing radiographic (PET/CT) versus surgical staging of paraaortic nodes (49). Positive PA nodes were found in 23%; 22% of those with positive histologic nodes had negative radiographic findings. PET/CT was superior to CT or MRI alone when nodes were negative on those modalities, with a specificity of 96%. Treatment was modified in 18% due to surgical findings. Kidd et al. evaluated 560 patients with PET/CT and correlated finding with prognosis (50). Almost half (47%) had positive nodes on PET/CT, which conferred a poor prognosis with a hazard ratio of recurrence based on positive nodes, depending on location of pelvic, paraaortic, and supraclavicular, of 2.4, 5.8 and 30, respectively. Gold et al. reviewed 555 patients with surgical paraaortic node sampling and 130 who had radiographic staging. For stages III and IV, the 4-year progression-free survival (PFS) was 49% versus 36%, with an OS of 54% versus 40%, favoring patients who were surgically staged (51).

With the advent of laparoscopy and the presumed lower morbidity, there has been some renewed interest in surgical nodal assessment as a method to refine treatment. Faggotti et al. reviewed 13 published series to investigate the role of pretreatment laparoscopic staging. They showed laparoscopic surgical staging can be performed safely and contribute to tailor treatment. However, the positive impact on DFS has still to be demonstrated (52).

Leblanc et al. evaluated 184 patients with stages IB2 through IVA with pretreatment extraperitoneal laparoscopic staging of paraaortic nodes (53). They found a 24% incidence of PANL involvement and an operative complication rate of 2%. They had a 13% symptomatic lymphocyst rate that decreased to about 3% with modification of techniques. Findings of surgical staging changed the management of 20% of patients who would have received only pelvic radical trachelectomy (RT) to extended field RT. Data suggested a survival advantage in patients with resected positive nodes.

Lai et al. compared clinical staging versus surgical staging (laparoscopic or extraperitoneal approach) in 61 patients (54). PANL metastasis was detected in 25% of the surgical group. The study was terminated early, as the surgical arm had a significantly worse progression-free and overall survival compared to the nonsurgical arm. The question of pretreatment surgical staging remains controversial, and ongoing prospective studies are in progress to determine the utility of surgical staging in the setting of quality PET/CT imaging (49–51).

Sentinel Lymphatic Mapping in Early Cervical Cancer

The standard surgical treatment for early cervical cancer (stages IA2 to IIA) is RH and pelvic lymphadenectomy (PL). The PL is complete and removes all nodal bearing tissues on the external iliac artery and vein (up to the circumflex iliac vein), internal iliac artery above the obturator nerve, and common iliac artery

up to the iliac bifurcation. The procedure carries some risk of injury to vessels and nerves, can lead to lymphedema, and can predispose to a higher complication rate if postoperative RT is needed. Lymphatic mapping (LM) refers to the concept of delineating the path of malignant cells through the lymphatics, identifying the nodes primarily at risk for early spread, and determining if this knowledge will safely allow a limited rather than a complete regional lymphadenectomy.

Thompson and Uren described the sentinel node (SLN) as “any lymph node that receives lymphatic drainage directly from primary tumor” (55). SLN has revolutionized care for women with breast cancer and for those with melanoma. It has also been shown to be of benefit in patients with vulvar cancer. In cervical cancer many reports have shown feasibility and high detection rate of SLN in stages 1A2 to IB. Levenback et al. reported 39 patients with early cervical cancer who underwent RH and PL. Preoperative lymphoscintigraphy was performed, revealing at least one SLN in 85%. Most SLNs were iliac, obturator, and parametrial nodes; however, approximately 20% were in the common iliac and aortic chains. Eight (21%) had nodes involved with tumor, and 5 of these 8 patients had SLN as the only positive node. Sensitivity was 87.5% and negative predictive value (NPV) was 97% (56).

Plante et al. followed with a larger series of 70 patients using laparoscopy. Bilateral SLNs were found in 60% of cases. Using both a gamma probe and blue dye, the SLN detection rate was 93%. Eighty-eight percent of SLNs were in the external iliac, obturator, and bifurcation area. Fifty-one percent had 2 SLNs, and 24% had $\geq$ 3 SLNs. The NPV was 100% and sensitivity was 93%. The rate of allergy to blue dye was 3% (57). Roy et al. studied 211 patients. One SLN was identified in 97% of patients, 16.7% of SLN were in aberrant sites, including about 4% in the paraaortic region. Of the latter group, 15% had a positive node. With ultrastaging the NPV of SLN was 100%, compared with frozen section sensitivity of 94%. The results were best in patients with tumor diameter of less than 2 cm (58). Lecuru et al. studied 139 patients and found at least 1 SLN in 98%. The NPV was 98% but the reliability was significant when bilateral SLN were identified (59). Diaz et al. evaluated their single-institution experience at Memorial Sloan Kettering Hospital and reported a 95% detection rate of SLN. Routine pathologic processing identified 71% of involved SLN with an additional 29% found on ultrastaging (60). Altgassen et al. reported a multi-institutional study of 590 patients, showing a detection rate of 93.5% when blue dye was used in conjunction with technetium-99. The sensitivity was 77% with a NPV of 94% (61).

At the present time, SLN is still investigational and not standard of care in cervical cancer. The overall SLN identification is around 90%, with a sensitivity of 92%, and an approximately 8% false negative rate, with a NPV of 97%. Challenges to adoption include the sensitivity of frozen section, availability of pathologic expertise, uniformity of technique, surgical experience, and clinical impact of tumor size (62).

PATHOLOGY

Squamous Cell Carcinoma

Squamous carcinoma of the cervix includes both microinvasive squamous carcinoma and more deeply invasive carcinoma. Variants of invasive squamous carcinoma, which may be associated with differences in biologic behavior, include verrucous carcinoma, papillary squamous and transitional carcinoma, warty carcinoma, and lymphoepithelioma-like carcinoma.

Preinvasive Disease

Squamous carcinoma *in situ* is a precursor lesion of invasive squamous carcinoma. Squamous carcinoma *in situ* is characterized

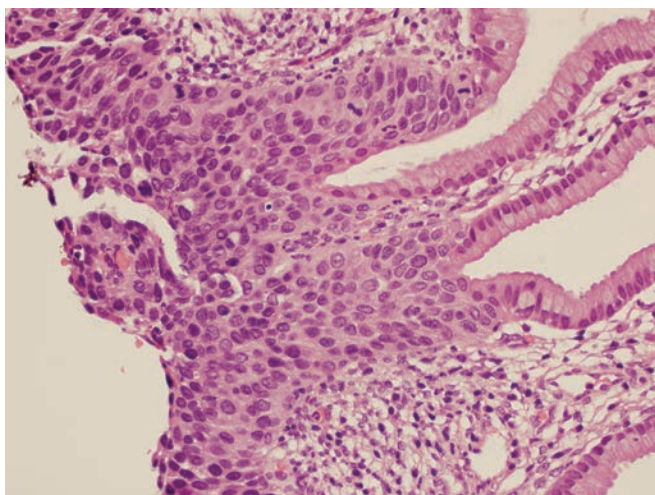


FIGURE 21.1. Squamous carcinoma *in situ*. The epithelium displays full thickness atypia. Cells have enlarged, hyperchromatic nuclei, and there is no evidence of maturation.

by full-thickness atypia of the cervical epithelium. Endocervical glands may also be involved. The normal maturation of squamous epithelium is absent. The epithelium is replaced by atypical cells that often have enlarged, oval nuclei and increased nuclear-to-cytoplasmic ratios. Mitotic figures are present. There is no breach of the underlying basement membrane (Fig. 21.1). A recent study of cervical biopsies found excellent interpathologist and intrapathologist agreement in the diagnosis of cervical biopsy specimens (63).

Microinvasive Carcinoma

Microinvasive squamous carcinoma is associated with squamous intraepithelial neoplasia, and may arise from either the surface epithelium or from endocervical glands involved by dysplasia. It is characterized by small nests of cells that have escaped the basement membrane of the surface or glandular epithelium (64). Microinvasive carcinoma often displays cells that are larger, with more abundant eosinophilic cytoplasm than cells in the adjacent dysplasia (Fig. 21.2). A desmoplastic stromal

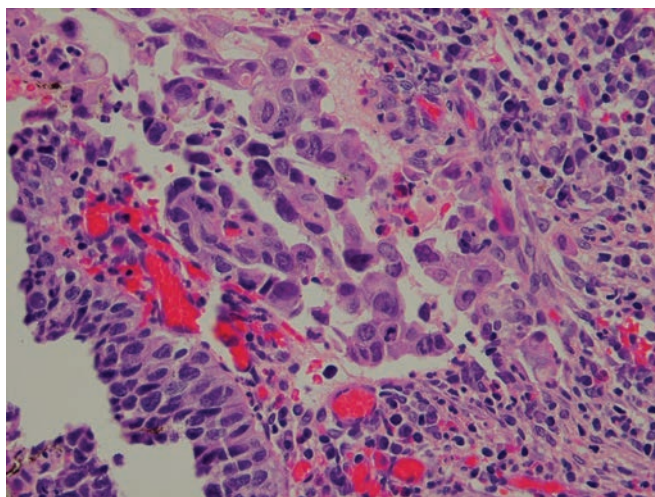


FIGURE 21.2. Microinvasive squamous carcinoma. There is an area of squamous carcinoma *in situ* (lower left). A nest of invasive carcinoma cells (center) has broken through the basement membrane. The invasive cells are larger, with more abundant cytoplasm and larger, more pleomorphic nuclei. A desmoplastic stroma response is present (right).

reaction is usually present. The nests of microinvasive tumor are irregular and haphazardly arranged. These features are useful in distinguishing microinvasion from rounded, well-circumscribed endocervical glands involved by squamous dysplasia.

DOI should be measured from the basement membrane of the site of origin. If the tumor arises from surface epithelium, depth is the distance from the basement membrane of the surface epithelium to the deepest nest of invasive neoplasm. If the tumor arises from an endocervical gland, depth is measured from the basement membrane of the gland. If the site of origin is not clear, depth is measured from the basement membrane of the surface epithelium.

Nests of superficial invasion seen in small biopsies should be reported as such, with dimensions of the tumor. A diagnosis of microinvasive squamous carcinoma of the cervix requires a LEEP or conization biopsy that encompasses the entire lesion and has negative margins.

Invasive Squamous Cell Carcinoma

Invasive cervical carcinoma arises from high-grade dysplasia that may be detected up to 10 years before invasive carcinoma develops. Untreated squamous carcinoma *in situ* results in invasive carcinoma in about one-third of cases over a period of 10 years. Invasive carcinoma occurs most often after the age of 40 years, although it may be seen in young women. It is associated with human papillomavirus infection in more than 99% of cases. These tumors may consist of firm, indurated masses, or they may be ulcerated or polypoid. Microscopic examination reveals irregular, haphazardly infiltrating nests of cells with eosinophilic cytoplasm and enlarged, atypical, hyperchromatic nuclei (Fig. 21.3).

Mitoses may be numerous, and atypical forms may be present. There is typically a desmoplastic stromal response around the nests of invasive neoplasm. Lymphatic and vascular space invasion may be present, especially in more deeply invasive tumors. Invasive squamous carcinomas are classified as keratinizing or nonkeratinizing, although this classification has no prognostic significance. Keratinizing squamous carcinomas display at least some keratin pearl formation. Nonkeratinizing squamous carcinomas are composed of irregular nests of cells that may display abundant eosinophilic cytoplasm and intercellular bridges, but do not contain keratin pearls. Some squamous carcinomas are composed of smaller cells without evidence of

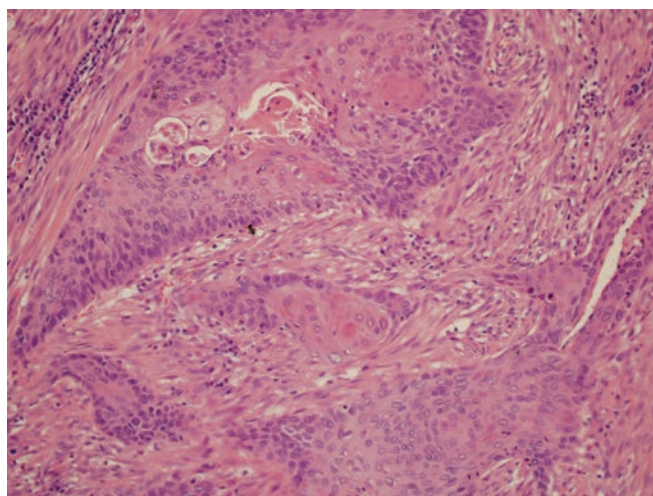


FIGURE 21.3. Invasive squamous carcinoma. Small, irregular nests of cells with markedly atypical nuclei are present. They are surrounded by desmoplastic stroma, containing inflammatory cells.

neuroendocrine differentiation; these neoplasms should be classified as nonkeratinizing squamous carcinomas.

Invasive squamous carcinomas are also graded (65), although treatment protocols do not depend on grade, and the histologic grade may not correlate with prognosis. Grade 1 (well-differentiated) tumors are not very common in the cervix. They display keratin pearls and large numbers of keratinized cells. Nuclei display only mild to moderate atypia, and mitoses are typically not numerous. Grade 2 (moderately differentiated) tumors represent the majority of invasive squamous carcinomas of the uterine cervix, and are usually nonkeratinizing squamous carcinomas with nuclear pleomorphism, numerous mitoses, and an infiltrative pattern. Grade 3 (poorly differentiated) tumors either have smaller cells without neuroendocrine differentiation, or are pleomorphic with anaplastic nuclei, and sometimes a tendency to form spindle cells that must be distinguished from sarcoma by positive cytokeratin stains.

Variants of Squamous Cell Carcinoma

Basaloid Squamous Cell Carcinoma

Basaloid squamous carcinoma is an invasive, highly aggressive tumor composed of basaloid cells resembling those seen in squamous carcinoma *in situ* (66).

Verrucous Carcinoma

Verrucous carcinoma occurs rarely in the uterine cervix (67). Examination of the cervix reveals a papillary excrescence that may resemble condyloma acuminatum. In fact, lesions termed “giant condyloma of Buschke and Lowenstein” in the past probably represent verrucous carcinomas. Microscopic examination displays papillary fronds of squamous epithelium not containing connective tissue cores. The fronds are often pointed and have a “church spire” appearance. Underlying connective tissue displays bulbous nests of squamous epithelium that invade the stroma with a pushing margin but display little cytologic atypia. Any lesion displaying significantly atypical nuclei does not represent verrucous carcinoma. The distinction between verrucous carcinoma and regular squamous carcinoma is important because verrucous carcinoma invades locally but does not metastasize. In order to diagnose verrucous carcinoma, it is necessary to see the invasive portion of the neoplasm. Superficial biopsies are usually not diagnostic.

Papillary Squamous and Transitional Carcinoma

Some cervical neoplasms are characterized by papillary superficial architecture with substantial nuclear atypia not seen in verrucous carcinomas (68,69). The most common presenting symptoms are vaginal bleeding and abnormal Pap smears. Papillary, polypoid, or granular lesions are often evident upon examination of the cervix.

These tumors have thin or thick papillae that contain connective tissue cores. The papillary processes may be covered by highly atypical epithelium displaying keratinization, or the epithelium may consist of multiple layers of cells with oval, hyperchromatic nuclei that do not show keratinization, and resemble transitional cell epithelium. Nuclear grooves may be present. Some tumors display epithelium with mixed features. Immunohistochemical studies have shown that most of these tumors are cytokeratin 7 positive and cytokeratin 20 negative; these results are consistent with squamous differentiation (69). HPV-16 has been identified in these neoplasms. It has been demonstrated that these tumors all have the same immunophenotype (uroplakin III negative, p63 positive, and p16^{INK4A} positive) regardless of light microscopic features (70). The authors concluded that

these neoplasms lack true transitional cell differentiation and share features with squamous carcinoma.

Many papillary squamous and transitional carcinomas are associated with an underlying invasive carcinoma. The invasive neoplasm is often typical squamous carcinoma, but some cases of invasive transitional carcinoma have been described. Superficial biopsies display only the papillary portion of the neoplasm. LEEP or conization biopsy should be performed to evaluate the possibility of underlying invasive carcinoma.

The invasive form of this neoplasm may be associated with local recurrence and metastasis. These tumors must be distinguished from verrucous carcinomas, which display little atypia and have a much more indolent clinical course.

Warty Carcinoma

Warty carcinoma of the cervix is a rare papillary neoplasm that displays marked condylomatous change but has features typical of routine invasive squamous carcinoma at its deep margin (71). These tumors are associated with HPV and may behave less aggressively than the usual type of invasive squamous carcinoma. Cellular change consistent with HPV infection (“koilocytotic atypia”) is shown in Figure 21.4.

Lymphoepithelioma-Like Carcinoma

Lymphoepithelioma-like carcinoma, more commonly seen in the nasopharynx, also occurs in the uterine cervix. Some patients may present with abnormal bleeding and have cervical masses, whereas others may have abnormal Pap smears and no visible cervical lesions. Lymphoepithelioma-like carcinoma of the cervix is seen most often in Asian women, and it has been associated with Epstein-Barr virus infection in those patients (72). In contrast, studies from Europe have not demonstrated Epstein-Barr virus DNA (73,74), but some have suggested a role for HPV in the etiology of this neoplasm (74–76).

Microscopically, this tumor is characterized by nests of cells with lightly eosinophilic cytoplasm and large vesicular nuclei with prominent eosinophilic nucleoli. Cell borders are indistinct, giving the tumor cell nests a syncytial appearance. Aggregates of tumor cells are surrounded by a prominent inflammatory infiltrate that includes lymphocytes, plasma cells, and varying numbers of eosinophils. This neoplasm can be distinguished from glassy cell carcinoma (which is also accompanied by prominent inflammation) by the lack of prominent cell borders and granular

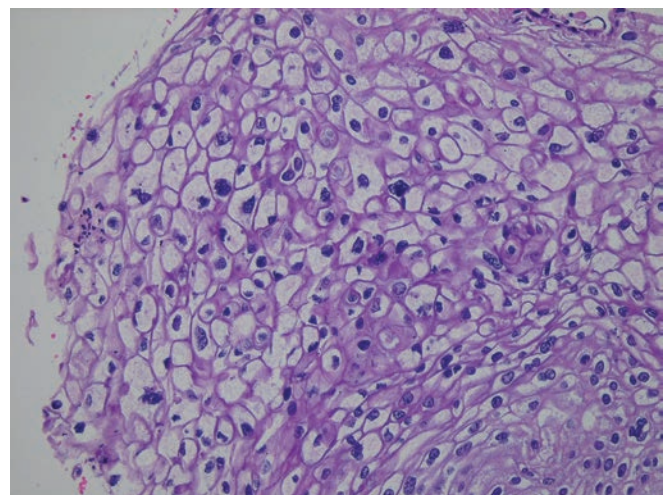


FIGURE 21.4. Human papillomavirus changes. This squamous epithelium displays cells with large halos surrounding atypical nuclei (“koilocytotic atypia”).

eosinophilic cytoplasm in lymphoepithelioma-like carcinoma. The lymphocytic infiltrate in lymphoepithelioma-like carcinoma of the uterine cervix is predominantly T cell in nature, and most of the T cells are suppressor/cytotoxic CD8 cells (73).

Adenocarcinoma

While the incidence of squamous carcinoma of the cervix has decreased in past decades owing to cytologic screening, the number of cases of cervical adenocarcinoma has increased (77–80). Adenocarcinoma of various types accounts for 20% to 25% of cervical carcinomas (78).

Adenocarcinoma *in situ* (AIS) is a precursor of invasive adenocarcinoma. It is found adjacent to many invasive adenocarcinomas, often accompanied by squamous dysplasia. Both AIS and invasive adenocarcinoma of the cervix are associated with HPV (usually type 18, but sometimes type 16).

AIS is characterized by preservation of the overall endocervical gland architecture. However, endocervical glands and surface epithelium are replaced to varying degrees by cells displaying atypia, including nuclear enlargement and stratification, nuclear hyperchromasia, and mitotic figures (Fig. 21.5). Most adenocarcinomas *in situ* occur near the transformation zone, and skip lesions are unusual (79).

Early Invasive Adenocarcinoma

Early invasive adenocarcinoma of the uterine cervix displays an alteration from the normal endocervical gland architecture (80). This abnormality may take the form of solid or cribriform nests of cells, architecturally irregular or incomplete glands lined by malignant cells, or small buds of highly atypical cells arising from glands involved by AIS. A desmoplastic stroma may be present. Diagnosis of early invasive adenocarcinoma may be difficult because endocervical glands normally have a complex pattern.

The FIGO definition of microinvasive carcinoma applies to all types of carcinoma, but application of this term to glandular lesions of the cervix has not been generally accepted. Some gynecologic pathologists believe that these lesions should be classified as early invasive adenocarcinomas, with a best possible measurement of the DOI (77,79) because an increased incidence of metastatic disease correlates with increasing depth of invasive disease.

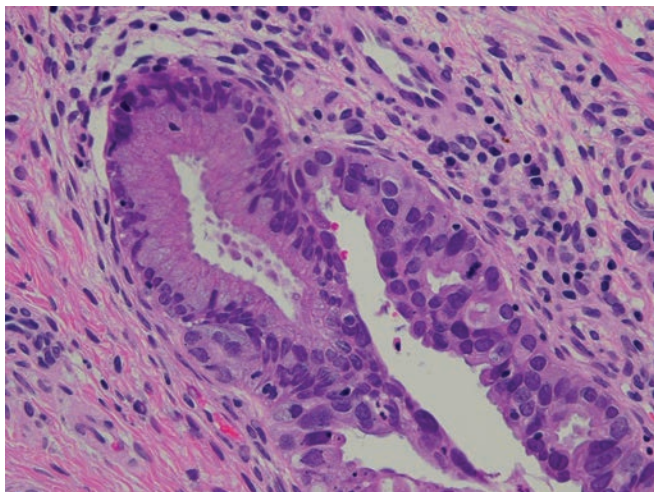


FIGURE 21.5. Adenocarcinoma *in situ*. Part of this endocervical gland is normal (upper left corner). The remainder of the gland has been replaced by stratified cells with atypical, large nuclei and mitotic figures.

Mucinous Adenocarcinoma

There are several variants of mucinous adenocarcinoma of the cervix, including endocervical, intestinal, signet ring cell, minimal deviation, and villoglandular variants. HPV DNA has been detected in more than 90% of mucinous adenocarcinomas of the cervix, including endocervical, intestinal, and endometrial subtypes (81).

Mucinous Adenocarcinoma, Endocervical Variant

The endocervical variant of mucinous adenocarcinoma is the most common type of cervical adenocarcinoma. It is composed of irregular, haphazardly arranged tubuloracemose glands lined by cells resembling those seen in normal endocervical glands, although they may sometimes have limited amounts of cytoplasmic mucin. Nuclei are basally located, stratified, and atypical (Fig. 21.6). Mitoses are present. Grade 1 (well-differentiated) tumors have uniform nuclei with minimal stratification and few mitotic figures. Grade 2 (moderately differentiated) adenocarcinomas have more marked cytologic atypia with frequent mitoses. They may also have solid areas accounting for less than half of the neoplasm. Grade 3 (poorly differentiated) adenocarcinomas contain more prominent solid areas, pleomorphic nuclei, and many mitoses. Desmoplastic stromal response is variable in this type of cervical adenocarcinoma.

Mucinous Adenocarcinoma, Intestinal Type, Signet Ring, and Colloid Variants

Rare endocervical adenocarcinomas have glands containing goblet cells; these tumors display intestinal differentiation. Signet ring cell carcinomas and colloid carcinomas are extremely rare and must be distinguished from metastatic tumors from the gastrointestinal tract.

Mucinous Adenocarcinoma, Minimal Deviation Variant

This uncommon tumor represents only about 1.3% of cervical adenocarcinomas (82). Patients range in age from 25 to 72 years. They may present with abnormal bleeding or a mucoid discharge. The cervix may appear normal, or it may display a

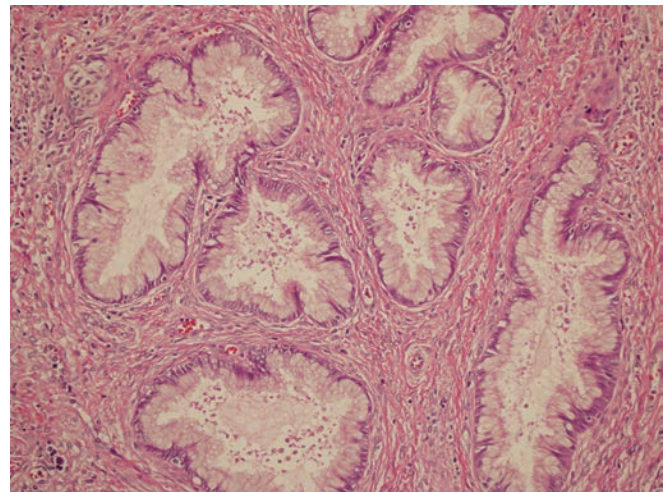


FIGURE 21.6. Well-differentiated glands infiltrate desmoplastic cervical stroma. The glands display a haphazard pattern. Nuclei are basally located but stratified and atypical.

firm area or a mass. The neoplasm is very difficult to diagnose on small biopsies because the infiltrative gland pattern cannot be appreciated. Conization specimens are more conducive to accurate diagnosis in this lesion, but some cases have been diagnosed only after hysterectomy. In contrast to most other types of cervical adenocarcinomas, minimal deviation adenocarcinomas are not associated with HPV infection (83).

Gross examination of hysterectomy specimens displays firm, tan-yellow neoplasms. Most cases contain mucinous glands, but some display endometrioid glands. Microscopically, glands infiltrate the cervical stroma in a haphazard manner; they do not conform to the normal endocervical gland pattern. They may display budding contours, and they typically have angular, sharply pointed outlines, in contrast to the rounded contours of benign endocervical glands. The glands of minimal deviation adenocarcinoma appear deceptively benign on low power. Lack of substantial cytologic atypia is a prerequisite for this diagnosis. However, high-power examination reveals at least some areas with mild to moderate atypia, in which some nuclear enlargement, stratification, and rare mitotic figures may be identified. The infiltrating glands may be devoid of any surrounding desmoplastic reaction.

Minimal deviation adenocarcinoma may occur as a sporadic neoplasm, although patients with Peutz-Jeghers syndrome are at risk of developing this cervical tumor.

Mucinous Adenocarcinoma, Well-Differentiated Villoglandular Variant

Well-differentiated villoglandular adenocarcinoma is a type of low-grade adenocarcinoma that displays similarities to villous adenomas of the intestine. Patients may present with polypoid or papillary endocervical masses upon pelvic examination, abnormal bleeding, or abnormal Pap smears. The age range has been 23 to 57 years, with most cases occurring in patients younger than 40 years of age.

Microscopic examination of these neoplasms reveals villous, papillary structures that may be either long and slender, or short and broad. These processes contain a connective tissue core that often displays inflammatory cells. The covering epithelium is a single layer of stratified cells with endocervical, endometrial, or intestinal differentiation. Nuclei display only mild to moderate atypia, and mitotic figures are infrequent (Fig. 21.7). Only tumors with low-grade cytologic atypia should receive this diagnosis,

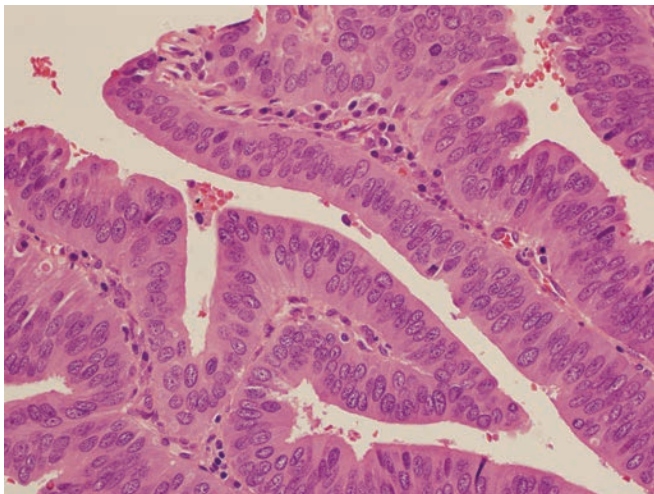


FIGURE 21.7. Well-differentiated villoglandular adenocarcinoma. Long, slender villous processes are covered with epithelium, displaying mild atypia. Nuclei are crowded, but they retain an oval shape, and are uniform in size.

since other endocervical carcinomas may have papillary features. Invasive adenocarcinoma may be seen deep to the papillary areas, and is characterized by branching glands lined by atypical cells and surrounded by desmoplastic stroma. These neoplasms do not display the marked nuclear atypia and epithelial tufting seen in the much more aggressive papillary serous carcinoma of the cervix. They may be associated with typical AIS of the cervix.

Well-differentiated villoglandular carcinoma has not metastasized unless it was associated with more aggressive types of carcinoma. Some cases have been successfully treated by conization if the tumor is completely excised and the patient wishes to retain fertility. Generally, this diagnosis should not be suggested on the basis of small biopsy specimens; definitive diagnosis should be made only in tumors seen on conization or hysterectomy specimens. Diagnosis of this type of neoplasm on the basis of only a small biopsy specimen could result in undertreatment of a potentially more aggressive neoplasm (78). Villoglandular tumors associated with a high-grade cytologic component or an underlying obvious invasive adenocarcinoma may be associated with lymphovascular invasion, recurrences, and lymph node metastases (84,85).

Endometrioid Adenocarcinoma

Endometrioid carcinomas of the uterine cervix are rare, and have probably been overdiagnosed. These tumors make up about 7% of all cervical adenocarcinomas. These neoplasms display histologic features identical to endometrial carcinoma. Therefore, the possibility of a primary endometrial adenocarcinoma with endocervical extension or drop metastasis must be excluded before the diagnosis of a primary endocervical endometrioid adenocarcinoma is established. A rare case has arisen from endocervical endometriosis. In difficult cases, immunohistochemical stains may be helpful since a combination of CEA positivity, ER negativity, and vimentin negativity is most often seen in endocervical primary tumors, while the reverse is more often characteristic of endometrial primary tumors. Evidence of association with HPV also supports an endocervical primary neoplasm.

Other Adenocarcinomas

Clear Cell Adenocarcinoma

Clear cell carcinoma of the cervix has been associated with intrauterine diethylstilbestrol (DES) exposure; however, it also occurs in the absence of DES exposure. Patients usually have a cervical mass. The solid pattern of tumor displays sheets of cells containing abundant glycogen-rich clear cytoplasm, atypical nuclei, and mitoses. The tubulocystic pattern contains tubules and cystic spaces lined by oxyphilic, hobnail, or clear cells. The papillary pattern is the least common variant and often coexists with solid or tubulocystic areas. Clear cell carcinomas of the cervix are not associated with HPV DNA (83).

Serous Adenocarcinoma

Papillary serous carcinoma of the uterine cervix has a bimodal age distribution, occurring in patients younger than 40 years and patients older than 65 years. This age distribution has also been seen in well-differentiated villoglandular carcinoma but differs from the typical mid-life age of patients with cervical adenocarcinomas in general. Serous carcinomas of the cervix are not associated with HPV DNA (83).

Gross examination may reveal a nodular mass, an indurated cervix, or no visible abnormality. Microscopically, these tumors are identical to serous tumors of the ovary, endometrium, and primary peritoneal serous carcinomas. Considering the rarity with which this type of neoplasm is seen in the cervix, the diagnosis of primary serous carcinoma of the uterine cervix should

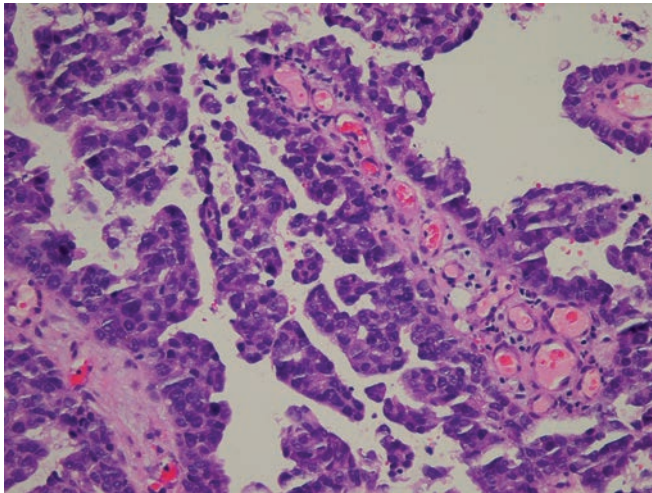


FIGURE 21.8. Serous adenocarcinoma. The papillary structures have a connective tissue core. There is marked tufting and stratification, and the nuclei are markedly atypical.

be made only after excluding metastasis or extension of disease from another site, especially the endometrium.

Histologic examination of serous carcinoma of the uterine cervix reveals fibrous papillae lined by atypical epithelial cells; secondary papillae and tufts of neoplastic epithelial cells are often present (Fig. 21.8). Glandular structures have irregular luminal borders due to tufting of tumor cells. Nuclei usually show high-grade atypia, and numerous mitoses are present.

These aggressive tumors may metastasize to pelvic, periaortic, and inguinal lymph nodes. Large and deeply invasive tumors are associated with a worse prognosis.

Mesonephric Adenocarcinoma

Remnants of the mesonephric ducts persist and can be seen in the lateral aspects of the cervix. They are often not identified because uteri are traditionally bivalved along their lateral aspects, and most microscopic sections are taken from the anterior and posterior portions of the cervix. Mesonephric duct remnants are seen as lobules of small, round, glandular structures lined by flattened cuboidal epithelium and containing intraluminal periodic acid-Schiff stain (PAS)-positive material. The cells of mesonephric duct remnants do not contain intracytoplasmic mucin, unlike the cells lining endocervical glands. Mesonephric duct hyperplasia may occur in the cervix. Mesonephric adenocarcinomas are thought to arise from mesonephric duct remnants. Only about 2 dozen cases have been documented (86). Early reports of lesions termed mesonephric carcinoma are now known to represent clear cell carcinoma, with no relationship to the mesonephric duct remnants.

Patients have ranged in age from 52 to 55 years (82). Some patients have not had grossly apparent lesions, but most present with abnormal bleeding and have visible cervical masses. These neoplasms occur deep in the lateral cervical wall. Mesonephric carcinomas display a variety of histologic appearances, including ductal, tubular, retiform, solid, and sex cord-like patterns. Mesonephric hyperplasia may be associated with the carcinoma. Like mesonephric remnants, mesonephric carcinoma tumor cells contain no intracytoplasmic mucin; however, glandular structures may display luminal PAS-positive material. CD10 staining may be useful in diagnosing mesonephric-type adenocarcinomas (87).

Microcystic Endocervical Adenocarcinomas

Eight cases of this type of endocervical adenocarcinoma have been described (88). Most patients presented with either abnormal

Pap smears or vaginal bleeding. Abnormalities of the endocervix were visible in 3 patients. These tumors are characterized by numerous cystically dilated glands simulating the appearance of a benign lesion at low power. However, higher power examination reveals areas of significant cytologic atypia and mitotic activity. Areas of more typical mucinous or intestinal endocervical adenocarcinoma may also be present. These lesions may be deeply invasive. Three patients had significant follow-up data. One patient died after a debulking procedure for a pelvic recurrence 2 years after her initial diagnosis, and 2 other patients are alive without evidence of tumor at 1 and 6.5 years after diagnosis.

Other Epithelial Tumors

Adenosquamous Carcinoma

Adenosquamous carcinoma is a tumor composed of admixed malignant glandular and squamous elements. This term should not be used for poorly differentiated squamous carcinomas, in which mucicarmine stains show only scattered mucin vacuoles. Likewise, it is different from collision tumors, which display adjacent adenocarcinoma and squamous carcinoma. Adenosquamous carcinomas are more commonly associated with higher tumor grade ($p < 0.001$) and vascular invasion ($p = 0.002$) than are adenocarcinomas (89). Adenosquamous carcinomas appear to be either histologically more aggressive or diagnosed at a later stage than adenocarcinomas of the uterine cervix.

Glassy Cell Carcinoma

Glassy cell carcinoma is a rare form of poorly differentiated adenosquamous carcinoma that displays cells with eosinophilic cytoplasm, well-defined cell borders, prominent nucleoli, and a prominent infiltrate of eosinophils and plasma cells. Occasionally, this morphology may be seen in recurrences of adenocarcinomas or adenosquamous carcinomas that have been treated with radiation therapy (78).

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma of the cervix is a rare but aggressive malignant neoplasm. These lesions are typically seen in elderly patients, many of whom present with postmenopausal bleeding. Examination of the cervix typically shows a lesion.

Microscopic examination of these tumors reveals a cribriform gland pattern. The glands may contain hyaline or mucinous material. Nuclei are larger and more pleomorphic than those seen in adenoid basal epithelioma, and numerous mitoses as well as areas of necrosis are present in adenoid cystic carcinoma. Electron microscopy has shown basement membrane-like material around the nests of tumor cells as well as in some gland lumina. The tumor cells stain with cytokeratin. In contrast to adenoid cystic carcinoma of the salivary glands, this neoplasm in the cervix has not displayed unequivocal evidence of myoepithelial cells, either by immunohistochemical staining for S100 protein or by electron microscopy.

Adenoid cystic carcinoma of the cervix often recurs. It may metastasize. Patients with advanced stage disease have a poor prognosis.

Adenoid Basal Epithelioma (Carcinoma)

Adenoid basal epithelioma is a rare cervical neoplasm. It was originally called adenoid basal carcinoma. The indolent behavior of most of these neoplasms led to the term “adenoid basal epithelioma.” More recently, Parwani et al. reported 10 tumors that had low-grade adenoid basal epitheliomas admixed or associated

with invasive carcinomas of various types, including adenoid basal/squamous carcinoma, pure squamous carcinoma, adenoid cystic carcinoma, or small cell neuroendocrine carcinoma. Most adenoid basal epitheliomas and associated invasive carcinomas contain HPV-16 DNA. It now appears that adenoid basal epitheliomas may be precursor lesions that may give rise to carcinomas of various types. These tumors should now be subclassified as adenoid basal epitheliomas and carcinomas (90).

The age of patients with adenoid basal epithelioma ranges from 30 to 91 years (82). This neoplasm is often seen in postmenopausal women who are asymptomatic, with normal appearing cervixes. These lesions are usually incidental findings in specimens obtained for the purpose of evaluating squamous intraepithelial neoplasia. A neoplastic squamous component is often an associated feature (82).

Microscopically, adenoid basal epithelioma is characterized by nests of cells that have a basaloid appearance, and may display peripheral palisading. Some gland lumina are present in the basaloid cell nests, although the number of glands is variable. Squamous metaplasia may also be seen. Mitotic figures are typically rare.

Adenoid basal epithelioma, in the absence of a coexisting invasive carcinoma, is a benign lesion with no reported cases of metastatic behavior (82). It must be distinguished from adenoid cystic carcinoma, which is an aggressive malignant neoplasm. Adenoid basal tumors with carcinomatous components should be reported as carcinomas.

Neuroendocrine Tumors

Standardization of terminology for neuroendocrine tumors of the uterine cervix (91) has facilitated evaluation of the incidence and biologic behavior of these neoplasms. Immunohistochemical (chromogranin and/or synaptophysin stains) evidence of neuroendocrine differentiation is necessary for diagnosis of all neuroendocrine tumors except small cell carcinoma.

Typical Carcinoid Tumors

Typical carcinoids of the cervix are rare neoplasms. This diagnosis should be made with caution, because most cervical neuroendocrine tumors are aggressive neoplasms. There are not enough documented cases of this neoplasm to permit assessment of biologic behavior.

Atypical Carcinoid Tumors

Atypical carcinoid tumors display organoid nests of cells, but the cells display nuclear atypia and a mitotic rate of 5 to 10 MF/10 HPF. Necrosis may be present. These tumors are also rare, precluding evaluation of biologic behavior.

Large Cell Neuroendocrine Carcinoma

Large cell neuroendocrine carcinomas (Fig. 21.9) display organoid nests of cells with peripheral palisading of nuclei, prominent nucleoli, variable amounts of necrosis, eosinophilic cytoplasmic granules, and numerous mitotic figures (>10 MF/10 HPF). Vascular/lymphatic space involvement is often seen, and many of these tumors are associated with coexisting AIS or adenocarcinoma of the cervix (92). These tumors are highly aggressive neoplasms (93). Evidence of neuroendocrine differentiation is necessary for diagnosis and is most easily obtained with immunohistochemical stains for chromogranin and synaptophysin.

Small Cell Carcinoma

Most neuroendocrine tumors seen in the uterine cervix represent small cell carcinomas. Even a small component of small cell carcinoma in a tumor of mixed type is associated with adverse

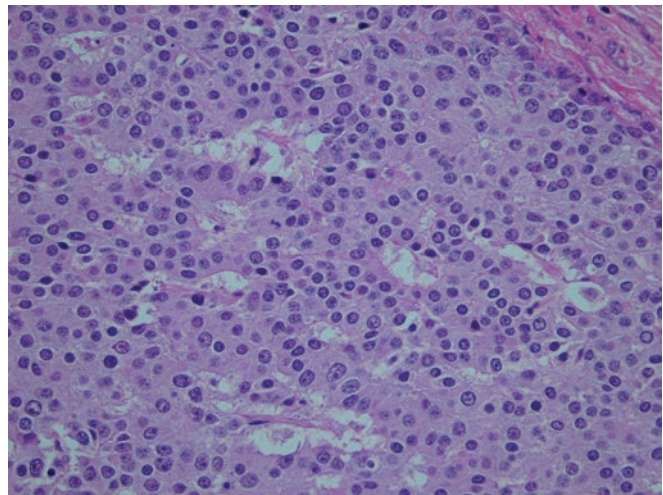


FIGURE 21.9. Large cell neuroendocrine carcinoma. This tumor displays organoid architecture. The tumor cells are much larger than those seen in small cell carcinoma. They have abundant eosinophilic cytoplasm, and there are numerous mitotic figures. Areas of necrosis were present elsewhere in the tumor.

outcome (93). Small cell carcinoma is characterized by cells with scant cytoplasm, inconspicuous nuclei with finely stippled chromatin, nuclear molding, extensive necrosis, crush artifact, and numerous mitotic figures (Fig. 21.10). Single-cell infiltration of the stroma is common. Vascular/lymphatic space invasion is often seen.

Mixed Epithelial and Mesenchymal Tumors

Müllerian adenosarcomas occur in the cervix (94). Patients may present with abnormal bleeding. These neoplasms consist of polypoid or papillary masses. Microscopically, they display benign glands and sarcomatous stroma with a periglandular cuff of condensed stroma. The sarcomatous component contains variable numbers of mitotic figures, and some cases display heterologous elements including cartilage and striated muscle. These tumors generally have a favorable prognosis, but deep invasion and sarcomatous overgrowth are adverse prognostic factors.

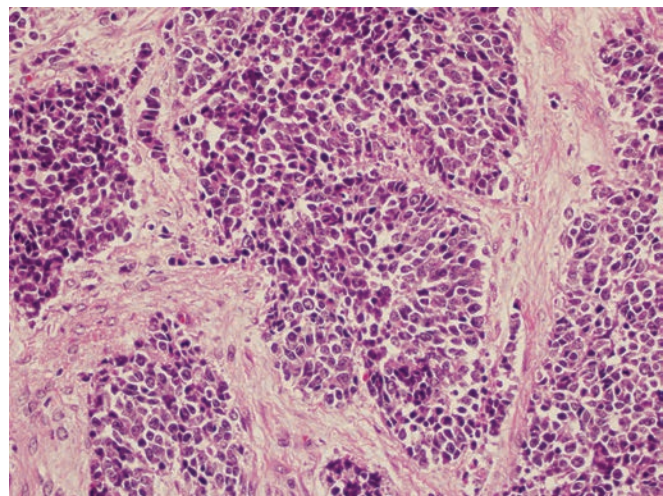


FIGURE 21.10. Small cell neuroendocrine carcinoma. This tumor displays cells that are smaller than those of squamous carcinoma. Nuclei are large and atypical with molding of adjacent nuclei. There is a very high mitotic rate.

Malignant mixed müllerian tumors may involve the cervix, although only about 40 cases have been reported (95). Patients have abnormal bleeding or abnormal Pap smears and cervical masses. The carcinomatous component of these tumors may be squamous or adenocarcinoma. The sarcomatous component may be homologous or heterologous. HPV DNA was detected by polymerase chain reaction in all cases of cervical malignant mixed müllerian tumors reported in one study (96).

Other Malignant Tumors

Various sarcomas have been reported in the uterine cervix, although they are uncommon. A recent review of 1,583 cervical malignant tumors revealed 8 cervical sarcomas (97). Five were carcinosarcomas, and the remainder were unclassified sarcomas, leiomyosarcomas, or endometrial stromal sarcomas. Primary extranodal lymphomas (98) of the uterine cervix are usually diffuse B-cell neoplasms. Primitive neuroectodermal tumors (99) and desmoplastic small round cell tumors (100) have also been described.

Secondary tumors of the cervix include those invading from contiguous organs and metastases from other sites. The former include tumors arising in the uterine corpus, urinary bladder, or rectum. Metastases can originate from many sites, including the ovary, uterus, and more distant primary tumors.

PROGNOSTIC FACTORS

Tumor Size, Volume, Margin Status

In a classic GOG study, Delgado et al. (101) described 3-year disease-free survival (DFS) rates of 94.8%, 88.1%, and 67.6%, respectively, for occult, ≥ 3 cm, and >3 cm stage I squamous cell carcinomas of the cervix treated by radical operation. Survival strongly correlated with depth of tumor invasion of the stroma: 86% to 94% for less than 10 mm, 71% to 75% for 11 to 20 mm, and 60% for 21 mm or greater. In patients without parametrial involvement, the survival rate was 84.9%, but it was 69.6% for those with parametrial tumor extension. These findings have been validated by others, including in FIGO stage II patients, utilizing a 4 cm cut point (102). Rutledge et al. compared patients with FIGO stage IB1 cancers with IB2 cancers treated with RH, finding that LVSI and depth of cervical stromal invasion were more significantly associated with poor prognosis in a multivariate analysis (103). In all these series, there was frequent use of postoperative RT with or without chemotherapy. The use of adjuvant treatment was preferentially given in higher risk patients, narrowing the differences in outcomes and affecting the analysis. In patients treated with curative intent RT, Perez et al. analyzed 1,499 patients treated curatively with RT, finding 10-year actuarial pelvic failure rates of 5%, 15%, and 35% for tumors <2 cm, 2 to 5 cm, and >5 cm, respectively, with the stage IB group. In stage IIB patients, medial parametrial involvement was significantly favorable compared to lateral parametrial extension, and in stage IIIB disease unilateral sidewall extension was significantly favorable to bilateral extension (104). Similarly, Eifel et al. (105) noted a strong correlation between central and pelvic tumor control, disease-specific survival, and tumor size. Pelvic tumor control was 97% with tumors less than 5 cm, and 84% with tumors 5 to 7.9 cm.

Chung et al. used FDG-PET/CT imaging to determine the “metabolic tumor volume” (MTV). In this study, MTV correlated with incidence of lymph node metastasis, parametrial involvement, FIGO stage, and maximum Standardized Uptake Value (SUV). On univariate analysis, DFS was statistically associated with MTV, LN metastasis, parametrial involvement, and LVSI.

On multivariate analysis, age and MTV were found to be independently prognostic for DFS (106).

In patients with stage IB cervical cancer treated surgically, with or without RT, positive margin status conveyed a hazard ratio of 3.92 compared to negative margins. Also, margin status (distance in millimeters in patients with close margins) was significantly associated with an increased recurrence rate. In this series, postoperative RT eliminated local recurrences in patients with close margins and halved the recurrence rate in patients with positive margins (107). Kodama et al. reviewed 84 patients with stage IB-IIB cervical cancer who underwent RH, were found to have positive parametrial margins, and received adjuvant treatment. On multivariate analysis, the presence of vaginal invasion, LN metastasis, and nonsquamous histology negatively impacted DFS. The 5-year OS rate was approximately 90% for patients without any of these factors. The status of the surgical margin did not impact survival in this study (108).

Stage

The FIGO stage is universally accepted for its prognostic significance. For example, Fyles et al. (109), in 965 patients with invasive carcinoma of the cervix, identified FIGO stage as the most significant prognostic factor. Stehman et al., reporting for the GOG on 626 patients treated in phase 3 trials (110), confirmed the prognostic significance of tumor burden, whether measured by FIGO stage, centimeter size, or bilateral disease. Paraaortic node metastases conferred a much greater risk than any of the measures of volume of tumor, however. This emphasizes the fact that FIGO staging does not take into account important prognostic information such as nodal status. Furthermore, stage is only indirectly related to tumor volume, since there can be significant variability in this important prognostic factor within a given stage, resulting in substantial overlap within stage groupings.

Nodal Status

Lymph node involvement is, in most studies, the most significant negative prognostic factor. Reports emphasize higher 5-year survival rates (90% or higher) among surgically treated patients with no evidence of metastasis in the regional nodes, compared to patients with positive pelvic (50% to 60%) or paraaortic nodes (20% to 45%). Delgado et al. (101) reported a 3-year DFS of 85.6% for 545 patients with negative pelvic lymph nodes, compared with 74.4% for patients with one or more positive nodes. In an extensive review of the literature, Creasman and Kohler found that lymph node involvement was reported as an independent risk factor for survival in 88% of series reporting multivariate analyses, versus tumor size/DOI in 61% of series (111). Decreasing 5-year survival rates have been associated with increasing numbers of positive pelvic nodes. As noted above, LN metastasis was shown to be a significantly negative independent prognostic factor in patients with stage IB-IIB disease who underwent initial surgical treatment followed by adjuvant therapy in the setting of parametrial infiltration. (108).

Even micrometastases appear to negatively impact prognosis. Marchiole et al. reported that recurrence was tenfold more likely in an early-stage population of patients treated with radical surgery compared to those without micrometastases (112). Similarly, in a retrospective study from Stanford, a much higher rate of recurrence was seen in early-stage surgically treated patients in whom lymph node micrometastases were detected immunochemically (113).

Lymphovascular Space Invasion

LVSI proved to be a significant prognostic factor in a surgical-pathologic study of 542 patients completed by the GOG (101).

DFS rates were 77% and 89%, respectively, in patients with and without LVSI. Furthermore, LVSI was shown to correlate strongly with pelvic adenopathy. In a case-control study, Marchiole et al. established a relative risk of recurrence of 2.64 in patients with LVSI compared to those without (112). Chernofsky et al. quantitated the amount of LVSI in 101 consecutive patients who underwent surgery for stages IA2-IIA cervical cancer, showing that amount of LVSI was an independent prognostic factor for time to recurrence (114). Milam et al. showed a very strong correlation between LVSI on preoperative biopsy specimen and nodal metastases in surgically treated early-stage cervical cancer (115).

Hypoxia and Anemia

In patients with cervical cancer, it is well accepted that significant anemia at presentation correlates with inferior response rates to RT and with inferior outcomes compared to those without anemia. For example, Ferrandina et al. reviewed 114 patients with locally advanced disease who received preoperative chemotherapy and RT prior to radical surgery. With a value of 10 g/dL as the cut point, the rate of treatment response, measured as pathologic complete response plus only microscopic residual, was significantly higher in patients without anemia at the time of diagnosis (116). A recent review by De Los Santos and Thomas further supports the relationship between anemia and poorer prognosis and decreased responsiveness to therapeutic radiation (117).

Fyles et al. published a review of the basic, translational, and clinical data regarding anemia and its potential impact on radiosensitivity and radiocurability (118). Clearly, the interactions are quite complex. For example, in the presence of anemia, adaptive mechanisms come into play that shift the oxyhemoglobin dissociation curve to the right, providing a compensatory increase in oxygen released into the tissues. There is also an increase in tissue perfusion and oxygenation as hemoglobin decreases due to reduced blood viscosity. However, these effects are potentially less effective in patients with diabetes, smokers, or patients who are vasoconstricting in the presence of marginal cardiac output.

Furthermore, the work of Fyles et al. shows that the relationship between pretreatment hemoglobin levels and direct measurements of oxygen tension in cervical cancers is tenuous. Interestingly, there was a positive correlation between hemoglobin and tumor oxygenation in nonsmokers, but the correlation was negative in smokers. Fyles et al. suggested that the negative prognostic impact of tumor hypoxia might be present only in subgroups of patients. Specifically, they observed worse outcomes with tumor hypoxia only in node-negative patients, manifested by an increase in distant metastases rather than poorer pelvic tumor control (119).

Fuso et al. looked at the impact of pretreatment serum hemoglobin as a predictive factor of response to neoadjuvant chemotherapy (NACT) in patients with locally advanced cervical cancer, finding hemoglobin level to be the most powerful predictor of response. A threshold of 12 mg/dL served to discriminate between optimal and nonoptimal response. However, the authors recognized that a lower hemoglobin level could also be simply a marker for more aggressive disease as opposed to a physiologic variable that could be manipulated for therapeutic benefit (120). The Southwest Oncology Group conducted a phase 2 study in 53 patients to determine whether erythropoietin along with oral iron therapy could safely correct anemia during chemoradiotherapy for cervical cancer. This study did show such an effect, at the cost of a higher-than-expected incidence of deep vein thrombosis (121).

The important question therapeutically is whether correction of the anemia will improve oxygenation status and treatment outcomes. Data from Fyles et al. along with other investigators shows an inconsistent and limited ability for transfusion to impact tumor oxygenation (118). Furthermore, the significant association between tumor hypoxia and tumor size suggests that improving oxygen delivery is unlikely to improve outcomes

owing to factors unrelated to oxygenation, such as number of clonogens, suboptimal brachytherapy dose distributions, and greater risk of metastatic disease.

In spite of the lack of a clear relationship between serum hemoglobin and tumor oxygenation status, various efforts have been directed to the correction of anemia as a therapeutic target. A common approach in cervical cancer and other malignancies has been the use of poietic proteins such as erythropoietin. The GOG initiated a trial to compare maintenance of hemoglobin about 12 g/dL with erythropoietin to “standard” transfusion to maintain hemoglobin above 10 g/dL. Eligible patients had cervical cancer and presented with hemoglobin below 14 g/dL. This study was closed with less than 25% of planned accrual due to a higher observed rate of thromboembolic events in the erythropoietin arm (122). De Los Santos and Thomas reviewed data regarding the incremental increase in thromboembolism with the administration of hemopoietic factors (117). Santin et al. investigated the effect of blood transfusion on immune function in patients receiving radiotherapy for cervical cancer. These investigators measured significant changes in percentages of lymphocyte populations that differed in transfused and nontransfused populations. Furthermore, interleukin-10, a potential dysregulator of lymphocyte function, was only observed in transfused patients. These findings provide a basis for implicating blood transfusion as a possible factor in diminished immune function (123). Additional basic and clinical research will be helpful in determining the reliability of these findings and the potential utility of altered hemoglobin and tumor oxygenation status on tumor sensitivity and treatment outcomes.

Another approach that has been used to potentially address tumor hypoxia is the application of hypoxic cytotoxins. Tirapazamine is one such agent that has shown promise. The GOG opened, but failed to complete, a study comparing RT plus weekly cisplatin to the same regimen plus tirapazamine. However, results from analysis of the 387 evaluable patients accrued showed no improvement in PFS or OS, although there were inadequate numbers of events to draw definitive conclusions (124).

Biomarkers and Bioimaging

Biomarkers and bioimaging have been used to assess prognosis in cervical cancer though clinicopathologic factors still remain the most important factors for prognosis. The earliest biomarkers to be evaluated have been the serum tumor markers. SCCA, cytokeratin fragment 19 (CYFRA 21.1), and cancer antigen 125 (CA-125) (26). While elevated levels of these tumor markers have been correlated with tumor stage, tumor size, cervical stromal invasion, LVSI, parametrial involvement, and lymph node status as mentioned previously, their prognostic value has been debated. In this review, the serial measurements of the most commonly investigated tumor marker, SCCA, were felt to reflect response to treatment and the clinical outcome. In a retrospective study of 550 women with cervical cancer, both pretreatment SCCA and CEA levels were found to be associated with clinical outcome (27).

Cellular biomarkers involved in apoptosis, angiogenesis, or invasive or metastatic potential have also been investigated as prognostic determinants in this disease. A systematic review of the prognostic and predictive significance of these biomarkers in women with cervical cancer was recently published (28). This review included only studies describing a relationship between the biomarker and survival in ≥ 50 women with cervical cancer treated with radiation alone or chemoradiation (28). Of the 1998 studies identified, only 42 studies with 82 biomarkers were included in the analyses. In a univariate analysis, 34 of the biomarkers showed a relation with survival, and 27 were independently associated with survival. The most interesting prognostic biomarkers consisted of SCCA, cyclooxygenase-2 (COX-2), and

markers involved in angiogenesis, hypoxia, and the HER family (EGFR and HER2). In addition, EGFR and HER2 were also associated with a poor response to treatment (28).

Bioimaging with PET and MRI has been explored to evaluate prognosis. There is a significant correlation between cervical tumor uptake of [^{18}F] fluorodeoxyglucose (FDG) measured as the function of a standardized uptake value (SUV_{max}) by PET and treatment response, DFS, and OS (48,125). In addition, a large prospective study with 560 women with clinical Stage IA1-IVB disease evaluated the role of pretreatment [^{18}F] fluorodeoxyglucose PET imaging for lymph node staging and found that disease-specific survival correlated with PET-positive lymph nodes (42). In addition, the pretreatment SUV_{max} of paraaortic lymph nodes by PET has been associated with survival (126). Further work by Grigsby and colleagues demonstrated that posttreatment PET (or PET/CT) scans performed on average 3 months after chemoradiation for locally advanced disease, correlated strongly with response to treatment and disease-specific survival both retrospectively and prospectively (127,128). These studies demonstrate that both pretreatment lymph node status and posttreatment FDG uptake as measured by SUV_{max} correlate with prognosis. While SUV_{max} serves as a functional marker of response, MTV, defined as the volume of tumor tissues with increased FDG uptake, has also been investigated. Chung and colleagues demonstrated that MTV correlated with incidence of lymph node metastasis, parametrial involvement, FIGO stage, and SUV_{max} in a small retrospective cohort of 63 women with Stage IB-IIA prior to surgery. On univariate analysis, MTV was statistically associated with DFS, LN metastasis, parametrial involvement, and LVSI, and SUV_{max} . On multivariate analysis, age and MTV were found to be independently prognostic for DFS (106).

Dynamic contrast-enhanced (DCE-MRI), diffusion-weighted (DWI-MRI), or MRI may be a useful biomarker for response to therapy, recurrence, and OS (35). Mayr and colleagues measured 3-D tumor volume with serial MRI examinations before, during, and after treatment, then defined and validated 4-dimensional volumetric tumor regression parameters, and assessed the correlation with local control, disease-specific, and OS in 115 women with locally advanced cervical cancer (47). Residual tumor volume, slope (representing velocity of tumor shrinkage and clearance during treatment), and area under the regression curve correlated with local control and survival. In addition, these investigators demonstrated that DCE-MRI and MRI parameters quantifying heterogeneous perfusion patterns and residual tumor volumes within 2 to 2.5 weeks into chemoradiation predicted tumor recurrence and survival in 62 women with cervical cancer (46). Others demonstrated a correlation between DCE-MRI and response to therapy (129–131) and locoregional control after treatment (132). Diffusion-weighted MRI correlated to response to treatment in several studies; further investigation will need to be performed to verify that this response to treatment translates into locoregional control and DFS (133–136). Fat saturation sequences with T2-weighting, which enhance the definition of tumor and reduce artifact on MRI, were performed on 23 patients undergoing chemoradiation prior to treatment and during week 4. Changes in T2 fat-saturation tumor intensity during chemoradiation correlated with disease-free but not OS in these patients (137).

At this time, available biomarkers and bioimaging do not replace the standard clinicopathologic prognostic factors for selection of initial treatment. However, given the variability of patient outcomes with standard treatment within several of these clinicopathologic categories, it is very possible that this will change in the near future given the rapid advances in molecular biology and bioimaging. As importantly, the use of biomarkers and bioimaging to predict early response to therapy and patient outcome should provide the opportunity to alter treatment and improve survival in women with this disease.

Histopathology

There have been many reports of similar and dissimilar survival rates for comparable stages of adenocarcinoma and squamous cell carcinoma (108,138–140). Kasamatsu et al. compared squamous and adenocarcinomas managed with initial surgery, finding no difference in prognosis after controlling for other prognostic factors (138). Katanyoo et al. published a large single institution study comparing outcomes of primary RT for locally advanced (IIB–IVA) squamous and adenocarcinomas, again noting no survival differences after controlling for known prognostic factors (139). The largest comparison in terms of patient numbers is found in the retrospective study of Galic et al. who identified nearly 2,500 cases of cervical cancer from the Surveillance, Epidemiology, and End Results (SEER) database. There were nearly 19,000 cases of squamous carcinoma and over 4,100 cases of adenocarcinoma. This study found that, stage for stage, patients with adenocarcinoma fared worse than those with squamous cancer (140). The authors acknowledged the multiple limitations of data within the SEER database.

Three randomized clinical trials of cervical cancer have included subset analyses comparing squamous carcinomas to adenocarcinomas (141–144). These studies, although not definitive, suggest possible differences in outcomes based on treatment delivered. Since the adenocarcinoma subtype is relatively rare, it is unlikely that randomized phase 3 trials could be performed with sufficient power to answer the therapeutic questions raised by these subset analyses (82).

A study of 505 patients with non-squamous cell carcinoma of the cervix examined histologic features for prognostic significance (145). In comparison with tumor limited to the cervix, tumor extension to the uterine corpus was correlated with twice the risk of dying of tumor. The grade and specific type of adenocarcinoma were not of prognostic significance in this study, although well-differentiated villoglandular adenocarcinoma and minimal deviation adenocarcinoma were not evaluated. There is no prognostic significance in the distinction between mucinous and endometrioid adenocarcinoma of the cervix. There is evidence that adenosquamous carcinoma is either a histologically more aggressive tumor than cervical adenocarcinoma or it is diagnosed later in the disease course (89).

Higher tumor grade and vascular invasion are statistically more common in adenosquamous carcinoma than adenocarcinoma of the cervix. The presence of small cell neuroendocrine carcinoma in any amount, even when associated with other types of neoplasm, is an independent prognostic factor associated with aggressive tumor behavior.

GENERAL MANAGEMENT AND RESULTS OF TREATMENT

Severe Dysplasia and Carcinoma *In Situ*

Patients with severe dysplasia/CIN and carcinoma *in situ* (CIS) have essentially no risk of lymphatic involvement and are often treated with local therapies such as conization, laser ablation, cryotherapy, or a simple hysterectomy. These various techniques have comparable efficacy. The more conservative approaches are preferentially used when a patient wishes to have more children. Patients with HIV infection, high HPV viral load, positive margins, older age, and residual high-risk infection following conservative management have a higher recurrence rate (146,147). Detection of residual high-risk HPV infection following conservative management predicts for a higher recurrence rate after conservative treatment (146,147). In a classic study, Kolstad reported results of conization in treatment of CIS.

Therapeutic conization was performed in 795 patients; 2.3% had recurrent CIS, and 0.9% developed invasive cancer (148). Two hundred and thirty-eight patients were treated with hysterectomy and the corresponding rates were 1.2% and 2.1%, respectively. Luesley et al. reported a 91% success in over 600 patients treated with LEEP (149). Martin-Hirsch et al. in a review of the Cochrane Gynecologic Cancer Group registry, evaluated 23 trials in treatment of CIN. They concluded that there was no clearly superior surgical technique for treating CIN (150).

Instances in which conization might be preferred to ablative procedures such as laser or cryotherapy include presence of a positive ECC, treatment of AIS, and inadequate colposcopy due to the advantage of having a pathologic specimen. All uterus-sparing procedures have potential adverse effects including cervical stenosis, predisposition to preterm labor in subsequent pregnancies, persistent vaginal discharge, and possible infertility.

Temkin et al. reviewed 146 patients who had undergone cold knife conization after having been treated with LEEP for CIS (151). Of 146 patients, 133 had residual CIN on cone biopsy, and 15.8% had invasive carcinoma. Patients with residual CIN 3, ectocervical and endocervical margins with CIN, and positive endocervical curettings after conization were more likely to harbor or develop invasive disease. Lu et al. evaluated 449 patients with CIN 3 treated with conization (152). They found that a positive postcone ECC was the most significant factor predicting persistent disease (65.5%), versus 7.6% with a negative postconization ECC. Positive endocervical margins and multiquadrant disease had an odds ratio of 2.97 for persistent disease. The only preoperative indicator of persistent disease was age greater than 50. Given these data, patients with positive ECC after conization or positive endocervical margins on a cone specimen for CIS should have repeat conization prior to hysterectomy to avoid inappropriate treatment for invasive disease.

Of interest is data reported by Case et al. evaluating CIN in adolescent women in which 192 patients with CIN 2,3 underwent conization. On follow-up, 55% had abnormal cytology but no invasive cancer was found (153). This may reflect a high infection rate and point prevalence with HPV in adolescents rather than true recurrence. The new screening guidelines suggest beginning at age 21, taking into account the transient nature of HPV infection in that population. This approach attempts to avoid unnecessary overtreatment in adolescents and young women and its possible consequences such as impaired fertility and adverse pregnancy outcomes.

Since patients with CIS have virtually no risk of pelvic adenopathy, it is also appropriate to treat with only intracavitary RT if the patient is deemed a poor surgical candidate. Tumor control rates of 100% have been reported. Grigsby and Perez successfully treated 21 such patients with intracavitary RT, finding excellent outcomes with no adverse treatment sequelae (154).

Stage IA

The concept of “microinvasion” (equating to FIGO stage IA) should define tumors that penetrate the basement membrane but have little or no risk of nodal involvement or dissemination. Controversies remain in regard to the clinically relevant definition of microinvasive squamous carcinoma of the cervix, particularly as conservative treatment options, including fertility sparing, have become more common. Takeshima et al. performed a clinico-pathologic analysis of 402 patients with invasive squamous carcinoma of the cervix whose tumors demonstrated no more than 5 mm of stromal invasion (155). Although the incidence of nodal metastasis was only 1% among 82 patients with invasion limited to 3 mm, it was nearly 7% in 73 patients with 3 to 5 mm of invasion. Nevertheless, recurrences were rare and were nearly exclusively limited to tumors with more than 7 mm of horizontal spread. In an accompanying editorial, Creasman

noted that this work validated the FIGO definition of microinvasion and potentially opens up the IA2 patients for consideration of more conservative surgical approaches (156).

Hou et al. conducted an extensive review of the literature regarding IA1 and IA2 microinvasive adenocarcinoma, defining a “high-risk” group to include LN involvement or LVSI, positive surgical margins, or recurrence. These “high-risk” patients were compared to a database of patients with MID by the SEER project. Although survivals approached 99% in both IA1 and IA2 subgroups, the IA2 patients were much more likely to have had more radical surgery and adjuvant treatment. Tumors of endometrioid histology were much more likely to be in the high risk group, and these tumors were associated with late recurrences and worse survival, irrespective of substage (157).

Stage IA1 carcinoma is usually treated with conization or hysterectomy, and the control rate approaches 100%. Absence of LVSI plays a key role in opting for conservative management of patients with MID, as its presence may herald a higher incidence of lymphatic involvement. Therefore, pelvic LND is only indicated if LVSI is present. If fertility is not a consideration and prognostic factors for recurrence such as positive postcone ECC or involved margins are present, a hysterectomy is the standard option for definitive treatment of stage IA1.

Management of stage IA2 disease is more controversial. Historically, patients with FIGO IA2 disease with LVSI are not candidates for conservative surgical approaches in most circumstances since the risk of pelvic lymphatic metastasis is 5% to 13%. It is probably the case that most clinicians recommend a modified (Type II) RH and PL for stage IA2 disease, although curative intent RT is an equivalent option. However, the role of RH and the need for parametrial resection have been challenged in this population. In the Covens et al. evaluation of 842 patients, 6% had positive pelvic nodes and 4% had parametrial involvement. Parametrial invasion was associated with LVSI, tumor size greater than 2 cm, higher tumor grade, greater depth of invasion (DOI), and pelvic node metastasis. The incidence of parametrial involvement in patients with tumors less than 2 cm, negative pelvic nodes, and DOI of less than 10 mm was 0.6%. They concluded that because most patients with positive nodes and deep invasion will likely receive adjuvant pelvic RT, resection of the parametrium may not be necessary (158). Similar data has been reported from other groups (159,160). In addition to these reported high control and cure rates, Bisseling et al. described a high level of successful pregnancies following conservative treatment (160).

In patients who are medically inoperable, intracavitary RT may be used successfully. Hamberger et al. studied 151 patients with stage I treated with intracavitary radium. None of the patients with stage IA recurred (161). Grigsby et al. treated 34 patients with stage IA with 13 receiving intracavitary RT only and the remaining 21 treated with pelvic RT. Only 1 patient with stage IA recurred. The overall complication rate was about 6% (154).

Adenocarcinoma—Early Disease

The incidence of cervical adenocarcinoma has increased in the past 40 years. AIS presents a potential diagnostic and therapeutic challenge. The term “microinvasion” is controversial in describing glandular lesions as accurate measurement of DOI in glands may be difficult. Schorge et al. provided some parameters for defining stage IA1 adenocarcinoma (162). Almost all AIS lesions are associated with HPV with 18 being the predominant type.

Management of AIS is controversial. Bull-Phleps et al. evaluated 101 patients with a mean age of 29 treated for AIS with excisional procedures. Cold knife conization had a much higher negative margin rate than LEEP (72% vs. 47%). Pregnancies followed in 49 patients, and 35 delivered at term. There were

2 preterm births and 8 spontaneous miscarriages. Approximately one-third had a repeat cone biopsy, and 5 required a hysterectomy (163). Shin et al. reported on 92 patients with AIS treated with conization with negative margins (164). During a 30-month follow-up, none had recurrent AIS. Sixty-two percent of those with positive margins after conization had residual disease on hysterectomy specimens. Lea et al. highlighted the importance of postconization ECC, demonstrating a positive predictive value of 100% for detecting residual disease (165). Salani et al. reviewed 1,278 patients with AIS of the cervix who underwent conization. Almost 7% required repeat excision. Of 671 patients followed conservatively, the rate of recurrence for those with negative versus positive margins were 2.6% and 19.4%, respectively. The rate of invasive cancer according to margin status was 5.2% in positive margins versus 0.1% in those with uninvolved margins (166).

Given the critical role of margin status postconization, a cold knife cone may be the preferred excisional method compared to LEEP in patients with AIS. The most successful conservative management protocols require negative margins and no LVSI. Therefore, careful counseling and follow-up are warranted. Margin status, postcone ECC, and LVSI are significant predictors of residual disease, recurrence and invasive cancer. The recommended surveillance after conization for AIS includes cytology and ECC every 4 to 6 months.

Stage IB–IIA (Nonbulky)

Stage IB is divided into IB1 (lesions less than 4 cm) and IB2 (lesions confined to cervix >4 cm). IB1 lesions and selected IIA 1 lesions without extensive vaginal involvement can be treated with either RH and pelvic lymph node dissection (PLD) (followed by tailored chemoradiation as indicated by surgical findings) or primary chemoradiation. The preference of one over the other depends on the institution, the oncologists involved, the general condition of the patient, and tumor characteristics. Surgery is the preferred option in younger women as ovarian function and vaginal length, and thus sexual function, can generally be better maintained. Transposition of the ovaries to the abdominal wall or the gutters away from the field of RT may prevent radiation-induced ovarian failure. The preservation of function correlates with the scatter dose to the ovaries. The rate of ovarian failure is low with scattered doses ≤ 300 cGy. Up to a quarter of patients with ovarian transposition will develop symptomatic ovarian cysts requiring operative interventions, which can lower the rate of preservation of retained ovarian function.

RH can be performed through an abdominal, vaginal, or minimally invasive approach (traditional laparoscopy and robotic assisted). As salpingo-oophorectomy is not part of RH, ovarian removal should be based on the patient's age or other factors. The rate of ovarian metastasis is very low. The two most common types of RH used in treatment are classes II and III, described elsewhere in the chapter. Landoni et al. compared these two approaches in a prospective, randomized trial in 238 patients (167). Type II had a significantly decreased mean operative time (135 vs. 180 minutes), and the rate of blood loss and transfusions was comparable. Immediate postoperative complications and length of hospital stay were also similar. The long-term complication rate was significantly less in Type II versus Type III (13% vs. 28%). The use of postoperative RT, recurrence rate, and death rate due to disease were similar in both arms. The OS was 81% and 77%, respectively.

Nam et al. performed a retrospective analysis of outcomes with laparoscopic RH with or without PLD with conventional RH (168). Operating time, complication rate, and number of lymph nodes obtained were similar with the two approaches. Hospital stay was shorter with the laparoscopic technique. Overall, recurrences were lower with the standard operative route, leading the

authors to recommend limiting the laparoscopic approach to patients with tumor diameters less than 2 cm.

Radical operation will shorten the functional length of the vagina, but pliability and transudative lubrication are usually preserved. Jensen et al. documented a substantial negative impact on sexual function that is persistent following RH (169). Radiation therapy can reduce length, caliber, and lubrication of the vagina; however, these symptoms can be alleviated in some patients with hormonal replacement and vaginal dilatation. The evidence to differentiate between surgery and radiation based on sexual function is poor. A strong predictor of posttherapy sexual function is the level of activity prior to therapy. The postmenopausal patient who is not sexually active may have complete obliteration of the vagina, precluding follow-up examination. Combined modalities appear to have a more pronounced effect than either radiation or operation alone.

Fromovitz et al. evaluated 350 patients who underwent RH and pelvic LND. Only 7.7% had parametrial involvement. Factors associated with parametrial spread were size greater than 2 cm, LVSI, high grade, and nodal involvement. Of patients with tumors less than 2 cm and no LVSI, there was no parametrial involvement. These data are provocative in that patients with small tumors with negative LVSI may be candidates for less radical surgery such as simple hysterectomy, simple trachelectomy, or conization (170).

In terms of outcome, radical surgery and definitive chemoradiation have similar good outcomes. Typically, 5-year survival for stage IB patients is 85% to 90% and 65% to 75% for stage IIA. Landoni et al. reported a prospective study of RH versus RT (144). In the RH arm, patients with parametrial involvement, deep stromal invasion, and/or positive nodes received postoperative RT. Fifty-four percent (62 out of 114) and 84% (40 out of 55) of stages IB1 and IB2 received postoperative RT, respectively. Severe morbidity was seen (28%) in the surgical arm (mostly combined surgery and RT) compared to 12% in the RT arm. No difference was seen in disease-related outcomes.

Results of therapy comparing modalities should include all patients evaluated for each therapeutic modality. This applies particularly to surgical series. Findings revealed at operation may change the treatment plan, excluding some high-risk patients. This is exemplified by a report by Delgado et al. (171) for the GOG. Member institutions entered 1,125 patients prior to operation. There were 80 ineligible patients after pathology review. An additional 129 patients were explored, but the hysterectomy was abandoned because of intraoperative complications in 49 patients, or because of extent of disease beyond the uterus in 80. Failure to account for these patients in other series overestimates the efficacy of the operative procedure.

Fertility-Sparing Surgery/Radical Vaginal, minimally invasive and Abdominal Trachelectomy

Almost 30% of women diagnosed with cervical cancer will be younger than 40 and 40% will have early-stage I disease. Preservation of fertility can be a major consideration in treatment if an acceptable oncologic outcome can be obtained. There have been major advances in fertility-sparing surgery (FSS) in women with stage IA2 to IB1 cervical cancer. Dargent pioneered the procedure of transvaginal resection of cervical and paracervical tissue (vaginal radical trachelectomy [VRT]) and proximal vaginal, placement of a permanent cerclage at the cervico-uterine junction, and a laparoscopic pelvic lymphadenectomy (LPL) (172).

Plante et al. reported on 72 patients treated with VRT and LPL (173). Median age was 32, with 74% being nulligravid. Fifty pregnancies occurred in 31 women. Miscarriage rates in the first and second trimester were 16% and 4%, respectively, and 72% of pregnancies reached the third trimester. The overall prematurity rate was 16% to 19% versus 12% in the general population.

In a review, Boss et al. reported that of patients electing FSS, 43% attempt conception, 70% conceive, 49% deliver at term, and 15% have cervical stenosis causing infertility (174).

Marchiole et al. compared VRT with LPL to radical vaginal hysterectomy (RVH) with LPL in patients with lesions less than 2 cm (175). They reported similar intraoperative complication rates (2.5% vs. 5.8%, respectively) and postoperative complication rates of 21.2% and 19.4%, respectively. The recurrence rates were also similar, 5.2% and 8.5%, respectively. Ungar et al., among others, have reported an abdominal approach to radical trachelectomy (ART) (176). Nick et al. reported their experience with robotic-assisted RT versus open and found a lower blood loss and decreased hospital stay. Long-term safety data are still pending (177).

In terms of patient selection, appropriate lesions include FIGO stage IA1 without extensive LVSI and IA2 or IB1 lesions less than 2 cm with limited endocervical involvement. Although early data is encouraging, no level I evidence exists to adequately compare safety and efficacy between conservative and radical surgical approaches. Whether adenocarcinomas are appropriately managed in this fashion is subject to debate; however, in the literature, close to 40% of cases were of glandular histology. Schneider reviewed the literature and found that in patients with tumor size less than 2 cm the recurrence rate was 2% to 5% with an increase in prematurity of 2 to 3 times, compared to women with intact cervix (178).

Bulky IB Carcinoma of the Cervix

Bulky endocervical tumors and the so-called barrel-shaped cervical cancers have a higher incidence of central recurrence, pelvic and paraaortic lymph node metastasis, and distant dissemination. Historically, adjuvant extrafascial hysterectomy following preoperative RT was an accepted treatment approach. The GOG performed a randomized trial in which 256 eligible patients with carcinomas of the cervix ≥ 4 cm were treated with external beam and intracavitary irradiation, or with a slightly lower dose of intracavitary irradiation and the same external beam pelvic irradiation followed by an extrafascial hysterectomy (179). The 3-year DFS and OS rates were 79% and 83%, respectively, and were virtually identical in the irradiation alone and the combined irradiation and surgery groups. The incidence of progression was somewhat higher in the irradiation alone group (46%) compared to the combined therapy group (37%) ($p = 0.07$). However, it appears that surgery does not contribute to increased survival compared to RT alone in patients with “bulky” stage IB disease. A favorable impact on the local recurrence rate with adjuvant hysterectomy is likely, and an improvement in survival for patients with tumors 4 to 6 cm in diameter is suggested. Although retrospective, a similar study done at the University of Virginia compared similar groups of patients with IB2 cervical cancer who received definitive chemo-RT or a preoperative regimen of chemo-RT followed by extrafascial hysterectomy. There was no significant difference in DFSs. Although there was a trend toward more GI toxicity in the definitive chemo-RT group, this did not reach statistical significance. A subset analysis suggested a higher recurrence rate in smokers, especially those receiving definitive chemo-RT (180).

A different retrospective comparison was done at Memorial Sloan Kettering Cancer Center, in which patients with FIGO IB2 cervical cancer treated either with RH with tailored postoperative RT or definitive RT or chemoRT. Medically compromised patients were more likely to be treated without surgery. The 3-year PFS rates were 52% and 55%, respectively, for the RH and definitive RT groups. Over half of the patients managed initially with RH received adjuvant RT. Complications were minimally lower in the definitive RT/chemoRT group (181). Kamelle et al. retrospectively analyzed 86 patients with IB2 tumors treated with RH (182). Over half the patients received

postoperative RT. This study identified presence of LVSI as the only independent predictor of recurrence and argued for the utility of RH up front in the management of patients with intermediate-risk IB2 cervical cancers when there is no evidence of LVSI. Two accompanying editorials questioned several aspects of the analysis, including the diagnostic accuracy of a cervical biopsy in determining LVSI, the small numbers of patients and wide confidence intervals, the possible inferiority of RH compared to modern chemoradiation, and the wisdom of relying on a single variable to determine therapy when there are a number of other recognized considerations for prognosis and treatment selection (183,184).

An alternative approach involving neo-adjuvant chemotherapy prior to RH and tailored postoperative RT was investigated in a GOG randomized trial. Although the trial closed due to slow accrual, 291 patients were enrolled and randomized. When these patients were analyzed, there was no evidence that NACT provided any advantage compared to patients who went directly to RH (185).

Stages IIB, IIIB, and IVA

Patients with stage IIB, IIIB, IVA disease are treated mainly with definitive concurrent chemoradiotherapy (CCRT) in the United States (186). RT alone series have shown 5-year survival rates of 60% to 65% for stage IIB, 40% to 50% for stage IIIB, and 10% to 20% for stage IVA patients (187,188) with complication rates of 4% to 13%. Based on multiple randomized clinical trials (189–191), concurrent cisplatin is a standard agent to combine with RT. Other chemotherapy agents that have been used successfully include 5-fluorouracil (5-FU), mitomycin, carboplatin, paclitaxel, epirubicin, and gemcitabine (192). This data is nicely summarized in an article by Eifel (Table 21.2) Subset analyses of these trials (189,190) and a meta-analysis (193) demonstrated significant improvement in OS in stage IIB patients and marginal significance in stage III/IVA. Based on these findings, the National Comprehensive Cancer Network (NCCN) guidelines suggest CCRT as standard treatment for stage IIB, IIIB, and IVA disease (194). As acute effects are increased when chemotherapy is added to RT, the clinician must always weigh the risk of acute side effects and the threat posed by them with the potential benefit in patients with significant comorbid illnesses and poor performance status.

In Japan as well as in some European and Latin American countries, some stage IIB patients have been treated with radical surgery, sometimes with NACT (NAC), despite lack of sufficient evidence of its efficacy (195–197). NCCN guidelines do not suggest surgery as a treatment of choice for stage IIB patients (194).

External Irradiation Alone

The Radiation Therapy Oncology Group's Patterns of Care Study (PCS) revealed that outcomes in patients treated with external beam radiotherapy (EBRT) alone were significantly lower than those treated with EBRT and intracavitary brachytherapy (ICBT) (198). Consequently, standard definitive radiotherapy for cervical cancer consists of combined EBRT and ICBT. However, patients who cannot receive appropriate ICBT (e.g., presence of vaginal fistula, narrow vaginal anatomy) may need to be treated with EBRT alone. Compared with poor treatment results from old series, encouraging preliminary data have been reported recently. Matsuura et al. reported their experiences of EBRT alone for seven patients with cervical cancer who could not receive ICBT for various reasons (199). They applied 3-dimensional EBRT with field-within-field accelerated hyperfractionation, and showed 2-year pelvic control of 86% with no severe late toxicities. Park et al. reported preliminary data using a 3-dimensional conformal boost with a “real-time tumor tracking radiotherapy system”

Table 21.2 Prospective Randomized Trials of Concurrent Radiotherapy and Chemotherapy for Patients with Locoregionally Advanced Cervical Cancer

Authors	Trial	Eligibility	Number of Patients	CT in Investigational Arm	CT in Control Arm	Relative risk of Recurrence (90% C.I.)	p
Rose et al. (381)	GOG-120	FIGO IIB–IVA	526	Cisplatin 40 mg/m ² /wk (up to 6 cycles)	HU 3 g/m ² (2×/wk)	0.57 (0.42–0.78)	<0.001
				Cisplatin 50 mg/m ²	HU 3 g/m ² (2×/wk)	0.55 (0.40–0.75)	<0.001
				5-FU 4 g/m ² /96 h			
Morris et al. (323)	RTOG 90-01	FIGO IB–IIA (≥5 cm), IIB–IVA or pelvic nodes involved	403	Cisplatin 75 mg/m ²	None ^a	0.48 (0.35–0.66)	<0.001
Eifel et al. (189)				5-FU 4 g/m ² /96 h (3 cycles)			
Keys et al. (382)	GOG-123	FIGO IB (≥4 cm)	369	Cisplatin 40 mg/m ² /wk (up to 6 cycles)	None ^b	0.51 (0.34–0.75)	0.001
Whitney et al. (191)	GOG-85	FIGO IIB–IVA	368	Cisplatin 50 mg/m ²	HU 3 g/m ² (2×/wk)	0.79 (0.62–0.99)	0.03
				5-FU 4 g/m ² /96 h (2 cycles)			
Peters et al. (142)	SWOG 87-97	FIGO I–IIA after radical hysterectomy with nodes, margins, or parametrium positive	268	Cisplatin 70 mg/m ²	None	0.50 (0.29–0.84)	0.01
				5-FU 4 g/m ² /96 h (2 concurrent + 2 adjuvant cycles)			
Pearcey et al.	NCIC	FIGO IB–IIA (≥5 cm), IIB–IVA, or pelvic nodes involved	259	Cisplatin 40 mg/m ² /wk (up to 6 cycles)	None	0.91 (0.62–1.35) ^c	0.43
Lanciano et al.	GOG-165	FIGO IIB–IVA, clinically negative aortic nodes	268	PVI 5-FU 225 mg/m/day, 5 days/wk (6 cycles)	Cisplatin 40 mg/m ² /wk (up to 6 cycles)		
Wong et al.		FIGO IB–IIA (>4 cm), IIB–III	220	Epirubicin 60 mg/m ² then 90 mg/m ² q 4 wk for 5 more cycles ^d	None	~0.65	0.02
Thomas et al.		FIGO IB–IIA (≥5 cm), IIB–IVA	234	5-FU 4 g/m ² /96 h × 2	None ^e		Not stated
Lorvidhaya et al. (415)		FIGO IIB–IVA	926	Mitomycin 10 mg/m ² and oral 5-FU 300 mg/m ² /d × 14 days (2 cycles); ±adjuvant 5-FU	None or adjuvant 5-FU only	Not stated ^f	0.0001

CT, chemotherapy; C.I., confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HU, hydroxyurea; PA, paraaortic; PVI, protracted venous infusion; RT, radiotherapy.

^a Patients in control arm had prophylactic paraaortic irradiation.

^b All patients had extrafascial hysterectomy after radiotherapy.

^c Survival.

^d Chemotherapy was begun on day 1 and continued every 4 weeks through and after radiotherapy.

^e Patients were also randomized to receive standard or hyperfractionated RT in a 4-arm trial.

^f Relative risks were not stated. Disease-free survival rates at 5 years for RT only and RT + concurrent chemotherapy only were 48.2% and 64.5%, respectively.

Source: Adapted from Eifel PJ. Chemoradiotherapy in the treatment of cervical cancer. *Semin Rad Oncol*. 2006;16:177–185, with permission.

for 10 patients with cervical cancer who were unable to receive ICBT (200). They demonstrated a 2-year local failure free survival rate of 54%. A grade 2 rectal complication was seen in one patient. Although some propose that IMRT could be an effective alternative to ICBT, there are some challenging issues concerning interfraction and intrafraction organ motion and changing anatomy due to tumor regression or even progression before and during treatment. At present, IBCT is still part of standard treatment, due to a long track record of success, avoiding the problem of organ motion, and its superior ability to protect normal structures (201).

UNUSUAL CLINICAL SITUATIONS

Node-Positive Early-Stage (Operable) Cervical Carcinoma

Should the Hysterectomy Be Completed?

Pathologic pelvic node metastases are present in 10% to 27% of stage IB and IIA patients (7,202). The incidence is related to various

factors including tumor diameter, depth of stromal invasion, parametrial involvement, and LVSI (202). Even with more advanced imaging techniques, sensitivity for detecting positive nodes preoperatively is still unsatisfactory. The ACRIN-6651/GOG-183 was an intergroup multicenter trial of MRI and CT as potential predictors of lymphatic metastases in women with early invasive cervical carcinoma. This study showed that histologic lymph node involvement was not recognized by imaging in 34% of RH and lymph node dissection (RH-LND) specimens (41). PET is a promising imaging modality for detecting small nodal metastases which are difficult to be detected with CT/MRI. However, some data are still worrisome in this regard (203). As a result, it is not uncommon for the surgeon to find grossly positive nodes intraoperatively. In this situation, the dilemma becomes whether to proceed with the RH or to abandon the surgery and opt for curative intent CCRT.

Whitney and Stehman reviewed the GOG #49 database and found that, in 98 of 1,127 patients with clinical stage IB tumors, the surgeon abandoned the operation. Sixty-eight of these were patients with squamous carcinomas whose surgery was abandoned due to tumor extension beyond the uterus rather than for medical reasons, forming the basis of their report (204). Of these, 17 patients (1.5% of the total group, 25% of the study group) had grossly positive pelvic lymph nodes as the sole manifestation of extrauterine disease. Most patients received curative intent RT when feasible. Patients with positive pelvic nodes did poorly, with 8 of 12 failing, including 3 with distant disease. The median recurrence-free interval was only 10 months, and the median survival was 17 months.

Leath et al. reviewed 23 patients with early-stage cervical cancer who had the RH aborted because of pelvic extension (11 patients) or positive nodes (12 patients). All received RT as definitive treatment. The 5-year OS was 83%, suggesting that the aborted RH did not negatively impact outcome (205). Suprasert et al. compared the outcome of 23 patients in whom the RH was aborted due to the intraoperative finding of grossly positive nodes with that of 35 patients who were diagnosed having positive node, after completion of the surgery. Although the outcome was substantially better in patients who completed surgery, the authors pointed out that surgical group had much better prognostic factors (206).

Richard et al. analyzed data for patients with completed versus abandoned RH identified from the SEER database from 1988 to 1998 (207). From a cohort of 3,116 women with stage IB cervical cancer, 265 (8.7%) had positive pelvic nodes and a complete pelvic and paraaortic lymphadenectomy. Of these, 163 patients completed their RH, while RH was abandoned in 55 patients. All patients included in the analysis received postoperative RT. The investigators found that 5-year survival for the completed RH group was 69% compared with 71% for the RH abandoned group ($p = 0.46$).

Based on available data, it is difficult to conclude that completing the hysterectomy improves the outcome. Possible disadvantages of surgery include delaying the initiation of RT, adding surgical morbidity, and utilizing 2 treatment modalities when 1 (RT) would likely suffice. Furthermore, leaving the uterus in place provides an appropriate conduit for intracavitary RT and probably lessens the risk of complications. Clinicians who believe that completing the RH improves outcome, even with positive nodes, will point to data suggesting that patients who undergo RH, as a group, have a better outcome than the patients in whom the procedure is aborted. Others will point out that the groups are not prognostically similar and suggest that a reasonable approach is to have the surgeon resect or debulk grossly positive nodes and surgically stage the paraaortics but abort the RH. RT with chemotherapy would then become the primary therapy.

Should the Lymphadenopathy Be Debulked?

Data suggests an advantage for surgically resecting grossly positive lymph nodes prior to definitive RT, although some have

questioned the benefit in the vast majority of patients (208). Theoretical bases of the strategy include adequate control of metastatic nodes leading to improve OS and better control of gross metastatic nodes than is achievable with RT alone. Kupets et al. calculated that only 7 out of 300 patients undergoing surgical debulking of positive nodes could benefit in terms of survival. These calculations are based on assumptions suggested to be faulty by Tammela et al. (209) who calculated that 43 patients out of 300 would benefit.

Lim et al. reported results of a prospective study of pretreatment laparoscopic surgical staging in patients with locally advanced cervical cancer. Patients with macroscopic node metastases that were fully resected had a poorer OS rate compared with patients without node metastases. The investigators concluded that the survival benefit of debulking lymph nodes is not clear (210).

Cheung et al. analyzed the therapeutic value of surgically debulking metastatic pelvic nodes. They demonstrated that pelvic control was excellent for both node-positive and node-negative patients. However, frequent distant failures were observed in node positive patients. From these results, they concluded that improving pelvic control by debulking positive pelvic nodes would not translate into improved survival (211).

Another approach for grossly positive pelvic nodes would be radiation dose escalation. Classical radiation dose-response data suggest that approximately 60 Gy is required to control lesions 2 cm in size. Work from Grigsby et al. supports this approach in patients with cervical cancer and grossly involved pelvic lymph nodes (212). By calculating cumulative radiation doses to point P (6 cm lateral to the midline of the patient from a point 2 cm superior to the lateral fornix in the ICBT), they found that only 5 out of 208 patients developed pelvic nodal failure with a mean dose of 67.2 Gy at point P. For 43 patient with PET positive/CT greater than 1 cm (≤ 5 cm) nodes, only 2 (5%) experienced nodal failure. Simultaneous integrated boost IMRT is an encouraging strategy to deliver sufficient dose to positive nodes without substantially increasing doses to surrounding organs.

Invasive Carcinoma Treated by Simple Hysterectomy

Given the frequency of simple hysterectomy or total abdominal hysterectomy (Type I), it is not surprising that occasionally a patient is found to have an invasive cervical cancer unrecognized prior to surgery. Although this occurs uncommonly in an era of cytologic screening, it can occur in patients operated on for what is felt to be carcinoma *in situ*, "microinvasive" disease, or for "benign" indications.

If only microinvasive carcinoma is found, with no evidence of LVSI, no additional therapy is necessary. However, in patients with more advanced disease, simple extrafascial abdominal hysterectomy is not curative, because the paravaginal/paracervical soft tissue, vaginal cuff, and pelvic lymph nodes are not removed.

A number of series have reported results for patients treated with adjuvant postoperative RT in this situation. Favorable outcomes and acceptable levels of toxicity have been reported with this strategy. A series of 90 patients, including 18 stage II patients, treated with RT following inadvertent hysterectomy was reported by Hsu et al. The overall 5-year and 10-year survival rates were 85.5% and 74.1%, respectively. A severe late complication requiring surgical intervention was observed in only 1 patient. They concluded that this strategy provides favorable outcomes (213). Smith et al. also reported favorable results (214).

Another strategy for this situation is to utilize a more aggressive surgical approach, that is, radical parametrectomy (RP). Although it may be technically difficult to perform an adequate radical operation after previous simple hysterectomy, this alternative deserves consideration for selected patients. In an exhaustive review of the literature comparing series of patients having reoperation with RP and pelvic node dissection (LND) versus

those having postoperative RT, the weighted average 5-year survival favored RT (68.7% vs. 49.2%) (215). However, this review included relatively older series. Recently, more promising data have been reported for patients treated surgically. Leath et al. reported good results with the radical surgical approach in 23 stage IA2 and IB1 patients (216). With a median follow-up of 61 months, overall 5-year survival was reported as 96%. There were 7 (30%) operative complications. Buda et al. reported their experience of laparoscopic RP with pelvic lymphadenectomy and partial colpectomy for 12 patients with occult invasive cancer. Three patients received adjuvant treatment (brachytherapy in 1 and CCRT in 2). No intraoperative complication occurred but two patients experienced postoperative complications. At a median follow-up of 50 months, all patients were alive without disease. Despite the small numbers of patients and the possible impact of patient selection, they concluded that this strategy is safe and feasible (217). Park et al. retrospectively evaluated outcomes in 147 patients with occult invasive cancer found after simple hysterectomy (218). Of the 99 patients with IA2–IIA lesions, 26 received no definitive treatment (observation group), 44 received RT or CCRT (RT/CCRT group), and 29 underwent RP (RP group). After a median follow-up of 116 months (range 3 to 235 months), recurrent disease was observed in 0%, 34.6%, 6.8%, and 0% of patients in the IA1, observation, RT/CCRT, and RP groups, respectively. Two patients (27%) had late complications related to RT requiring further management. Five patients in the RP group (17%) experienced perioperative complications which were easily managed, intraoperatively or conservatively. Late complications were not reported in the RP group.

If the postoperative RT approach is employed, treatment should be administered immediately after recovery from the operation, as prognosis is worse if therapy is delayed. When there is any gross tumor present, external RT to the whole pelvis (40 to 45 Gy) is required. In some cases, a small external beam boost might be advisable for an additional 10 to 15 Gy. An intracavitary insertion, as outlined previously, should be performed in most cases. If there is residual tumor, an interstitial implant, when feasible, should be carried out to increase the dose to this volume.

The potential contribution of concurrent platinum-based chemotherapy must be considered, particularly in view of the randomized study of patients treated after RH with high-risk features (142). Although not directly comparable, it is reasonable to extrapolate these results favoring concurrent chemotherapy to patients treated after simple hysterectomy for invasive disease, particularly in patients with gross residual, positive margins, positive nodes, LVSI, and, possibly, adenocarcinoma.

The NCCN guidelines suggest treatment algorithms based on the status of the surgical margins (194). These guidelines suggest that stage 1A1 patients with no LVSI should undergo surveillance. Pelvic RT with concurrent cisplatin-containing chemotherapy with or without brachytherapy is recommended for patients with stage 1A1 with LVSI or with stage 1A2 or higher. If margins are positive and imaging is negative for nodal disease, if margins and imaging are negative in stage 1A2 or greater tumors, options include (1) pelvic RT with (or without) concurrent cisplatin-containing chemotherapy and brachytherapy; or (2) a complete parametrectomy, upper vaginectomy, and PLD with (or without) paraaortic lymph node sampling. In this patient group, those with negative lymph nodes should be observed or treated with pelvic RT with (or without) vaginal brachytherapy if they have high-risk factors, that is, large primary tumor, deep stromal invasion, and/or LVSI.

Stage IIIA Carcinoma of the Cervix

Cervical carcinomas extending to the lower third of the vagina without pelvic sidewall extension or hydronephrosis are uncommon, representing less than 2% of patients with cervical cancer. As a result, these patients are often not reported separately,

although management presents a significant challenge to the radiation oncologist. In general, these patients have a better prognosis than stage IIIB patients, especially when there is limited parametrial extension and the vaginal involvement is continuous with the cervix.

Kavadi and Eifel found a local control rate of 72% in 44 patients, but 5- and 10-year actuarial survival rates were 37% and 34%, respectively, reflecting the impact of distant failure seen in 13 patients. In this series, patients with no parametrial extension and direct extension from the cervix (as opposed to “skip” lesions in the lower vagina) had a 5-year survival of 73%. (219).

The inguinal lymph node areas must be assessed clinically and radiographically. When this assessment is negative, RT is given to the inguinofemoral nodes prophylactically. When the lymph node assessment suggests gross disease, it might be appropriate to confirm this with needle biopsy or consider the role of inguinal lymph node dissection following RT. Alternatively, RT doses can be escalated to reflect the presence of gross tumor. Treating the inguinal nodes adequately while limiting the dose to the underlying femoral heads is a challenge. Considerable appropriate techniques will be described in a later chapter.

More difficult is the challenge of delivering tumoricidal doses of radiation to the entire vagina while respecting tolerances of the normal tissues, in particular the rectum. Given that virtually the entire length of rectum will be treated with an intracavitary approach encompassing the entire vagina, the tolerance will be lessened, and the risk of complications will increase. In addition, because of the typical “slope,” or decrease, in thickness in the superior-inferior direction, there will be a dose gradient that can result in “hot” spots of 120% to 125%. This is potentially remediable with intensity-modulation techniques, although another approach is simply to measure the dose gradient and take it into account by raising the lower border accordingly, and/or taking the gradient into account during the brachytherapy portion of the treatment.

A general approach is to give external beam RT to the pelvis and entire vagina of approximately 40 to 44 Gy over 5 weeks (delivering 50 Gy to the inguinal areas at depth if clinically and radiographically negative), and follow this with 1 or 2 intracavitary implants. An intrauterine tandem combined with Delclos rings permits delivery of a controlled, measurable dose to the vagina (Fig. 21.11). One should aim for a total dose of approximately 65 Gy (LDR or LDR equivalent) to the entire vagina, combining the external and intracavitary doses. One can consider a second implant that does not treat the entire vagina, typically with a Fletcher-Suit applicator, particularly when there is parametrial extension. Ideally, one will deliver 80 to 85 Gy to point A in this fashion, but if the maximum rectal dose is limited to 60 to 65 Gy some compromise in point A dose may be required. These doses are appropriate only for low-dose-rate techniques, which may be preferred when treating the entire vagina. When HDR techniques are employed, greater fractionation will be necessary and tolerance doses will be lower, but with proper care it can be successfully utilized. No matter how the brachytherapy portion of the treatment is done, careful attention to the rectal dose and length of rectum is important. In many cases of IIIA cervical cancer, the tumor will involve only and extend down the anterior vaginal wall, sparing the lateral and posterior walls. When this is the case, the radiation oncologist might consider using smaller vaginal rings (e.g., Delclos rings), and placing packing posterior to the vaginal component of the applicator, in order to further limit the rectal dose. Considerable rectal sparing can be obtained in this fashion. Kazumoto et al. reported a unique ICBT planning program (referred to as “utero-vaginal brachytherapy” [U-V brachytherapy]) and its clinical outcomes for 22 cervical cancer patients including 9 stage IIIA patients (220). With a simple

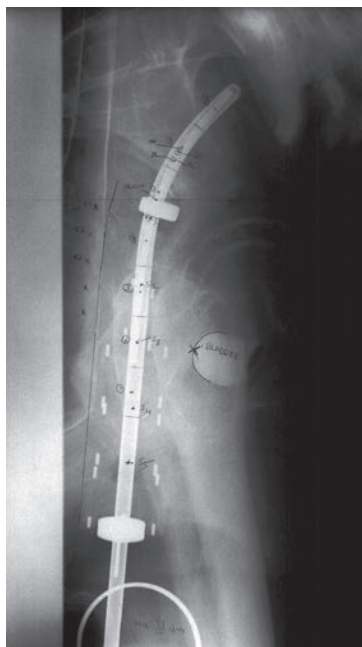


FIGURE 21.11. Lateral view of an intracavitary implant for a stage IIIA cervical carcinoma with extension to the lower third of the vagina. The tandem extends from the uterine fundus through the vagina. Delclos rings are placed over the tandem throughout its course in the vagina. This controls the distance from the radioactive sources (Cesium-137 in this case) and allows the vaginal radiation doses to be measured and controlled.

determination of the treatment volume, the cervix-parametrium, and the lower vagina were covered automatically and simultaneously by this program. Isodose curves for this program were “galaxy-shaped.” Five-year local-PFS and OS rates were 90.7% and 81.8%, respectively. Among those patients with late complications or morbidity scores higher than Grade 2 Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC), only 1 (4.5%) developed severe proctitis.

It is appropriate to administer cisplatin-based chemotherapy with the external RT with the hope of improving survival. However, concurrent chemotherapy will likely increase acute toxicities, particularly given the increased volume encompassed by the RT port and the sensitivity of the vulva to RT. Considerable individualization of therapy is required.

Small Cell Carcinoma of the Cervix

The term “small cell” should be limited to those rare tumors with counterparts in the lung and other anatomic locations noted for a high proliferation rate, marked propensity to regional lymph node and distant metastases, and positive staining with neuroendocrine markers (221). Epidemiologic analysis using materials identified from the SEER database demonstrated that the mean annual incidence for small cell carcinoma was 0.06 per 100,000 women, compared with 6.6 and 1.2 for squamous cell carcinoma and adenocarcinoma, respectively (222).

Small cell carcinomas are not often confined to the cervix and surrounding tissues at diagnosis. Therefore, workup may include bone marrow aspiration and other tests to detect the metastatic spread characteristic of this histology. Lymph node involvement is present in over 50%, and vascular invasion is frequently present. Viswanathan et al. reviewed 21 patients meeting stringent criteria for neuroendocrine type small cell cervical carcinomas (223). Ten patients had IB1 disease (although 2

of these had radiographic evidence of nodal metastases), and 11 patients had IB2-IIIIB disease. Six patients underwent RH (5 of these were IB1), and 15 patients had RT as curative intent treatment. Cisplatin-based chemotherapy was given to 62%, either neoadjuvantly and/or following surgery or RT. No patient with greater than stage IB1 survived, and even for stage IB1 patients, the survival was much worse than would be expected in more common histologies. In-field RT failures were uncommon, but metastatic failures were not.

Zivanovic et al. analyzed PFS and OS in 17 patients with small cell neuroendocrine carcinoma of the cervix to determine whether platinum-based combination chemotherapy is beneficial (224). In the early-stage disease group, the 3-year distant recurrence-free survival rate was 83% for patients who received chemotherapy and 0% for patients who did not receive chemotherapy as part of their initial treatment ($p = 0.025$). They concluded that the natural history of the patients with small cell neuroendocrine cervical cancer is akin to that of small cell lung cancer, and should be treated with systemic chemotherapy in addition to radiotherapy in early-stage disease.

Cohen et al. reported survival outcomes for 188 patients with small cell carcinoma of the cervix (225). The study population consisted of patients collected from case-series reported in the literature and additional patients treated at their own hospitals. Of 188 patients, 135 had stages I to IIA, 45 stages IIB to IVA, and 8 stage IVB disease. A total of 55.3% underwent surgery, 16.0% had chemoradiation, 12.8% radiation, and 3.2% chemotherapy alone. The 5-year disease-specific survival in stage I to IIA, IIB to IVA, and IVB disease was 36.8%, 9.8%, and 0%, respectively ($p = 0.001$). Adjuvant chemotherapy or chemoradiation was associated with improved survival in patients with stages IIB to IVA disease compared with those who did not receive chemotherapy (17.8% vs. 6.0%; $p = 0.04$). They concluded that use of adjuvant chemotherapy or chemoradiation was associated with higher survival in small cell cervical cancer patients.

Prophylactic cranial RT has also been given following this chemoradiation in the absence of progression. However, its role remains unclear.

Cervical Lymphoma

Lymphomas primarily arising and confined to the cervix are quite rare. Patients often present with signs and symptoms including vaginal bleeding, discharge, and pelvic pain. Cervical lymphomas typically develop and grow submucosally; therefore, Pap smears often do not detect these neoplasms. Generous punch biopsies or conizations are often required for diagnosis. Histologically, these lymphomas are typically of the diffuse, large B-cell variety (226,227).

Due to the rarity of this diagnosis, reports of management approaches are anecdotal and there is no clear consensus. However, general guidelines can be suggested. Clearly, treatment with systemic therapy using combination chemotherapy regimens is indicated in the majority of cases (226–229). The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) is commonly used. Surgery has been used as an adjunct to chemotherapy, either before or after chemotherapy, especially in patients with stage I or II disease. Radiation therapy following chemotherapy should be considered, particularly for larger tumors, tumors that do not completely respond to chemotherapy, and in patients with early-stage disease who are not candidates for or who refuse hysterectomy (228,229).

Young patients who wish to preserve fertility can be counseled about the possibility of conization followed by fertility-preserving chemotherapy and close follow-up. Conception has been reported in patients treated in this fashion, although the outcome of these pregnancies is unclear due to their overall rarity (226,230).

Cervical Sarcoma

Primary sarcomas arising in the cervix are exceedingly rare. In a tumor registry of 1,583 patients with cervical malignancies conducted at Washington University, only 8 sarcomas were identified. Five of these were carcinosarcomas. All 6 patients treated with curative intent remained alive with a mean follow-up of 2.5 years, although 2 patients had developed pulmonary metastases. Fadare reviewed uncommon sarcomas of the cervix and reported 11 cases of alveolar soft part sarcoma. All cases seemed to be cured, with varying follow-up periods (231). An additional case of alveolar soft part sarcoma of the cervix, cured by surgery and postoperative RT, was reported by Gitau et al. (232) Radical surgery and chemoradiation were both effective in curing patients with localized pelvic disease (233).

Granulocytic sarcoma can present as a cervical neoplasm. It is important to distinguish this lesion from primary cervical lymphoma, as this is a manifestation of acute myelocytic leukemia and the chemotherapy regimens are quite different. Outcomes for these patients are generally dismal (234).

Carcinoma of the Cervical Stump

Historically, in patients who have undergone subtotal or supracervical hysterectomy, carcinoma of the cervical stump made up nearly 4% of cases treated with RT. Although the incidence has greatly declined, these increasingly rare patients remain at risk of developing cervical carcinoma. The natural history and patterns of spread of these cancers are similar to those of the cervix in the intact uterus. The diagnostic workup, clinical staging, and basic principles of therapy are the same. However, there are potentially important differences in treatment.

Radical operation for stage I cervical stump carcinomas (trachelectomy) is made more difficult by the previous procedure. Barillot et al. prospectively accrued 213 cases of cervical stump carcinoma (235) and reported that stage for stage, local control and survival were equivalent among the surgically treated and the RT-treated patients. However, lethal complications were much more likely in the surgically treated patients. Patients receiving RT including brachytherapy had significantly better results than those having only external RT. Severe complications with RT were similar to those observed among patients with intact uteri.

The higher complication rate probably relates to the lack of adequate uterine cavity length to accommodate a tandem containing 2 or 3 sources. However, some patients with a history of supracervical hysterectomy retain enough lower uterine segment to insert 2 standard cesium-137 sources. As many sources or source positions as technically feasible should be inserted or used in the remaining cervical canal without protruding active source length through the cervical os. Comparably higher activity sources or increased dwell times should be used in the tandem, allowing a greater contribution from these sources to the point A dose and a correspondingly lower vaginal mucosal dose.

In early-stage tumors, it is critical to maximize the brachytherapy portion of the treatment, because this allows higher doses to be delivered to the tumor while limiting dose to normal structures. Early midline shields (MLSs) (e.g., at 20 to 30 Gy) are desirable. Limiting the total external beam dose to 40 Gy, optimizing the intracavitary RT with proper packing and distribution of activity, and respecting the tolerances of the rectum and bladder will keep complication rates reasonably low (Fig. 21.12). Limiting the maximum rectal dose to 65 or 66 Gy and the bladder dose to around 80 Gy (LDR or LDR equivalent) are desirable, even if the point A dose is somewhat compromised (<80 Gy). More advanced stages should be treated with 40 Gy to the pelvis, combined with the maximum intracavitary doses

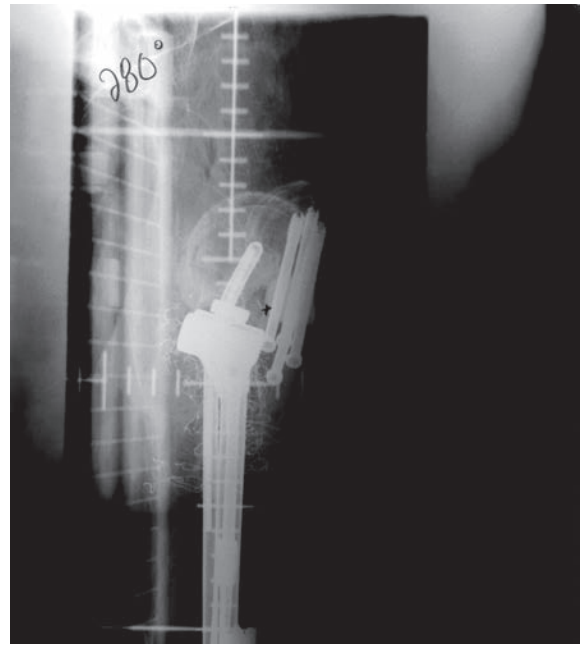


FIGURE 21.12. Approximately lateral view of intracavitary implant for a cervical stump carcinoma. The intrauterine length is only 2.5 cm, limiting the number of sources or source positions that can be placed into the uterus. The vaginal mucosa, anterior rectal wall, and bladder base will get relatively higher doses for an equivalent point A dose in most cases like this.

permitted within tolerance. Platinum-based chemotherapy will be indicated in most cases. Limited sidewall boosts may be necessary, depending on the dose to the sidewalls from the brachytherapy and the radiographic evaluation of the nodes. When there is no opportunity to insert any sources in the cervical canal, the whole pelvis dose should be increased to 45 Gy, and the primary tumor boosted to around 60 to 65 Gy with shrinking fields. Stereotactic and intensity-modulated RT (IMRT) techniques can be used to escalate doses to the primary tumor.

The 5-year survival for carcinoma of the cervical stump treated with irradiation is similar to that reported for patients with carcinoma of the intact uterus.

MANAGEMENT OF CERVICAL CANCER DURING PREGNANCY

Of all patients with cervical cancer, about 1% are pregnant at diagnosis. Most will present with abnormal cytology or abnormal vaginal bleeding. Overall incidence of abnormal cytology in pregnancy is about 5%. The availability of cervical cytology in developed countries affords an opportunity to diagnose early dysplastic changes during pregnancy, which may contribute to a higher incidence (3:1) of stage I cervical cancer diagnosed during pregnancy compared to the nonpregnant state. Either conventional or liquid-based cytology is effective in pregnancy. The use of an endocervical brush is safe and can enhance the rate of optimal smears. ECC is not recommended due to predisposition to premature rupture of membranes and bleeding.

Hopkins and Morley published their experience with cervical cancer during pregnancy and outcomes compared to those in nonpregnant state (236). They found similar survival rates when controlled for confounding factors such as age and stage.

Diagnosis

All abnormal cervical lesions during pregnancy require a biopsy. Colposcopy in pregnancy is used to rule out invasive disease. Colposcopic evaluation and directed biopsies are safe in pregnancy. In a series of 612 women with abnormal smears during pregnancy reported by Economos et al., 449 colposcopies were performed (237). All patients had satisfactory colposcopy by the 20th week of gestation, as the squamo-columnar junction (SCJ) everts during pregnancy. They reported a 95% concordance rate between colposcopic impression and directed biopsies within one degree of severity. No complications were noted. Failure to visualize the entire SCJ is not an indication to proceed to conization during pregnancy, as most repeat colposcopies will be satisfactory due to eversion of the SCJ as the pregnancy progresses.

A diagnosis of cervical cancer during pregnancy requires a multidisciplinary approach involving gynecologic and radiation oncologists, perinatologist, neonatologist, and psychologic counselors. MRI can be used safely during pregnancy to evaluate spread of disease and lymph nodes. There are reports of laparoscopic staging of lymph nodes during the second trimester as a tool to tailor the decision for treatment, but again there are potential risks with such procedures and treatment decisions should be considered carefully by members of an experienced team (238).

Management of Dysplasia

The progression rate from dysplasia in pregnancy to higher-grade dysplasia in the postpartum period is low, below 10% according to most information. Given these data it is reasonable to manage abnormal cytology in pregnancy according to guidelines in nonpregnant states. Given the low rate of progression and high reliability and safety of colposcopy, a conservative approach is likely to be safe for the patient and the unborn child. Dysplasia diagnosed by colposcopy and biopsies in pregnancy should be followed conservatively with serial colposcopic examinations every 8 weeks and managed definitively in the postpartum period.

Conization During Pregnancy

In an early series of 180 conizations during pregnancy, Averette et al. reported a first trimester fetal loss rate of 24% (239). Second trimester fetal loss was less than 10%. Hannigan et al. reported 13 conizations during the first trimester and no fetal loss. The rate of severe bleeding was 9%. Fetal loss rate in the second trimester was less than 10% (240).

In a small series of 17 patients, Goldberg et al. reported a novel approach to conization in pregnancy. The cervix was injected with vasopressin, and lateral hemostatic sutures and a cerclage were placed following the conization. The mean gestational age was 18.8 weeks (10–32). There was no major bleeding or other complications and no second trimester loss (241). An argument against the use of a cerclage is that the majority of postconization fetal deaths are delayed and presumably due to chorioamnionitis, and not necessarily a function of cervical incompetence. The cerclage may also act as a nidus for infection.

Robinson et al. reported their experience with loop electrocautery excisional procedure (LEEP) excision during pregnancy in 20 patients with gestational ages ranging from 8 to 34 weeks (242). They found that 57% had involved margins and 47% had residual disease after LEEP. There were 3 preterm deliveries, two patients requiring blood transfusions, and one intrauterine fetal demise 4 weeks after LEEP excision (chorioamnionitis was found on autopsy). They concluded that LEEP excision during pregnancy does not yield consistent diagnostic specimens and is

associated with a high complication rate. If conization is indicated during pregnancy, a cold knife technique may be the preferred method. The optimum timing would be sometime in the second trimester.

Treatment of Adenocarcinoma *In Situ* and Microinvasive Disease

Diagnosis of glandular abnormalities in pregnancy can be difficult, as glandular hyperplasia and decidual and glandular cells may exhibit benign Arias-Stella reaction, which may appear ominous to someone who is not experienced with these conditions during pregnancy. An expert evaluation is mandated for accurate diagnosis of glandular disease in pregnancy.

There is a paucity of data on management of AIS in pregnancy. Lacour et al. reported the safety of conization in the second trimester as treatment of AIS in pregnancy in 5 patients. All patients delivered at term, and only 1 required RH for stage IB disease after delivery (243).

It is believed that there is no significant difference in outcome in squamous MID versus AIS. It is difficult to know how to best treat these lesions in pregnancy. It is recommended that similar guidelines be adopted as in nonpregnant patients.

Most patients with MID in pregnancy can be safely followed even if margins are involved with dysplasia (not invasive disease). Vaginal delivery should be safe in women with microscopic disease, and definitive management may be delayed safely until the postpartum period.

Management of Invasive Cancers During Pregnancy

Surgery

Over 70% of cervical cancers in pregnancy present as stage I disease and have an excellent survival rate. Stage, tumor size, nodal status, gestational age, and the patient's desire to maintain the pregnancy are key elements in making therapeutic decisions. Treatment options can be separated according to gestational age of less than 20 or more than 20 weeks.

Invasive disease diagnosed in a pregnant patient of less than 20 weeks gestation should generally be managed immediately, resulting in loss of the fetus. However, there are reports of delaying treatment until fetal maturity without harm to the mother or the fetus. Most of the reported cases of delay in treatment were stage I disease. The delay of treatment ranged from 3 to 32 weeks. The overall mortality is about 5% to 6% with a similar recurrence rate. These data are limited by small numbers of patients but are reassuring when considering a delay in treatment. This approach is appropriate only in selected well-counseled patients with early-stage, small-volume disease.

Patients choosing to delay definitive surgical treatment of stage I disease until after delivery may safely undergo appropriate surgical treatment, including RH. Some data suggest that blood loss and postoperative febrile illness may be increased compared to the normal, non-postpartum patient.

For stage I disease, RH and PL can be safely performed prior to 20 weeks with fetus *in situ* or as a planned procedure after cesarean section in the third trimester after documentation of fetal lung maturity. Excellent oncologic outcomes are generally obtained. There are scattered case reports of treatment of locally advanced disease with NACT using cisplatin alone or in combination with paclitaxel followed by radical surgery after delivery with good results, although there are no large datasets to support routine use (244). NACT can be considered after extensive discussion with mother and family if there is strong desire to maintain the pregnancy despite the diagnosis. The use

of these drugs appears to be safe during pregnancy after first trimester but caution and a careful, multidisciplinary approach are necessary.

Radiotherapy

Most reports of RT or chemoradiation for cervical cancer during pregnancy are in patients with locally advanced disease. NCCN guidelines suggest that patients with early-stage disease have RH and node dissection instead of RT in an effort to avoid radiation fibrosis and to preserve ovarian function (194).

Benhaim et al. reported the use of chemoradiation in 2 pregnant patients (245). The first patient was diagnosed with stage IVA squamous carcinoma at 12 weeks gestation. She was treated with RT and weekly cisplatin with the fetus *in situ*. Spontaneous miscarriage occurred at about 40 Gy, which is consistent with other reports in the literature. The patient died of metastatic disease 20 months after treatment. The second patient was diagnosed with stage IIB squamous cancer at 12 weeks gestation and received the same treatment regimen. Spontaneous miscarriage occurred 3 weeks after beginning RT. The patient remained disease-free at 29 months follow-up. Ostrom et al. reported 2 cases of stage IB2 disease diagnosed at 15 weeks gestational age. Fetal losses occurred 3 to 4 weeks after initiation of RT. Both patients were disease-free 12 months after completing treatment (246). Although experience is limited with chemoradiation in pregnancy, it seems to be feasible and safe. If RT is used in the postpartum setting, it should begin within 3 weeks after uterine involution.

Neoadjuvant Chemotherapy in Pregnancy

NACT in pregnant women with cervical cancer is guided by gestational age at diagnosis, the woman's desire to maintain the pregnancy, stage of disease, lymph node involvement, and histology (247–249). Although rare histologic subtypes such as small cell carcinoma have a poor prognosis and pregnancy termination with immediate treatment is recommended, conventional histologic subtypes including squamous cell, adenocarcinoma, and adenosquamous may be managed without pregnancy termination depending on stage and lymph node involvement (247).

In 2009, a French Working Group and a European International Consensus Meeting published separate guidelines with specific management recommendations (248,249). These guidelines differed slightly. However, they both agreed that for women with cervical cancer who wish to maintain their pregnancy, proper staging with the determination of lymph node involvement was necessary prior to the determination of treatment. Women with Stage IA disease and no lymph node involvement have an excellent prognosis and delayed treatment until fetal maturation is the standard of care. Women with Stage IB1 disease and no lymph node involvement may undergo a RT or proceed with NACT to commence after the first trimester of pregnancy and continue until fetal maturation (247). Women with Stage IB1 with lymph node involvement and those with Stage IB2 or greater disease may also receive NACT to allow for fetal maturation following the first trimester of pregnancy (247). Of the 25 women in the literature treated with NACT (reviewed in, the most commonly used agents were cisplatin alone or in combination with paclitaxel (247). No infant was reported to have abnormalities, with follow-up ranging from birth to 80 months. Interestingly, Marnitz et al. (244) evaluated cisplatin concentrations in the mother and fetoplacental compartment of 7 women with cervical cancer, and noted significantly lower levels of cisplatin in umbilical cord blood and amniotic fluid compared with maternal blood, suggesting that NACT may be safely given. Although the literature is limited and long-term follow-up lacking, neoadjuvant platinum-based chemotherapy in pregnant

women with cervical cancer appears to be feasible and safe for both the mother and infant.

Radical Trachelectomy During Pregnancy

Vaginal or abdominal trachelectomy and cerclage placement along with laparoscopic or pelvic lymphadenectomy is an option for treatment of stage I cervical cancers less than 2 cm in women interested in preserving pregnancy and fertility (173). Ungar et al. reported birth of 2 healthy term infants to 2 of 5 pregnant patients with stage IB disease who were so treated (176). Gestational age ranged from 13 to 18 weeks. Fetal losses were reported on postoperative days 1 and 16. All patients remained disease-free with follow-up ranging from 10 to 54 months.

Recently 2 case reports demonstrated successful treatment of stage IB cervix cancer during pregnancy at 16 and 16 weeks with abdominal and vaginal trachelectomy, respectively, with completion of pregnancy at term (250,251). It is important to note that these are highly selective cases performed by a multidisciplinary team with high level of expertise and should be considered investigational.

Route of Delivery

Sood et al. studied outcomes of women diagnosed with cervical cancer during pregnancy or within 6 months after delivery. One of 7 women who had cesarean sections developed local and distant metastasis compared to 10 of 17 (59%) of those who delivered vaginally. In multivariate analysis, vaginal delivery was the strongest predictor of recurrence. They concluded that pregnant women with cervical cancer should delivered by cesarean section (252).

Except in stage IA1 where vaginal delivery is reasonable, a cesarean section should be performed in the presence of cervical cancer. This should be done through a classical uterine incision to avoid encroaching into the lower uterine segment or cervix. In addition, cesarean section can be followed by RH as definitive treatment or to allow surgical exploration to delineate extent of disease. Performing oophorectomy during the procedure may assist in preserving ovarian function after pelvic RT.

HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME, AND CERVICAL NEOPLASIA

About 2.1 million people live with HIV in North America, of whom approximately 1.2 million are in the United States. Heterosexual transmission accounts for 34% of cases. The proportion of women among new HIV and AIDS diagnoses has increased greatly in the United States. Over 50% of HIV-positive women are also infected with HPV. In 1993, the CDC designated high-grade dysplasia as a marker for early HIV infection and cervical cancer as an AIDS-defining illness (253).

Prevalence

Ahdieh et al. reported that the HPV point prevalence in HIV-positive women is as high as 60%, compared to about 30% in HIV-negative women (254). The relative risk (RR) of HPV-associated cancers in patients with HIV/AIDS is significantly increased, with a relative risk of over 5. The clearance of HPV in an HIV-positive individual correlates directly with the CD4 count. HPV DNA prevalence is as high as 85% in those with CD4 counts of 0 to 500 and as high as 70% in those with CD4 counts over 500. This is compared to a range of 30% to 50%

in HIV-negative women. Even with a normal CD4 count, HIV-positive women still have a twofold increase in incidence of HPV compared to HIV-negative women (255).

Pathophysiology

In HIV-infected women with no evidence of CIN on Pap smear and colposcopy and negative HPV testing, the probability of developing CIN is much greater than in women who are HIV-negative (20% vs. 5%). The strongest predictor of development of CIN in HIV-positive women is the degree of immunosuppression delineated by CD4 counts (255). When matched for sexual behavior, HIV-positive women have a one- to twofold increase in HPV sero-prevalence compared to HIV-negative women. When controlled for exposure to HPV, the persistence and detection of HPV is much greater in HIV-positive women compared to HIV-negative women (256–258). In immunocompetent women, the rate of HPV clearance within 2 to 4 years is 80% to 90%. This is affected by multiple factors such as smoking, re-exposure, prolonged oral contraceptive use, and other sexually transmitted infections (e.g., *Chlamydia trachomatis*, herpes simplex virus). The clearance rate of HPV is twofold greater in HIV-negative women as compared to those infected with the virus, despite adequate CD4 counts and low HIV viremia (256,258,259). Infection of vaginal Langerhans cells (LC) by HIV is a primary mode of entry and propagation into systemic infection. LCs constitute an important local defense against HPV infection. The numbers of LCs are lowered significantly in patients with AIDS with a resultant decrease in their immunologic response to HPV.

HPV Genotype Distribution in HIV-Positive Women

Most HIV-positive women are infected with multiple types of high-risk HPV including 11, 16, 18, 33, 51, 52, 53, 58, and 61. Clifford et al. found HPV-16 to be the most common HPV subtype in HIV-positive women; however, when compared to HIV-negative women the rate of type 16 infection is lower and type 18 may be more prevalent (260). HIV-positive women showed a higher proportion of multiple and HPV types other than 16 as compared to HIV-negative women.

Screening

Despite conflicting reports in the literature regarding the reliability of cervical smears as a screening tool for CIN in HIV-infected patients, it remains an important tool in primary screening. In a study of 189 HIV-infected women versus 95 controls, Anderson et al. found that the incidence of biopsy-proven CIN, despite normal cytology, was greater for HIV-infected women (14.3% vs. 1.2%, $p < 0.01$) (261). However, in the small number of HIV-infected women with normal cytology and biopsy-proven CIN, 95% had an abnormal cytologic smear within the preceding 12 months, most commonly ASCUS. Even after treatment for cervical dysplasia, over 40% will have persistent cytologic abnormality, with most being low-grade CIN 1. The authors concluded that these data did not support routine colposcopy in all HIV-infected women. These data also highlight the importance of vigilance in follow-up and colposcopic examination of even low-grade cytology including ASCUS in HIV-infected women, especially those with low CD4 counts. A finding of ASCUS on cervical smears of HIV-infected women is more common than in uninfected women. The probability of development of CIN in those with ASCUS was greater in the infected group compared to controls (60% vs. 25%) (262). According to USPSTF recommendations, women with HIV infection should undergo

semiannual screening in the first 12 months after diagnosis, and then annually if the results are normal. If any abnormality is detected, then closer follow-up and colposcopic examination are warranted.

In a low-resource setting where cervical cytology and adequate follow-up is problematic, a new approach has been devised and tested called the “see and treat,” or visual inspection with acetic acid (VIA), or visual inspection with Lugol’s iodine (VILI). In this approach, health care extenders are trained to use immediate visual inspection to detect dysplastic changes on the cervix. If detected, immediate treatment of the area with cryotherapy is offered. Multiple studies addressing the accuracy of VIA demonstrated a sensitivity of 66% to 96% with median of 84% and a specificity of 64% to 98% with median of 82%. The positive predictive value was 10% to 20% with a NPV of 92% to 97%. Overall VIA is found to be more sensitive but less specific than cytology. The overall sensitivity and specificity of VIA and VILI are 92% and 85%, respectively. Although these methods can be helpful in a low-resource setting, debate continues on their use in HIV-positive women.

HPV Subtype Testing

Given the high prevalence of HPV in HIV-infected women, the value of HPV testing is unclear. Adding HPV testing to the initial 2 cervical cytologies in the first year after diagnosis of HIV may modify subsequent cytology screening intervals, and may be cost-effective in patients with CD4 counts greater than 500 with normal cytology whose risk would be equivalent to women without HIV infection. There is no consensus regarding its use, and the best recommendation is to individualize testing to the patient and specific risk factors.

Vaginal Cytology After Hysterectomy

There is a paucity of data regarding cytologic screening of the vaginal vault in women infected with HIV. Paramsothy et al. evaluated 102 HIV-infected women after hysterectomy for varying indications (263). Among those with a history of CIN prior to hysterectomy, 63% were found to have vaginal intraepithelial neoplasia (VAIN) in follow-up. CD4 count of less than 200 and HIV viral load of greater than 10,000 copies/mL at time of hysterectomy were highly predictive of subsequent VAIN. Overall, out of 102 women, 16% developed VAIN in follow-up. The authors concluded that close follow-up with vaginal cytology is warranted in HIV-infected women after hysterectomy, particularly in those with severe immunodeficiency and a previous history of CIN. A more recent study by Massad et al. evaluated 335 HIV-positive and 75 HIV-negative patients with vaginal cytology after hysterectomy for prior cervical dysplastic disease. Over 5.6 years, 29% of HIV-positive patients had abnormal cytology versus 4% of controls. The most common abnormality was ASCUS and LGSIL. The incidence of VAIN 2 or worse was 0.2% in the HIV-positive population versus 0.01% in the control arm. Two HIV-positive patients developed vaginal cancers treated successfully with radiation. The severity of vaginal dysplasia was related to the CD4 count (264).

Effects of Highly Active Antiretroviral Therapy on HPV

The introduction of highly active antiretroviral therapy (HAART) has made a significant impact on the prognosis of patients with HIV, but it has not been shown to affect the rate of HPV detection, and data regarding its effect on cervical dysplasia are mixed. The close relationship of low CD4 count and cervical dysplasia makes HAART attractive in halting progression of HPV infection.

Ahdiel-Grant et al. studied 2,059 HIV-infected women receiving HAART (265). In 312 women with CIN, 141 had regression of CIN to normal with a median time to regression of 2.7 years. After HAART, elevated CD4 counts were associated with greater regression of CIN. However, there are no clear data to support HAART's role in regression of high-grade dysplasias. Therefore, the recommendation remains active surveillance and aggressive treatment for HPV in HIV-positive women who have responded well to HAART with low viral loads and adequate CD4 levels. Omar et al. studied 2,325 women in South Africa and noted a low risk of regression to normal of high grade and low grade disease in HIV-positive patients. HAART therapy appeared to protect against progression (266).

HPV Vaccination and Its Effect on HIV-Positive Women

In Phase 3 clinical trials, HPV vaccination has been shown to be effective in reducing the rate of HPV infection by over 90% by inducing a much higher antibody titer for almost 5 years, compared to the natural immune response (267,268). None of these trials included women known to have HIV infection, and data demonstrating the efficacy of HPV vaccines in HIV-positive women are lacking. A trial of HPV vaccination in HIV-positive men demonstrated a high rate (>90%) of seroconversion to types 16 and 18 without any adverse effect on CD4 counts or viral load (269). Another published study of HPV vaccine in an HIV-positive population was in children between 7 and 12 with CD4 counts greater than 15 who were stable. The quadrivalent HPV vaccine was safe and immunogenic in this patient population, and no effect was seen on the CD4 counts or the plasma HIC RNA (270).

Larger studies in women evaluating for effects on dysplasia are pending.

Treatment of Dysplasia

The indolent nature of low-grade CIN in HIV-positive women allows for a conservative treatment approach. These patients have a low rate of progression to high-grade CIN, especially if CD4 counts are above 500. Delmas et al., in a large study of the natural history of CIN in HIV-positive women, demonstrated that almost 30% of low-grade CIN lesions would regress (271). Close follow-up with cytology or colposcopy every 4 months will help in detecting progression. It is important to collaborate with other health care professionals caring for the patient, particularly to determine the CD4 count status. As mentioned, HAART therapy may also contribute to regression of low-grade CIN.

For high-grade CIN, cervical conization by cautery or cold knife technique, or ablative techniques such as cryotherapy or laser vaporization are adequate, provided that invasive disease has been ruled out and that a satisfactory colposcopy is documented.

Although these techniques are effective in treatment of CIN in patients with HIV, the rate of recurrence is higher than in HIV-negative women. Wright et al. reported outcomes from LEEP procedures, finding a recurrence rate of 56% in patients with HIV versus 10% in HIV-negative patients (272). The quality and size of the LEEP was an issue, as all HIV-positive patients had positive margins compared to only 32% of controls. However, even when controlling for margin status, the rate of recurrence was higher among HIV-positive women, highlighting other risk factors for disease recurrence; for example, CD4 counts.

Role of Medical Therapy

Maiman et al. evaluated 5-fluorouracil (5-FU) as maintenance therapy in HIV-positive women after treatment for high-grade

dysplasia (273). Women received either biweekly 5-FU (2 g) or no further therapy. The recurrence rate was 28% in the treatment arm compared to 47% in the observation arm. Those with CD4 counts less than 200 had a 46% recurrence rate versus 33% in patients with CD4 counts greater than 200. There was no grade 3 or 4 toxicity.

Robinson et al. studied the effects of isotretinoin for low-grade dysplasia in women infected with HIV and found no significant effect on time to progression (274).

Treatment of Invasive Cancer

The age at which HIV-infected women present with cervical cancer is, on average, 15 years younger than HIV-negative cohorts. Lomalisa et al. found that CD4 <200 was an independent risk factor for advanced stage of presentation (275). The treatment of invasive cervical cancer in HIV-infected women differs little from that used in HIV-negative women. There is little data on the role and long-term follow-up of RH for early-stage disease. Gichangi et al. evaluated the impact of HIV status on morbidity and pelvic tumor control following pelvic RT and found that 53% had acute radiation-related grade 3 to 4 toxicity (276). HIV infection was associated with a sevenfold higher risk of multisystem toxicity, and was found to be a major factor in treatment interruption; it was also associated with a sixfold increased risk of residual tumor 4 to 7 months after treatment. Mugambe and Kavuma compared outcomes of HIV-infected women with cervical cancer treated with RT, finding that 4-year survival was significantly lower for sero-positive patients as compared with sero-negative (277). Simonds et al. evaluated 59 HIV-positive versus 324 HIV-negative patients with stages IB to IIIB treated with chemo-radiation. They found that only 53% of HIV-positive patients completed treatment compared with 74% of HIV-negative controls (278). Further studies are needed to address the specific challenges of treating HIV-positive patients with cervix cancer with chemo-radiation.

SURGERY

A generally accepted classification of types of hysterectomy is given in Table 21.3 and described below.

Class I: Extrafascial Hysterectomy

This is the most common hysterectomy performed for a variety of gynecologic disorders. It consists of removing the uterus by separating it from the adnexal structures and round ligaments, dissecting the bladder off of the vesicouterine fold past the level of the cervix, ligation of the uterine vessels at their insertion close to the cervicouterine junction, serial application of surgical clamps next to the uterine and cervical wall as the parametrial tissues are separated from these walls, and completed by removal of the cervix off the upper vaginal vault with sparing as much vaginal tissue and length as possible. The pubovesico-cervical fascia is removed with the uterus. The opened vaginal cuff is usually closed with simple running or interrupted sutures. This hysterectomy is adequate for treatment of stage IA1 and advocated by some for stage IA2. This procedure can be accomplished abdominally, vaginally, laparoscopically, or by robotic assistance technology.

Class II: Modified Radical Hysterectomy

The modified radical hysterectomy (MRH) has gained popularity as the operation of choice for treatment of early-stage cervical

Table 21.3 Types of Abdominal Hysterectomy

Type of Surgery	Intrafascial	Extrafascial Type I	Modified Radical Type II	Radical Type III
Cervical fascia	Partially removed	Completely removed	→	→
Vaginal cuff removal	None	Small rim removed	Proximal 1–2 cm removed	Upper one-third to one-half removed
Bladder	Partially mobilized	→	→	Mobilized
Rectum	Not mobilized	R-V septum partially mobilized	→	Mobilized
Ureters	Not mobilized	→	Unroofed in ureteral tunnel	Completely dissected to bladder entry
Cardinal ligaments	Resected medial to ureters	→	Resected at level of ureter	Resected at pelvic sidewall
Uterosacral ligaments	Resected at level of cervix	→	Partially resected	Resected at postpelvic insertion
Uterus	Removed	→	→	→
Cervix	Partially removed	Completely removed	→	→

Note: Type IV, extended radical hysterectomy (partial removal of bladder or ureter), in addition to type III.

Source: Stehman FB, Perez CA, Kurman RJ, et al. Uterine Cervix. In Hoskins WJ, Perez CA, Young RC, eds. Principles and Practice of Gynecologic Oncology. 3rd ed. Philadelphia: Lippincott Williams and Wilkins, 2000:864.

cancer, depending on extent of the lesion. MRH involves opening the paravesical and pararectal spaces to determine resectability of the tumor with the goal of obtaining adequate negative surgical margins. This is accomplished by palpating the parametrial tissues and surrounding structures by placing the index finger in the paravesical space and the middle digit in the pararectal space to feel the parametrium directly. The pelvic nodal tissues are examined for gross involvement. Once resectability is established, the rest of the operation is carried forward.

MRH involves dissection of the uterine artery at its junction with the ureter. The ureters are partially dissected off the parametrial tissue and tunneled to their insertions into the bladder. The bladder is dissected off the lower uterine segment past the cervix. The parametrial tissue is resected medial to the ureter. The ureterosacral ligaments are isolated, and the proximal portions medial to the ureter are resected. A 1- to 2-cm vaginal margin is resected along with the cervix. A PL is typically performed along with MRH. Type II MRH is reserved for microscopic or smaller tumors (<2 cm), depending on the surgeon's experience and preference.

Class III or Radical Abdominal Hysterectomy

The RH differs from the MRH in the extent of dissection and resection of parametrial tissue. The paravesical and pararectal spaces are opened in a similar fashion as the MRH. The uterine artery is ligated this time at its origin from the anterior division of the internal iliac (hypogastric) artery. The ureters are dissected with complete tunneling to their insertion into the bladder trigone. The ureterosacral ligaments are isolated after the rectovaginal space is developed. The bladder is dissected off the cervix anteriorly. The cardinal ligaments are resected to the pelvic sidewall. Complete resection of the ureterosacral ligaments to their attachment may not be necessary in all cases. An alternative is resection of the ureterosacral ligaments midway and resection of 2 to 3 cm of proximal vagina, but the operation can be tailored according to tumor size and patient's anatomy.

The choice of abdominal incision for RH depends on body habitus. A Maylard incision keeps the fascia on the rectus muscles. The epigastric vessels are ligated and the muscle is transected in the middle to have greater access to the sidewall and to facilitate PL. The other option is a Cherney's incision, which involves detachment of the rectus muscle from its tendinous insertion,

allowing for greater access to the pelvis and common iliac and lower paraaortic nodes. The muscle is reattached to the tendon that is inserted into the symphysis at the end of the procedure. The peritoneum is closed in both of these approaches. In properly selected patients, these incisions provide excellent exposure compared to a vertical incision with better cosmetic outcome and perhaps less discomfort to the patient. Both MRH and RH can be performed by minimally invasive approach using laparoscopic and robotically assisted methods. The advantages of these approaches such as less pain, length of stay, and faster recovery has made them more popular in the last few years. It is important to note that the approach must be tailored to the patient's clinical situation and the surgeon's experience and expertise (279).

Class IV or Extended Radical Hysterectomy

There is little indication for extended radical hysterectomy (ERH) with availability of modern RT and chemosensitization for locally advanced tumors. As distinct from Type III RH, ERH involves complete dissection of the ureter off the vesicouterine ligament, sacrifice of the superior vesical artery, and resection of three-fourths of the vagina. The risk of bladder dysfunction and fistula formation is greatly increased compared to Types I to III hysterectomy.

Class V: Hysterectomy

A rarely performed operation, a Type V hysterectomy involves resection of the distal ureter or bladder with reimplantation of ureter if needed.

New Classification of Radical Hysterectomy

In 2008, a new proposed classification of RH was presented based mainly on the lateral extent of the resection (280). There are four types (A–D). Type A is an extrafascial hysterectomy. The paracervix is transected medial to the ureter. The uterine vessels are ligated at the insertion of the cervico-uterine junction and minimal vagina is removed.

Type B involves transection of the paracervix (parametrium) at the level of the ureter, and there are 2 subtypes. Subtype B1 is Type B without removal of the lateral paracervical lymph nodes. Subtype B2 includes removal of the lateral paracervical lymph nodes. The ureter is dissected from the tunnel under the uterine artery and vein and rolled laterally. The paracervix is then resected at the level of the rolled ureter. A 1- to 2-cm vaginal margin is obtained. This classification is similar to a modified or a Type 2 RH as described previously.

In a Type C RH, the paracervix is resected at a more lateral margin next to the hypogastric vessel. It also has 2 subtypes: C1, with nerve preservation, and C2, without nerve preservation. The uterosacral ligaments are resected close to the rectum. The ureter is completely mobilized and the paracervix is removed closer to pelvic sidewall close to the hypogastric vessels. The uterine vessels are ligated at their origin. Preservation of the hypogastric plexus is highlighted in this category (C1), which differentiates it from the classical Type 3 RH as previously described. The bladder branches of the plexus near the bladder pillars are preserved.

In a Type D RH, the entire paracervix is removed. Again, there are 2 subtypes. Subtype D1 constitutes removal of the entire paracervix with the hypogastric vessels. Subtype D2 is similar to D1, with the additional removal of fascial and muscular structures. These are rare operations, with type D1 removing the entire paracervix at the pelvic sidewall with the hypogastric vessels with view of the exposed sciatic nerve. D2 includes D1 with further extension of adjacent fascial and muscle resection. This corresponds to a radical procedure called a laterally extended endopelvic resection (LEER).

Radical Vaginal Hysterectomy

The first description of performing a RH through a vaginal approach dates back to early 20th century. The procedure had fallen out of favor due to the introduction of pelvic lymphadenectomy for management of cervical cancer and the inability to perform this component vaginally. With the introduction of laparoscopic lymphadenectomy, RVH has gained greater acceptability in the oncology community, and many centers are now offering that as an alternative to radical abdominal hysterectomy (RAH). The main advantage of minimally invasive surgery is the omission of the abdominal incision, hence a quicker and less painful recovery.

The technique for RVH starts with a LPL. The paravesical and pararectal spaces can be opened laparoscopically in a similar fashion as described during a RAH. The vaginal approach begins with demarcation of about 1 to 2 cm of vaginal margin with a circumferential incision around the vaginal mucosa and its separation from the cervix. The vaginal mucosa is then folded over the cervix and used as an anatomic marker, and is helpful in downward traction of the specimen. The vesico-uterine space is then opened and the bladder pillars identified and ligated. The paravesical space is further explored with digital dissection, and the ureters are palpated and identified. The uterine vessels are now identified and ligated at their origin from the hypogastric vessels. Attention is then turned to the posterior portion, where the pouch of Douglas is opened, and the uterosacral ligaments are then identified and ligated midway. The ureters are further retracted laterally, allowing for resection of the parametrial tissues. The specimen is then released and removed. The vaginal cuff is then closed in the usual fashion with delayed absorbable sutures.

Radical Trachelectomy

Great care must be exercised to assure proper selection of the right candidate. This procedure is generally recommended for

patients with tumor sizes less than or equal to 2 cm. There should be no endocervical lesion or extension, and workup for metastatic disease should be negative, including nodal basins. Currently no histologic type is seen as a contraindication, although some view glandular lesions as more risky. The procedure can be done abdominally or vaginally. The vaginal approach has gained greater popularity due to benefits of minimally invasive surgery. The procedure has been described as performed robotically, although large data sets are not available.

For RVT, a LPL is performed. The vaginal component begins as the RVH with delineation of 1 to 2 cm of vaginal margin and a circumferential incision to separate the vaginal from cervical mucosa. The spaces are opened in a similar fashion as an RVH. The main difference is the preservation of the uterus by amputating the cervix off the cervico-uterine junction. Usually about 1 cm of cervix is left. A frozen section may be used to determine that the endocervical margin is free of tumor. Once complete resection is secured, a cerclage is placed around the cervico-uterine junction. A probe is placed into the remaining endocervical canal to prevent a tight closure, thereby preventing cervical stenosis. The posterior cul de sac is then closed. The remainder of the vaginal cuff is sewn to the uterine stump in an interrupted manner. Patients are followed with cytology and clinical examination as per protocol.

Nerve-Sparing Radical Hysterectomy

RH can disrupt the hypogastric plexus, which contains sympathetic fibers that fuse with parasympathetic fibers located in the parametrium to control bladder contraction and compliance. Bladder dysfunction occurs in about 5% of patients, which may require continuous or intermittent drainage for several weeks. Some patients may also experience some rectal dysfunction, depending on the extent of the dissection and resection. Nerve-sparing radical hysterectomy (NSRH) has been proposed as a possible technique to identify and spare nerves and preserve good oncologic outcomes (281–283).

NSRH is described as identification of the hypogastric nerve beneath the ureteral sheath lateral to the ureterosacral ligament, identification of the inferior hypogastric plexus during resection of the cardinal ligament, and preservation of the distal inferior hypogastric plexus during dissection of the posterior aspect of the vesicouterine ligament.

Although intriguing, large studies to clearly define the benefit of NSRH are lacking. Most studies are small series, but there are some data suggesting the benefit of preserving urinary function without compromising the oncologic outcome (281). Charoenkwan et al. reported on postvoid residual (PVR) of patients with NSRH versus standard RH (282). At 7 days, 36% and 27% of NSRH patients had PVRs less than 100 and less than 50 cc, respectively, increasing to 82% and 77% by day 14. Raspagliesi et al. reported that Type III NSRH had a similar rate of bladder dysfunction as MRH, and both were lower than standard RH III (283).

Minimally invasive NSRH has been described and feasibility confirmed (284). Magrina et al. investigated the feasibility of robotic nerve-sparing hysterectomy in a small number of patients and found that this technique could be performed using the robotic platform, without compromising radicality of the operation (285).

Pelvic Exenteration

Although total pelvic exenteration (TPE) has been employed in selected patients with stage IVA cervical cancer, it is mainly used for patients with limited central recurrences and no metastatic disease following treatment with primary RT or combined surgery and RT. It involves *en bloc* removal of bladder, uterus, rectum, vagina, and, at times, vulva, depending on the exact

site and extent of recurrence. The procedure can be tailored to remove only the anterior or posterior structures, including the bladder (anterior exenteration) or rectum (posterior exenteration). In treatment of central recurrence of cervical cancer, TPE is the most common approach. Reported survival rates are quite variable, possibly due to varying follow-up intervals, patient selection factors, and whether the cohort includes patients in whom the exenteration was attempted but abandoned.

As part of TPE, reconstruction can involve diversion of the urine through a conduit utilizing a segment of the bowel (ileum, transverse, and sigmoid colon) and/or vaginal and pelvic reconstruction with placement of flaps using either transposed muscle (rectus or gracilis), segments of colon (rarely), or omentum. Depending on the location of tumor and the extent of resection, the colon may be reanastomosed with the rectal stump (supralevator) or a permanent colostomy placed.

TPE is a morbid operation that should only be undertaken in selected patients with limited recurrences. Sidewall extension, metastatic disease, and, usually, hydronephrosis are possible contraindications to the procedure. Even with appropriate workup and evaluation, a significant minority of candidates will have the procedure aborted due to intraoperative findings of metastatic or locally advanced disease. Limited data suggest that the use of PET/CT technology may assist in detecting occult metastatic disease prior to consideration of TPE (286). Equally important are evaluations of patients' overall health status, and a careful psychological and social evaluation and counseling to ensure that the patient realizes the sequelae of TPE. Perioperative complications can include bleeding, infection, cardiac and pulmonary complications, gastrointestinal and urinary leaks, fistulas, bowel obstruction, and reconstruction flap failure. Sexual dysfunction and psychosocial effects are often longer-term sequelae that can be permanent.

RADIATION THERAPY

External Irradiation

Standard Fields (Whole pelvic radiotherapy, Non-IMRT)

Treatment of invasive carcinoma of the uterine cervix requires delivery of adequate doses of RT both to the primary disease

(including surrounding at-risk tissues) and the pelvic lymph nodes. Treatment portals of whole pelvic RT have historically been designed in reference to pelvic bony structures as an anatomic surrogate (287) reported on intraoperative retroperitoneal measurements carried out in 100 patients at the time of radical surgery. Both common iliac bifurcations were cephalad to the level of the lumbosacral prominence in 87% of patients. Therefore, the superior border of the pelvic portal should be at the L4–5 interspace if the intention is to include the external iliac and hypogastric lymph nodes. This margin should generally be extended to the L3–4 or even the L2–3 interspace if common iliac nodal coverage is indicated. The width of the pelvis at the level of the obturator fossae averaged 12.3 cm, and the distance between the femoral arteries at the level of the inguinal rings averaged 14.6 cm. Posterior extension of the cardinal ligaments in their attachment to the pelvic wall was consistently posterior to the rectum and extended to the sacral hollow. The uterosacral ligaments also extended posteriorly to the sacrum. These anatomic landmarks must be kept in mind in the correct design of lateral pelvic portals, particularly in patients with stage II or higher lesions. It is also important to recognize that ligamentous tumor extensions may be present but unrecognized, even with modern imaging.

Standard pelvic portals based on bony structures are as follows (Fig. 21.13). For anteroposterior–posteroanterior (AP–PA) fields, the superior border should be between L4 and L5, the lateral border should be 1 to 2 cm lateral to the true pelvic diameter, and the inferior border should be at the lower extent of the obturator foramen at least 4 cm below the inferior extent of disease. For the lateral fields, superior/inferior borders should be identical to AP–PA fields, the anterior border should slightly anterior to the symphysis pubis and at least 1 to 2 cm anterior to common iliac nodes. It is advisable to include the uterine fundus in the treatment volume, by employing imaging techniques such as CT/MRI. Routinely placing the posterior border at the S2–3 interspace frequently results in inadequate coverage of the planning target volume. For patients with advanced disease, the posterior border should be placed behind the anterior surface of the sacrum. When there is vaginal involvement, the field should extend distally beyond the tumor a minimum of 4 cm, although some contend that the entire length of vagina should be treated down to the introitus.

The use of pelvic bony structures to design treatment portals has the advantages of being relatively simple to reproduce and will, in the majority of cases, include all gross tumor and likely

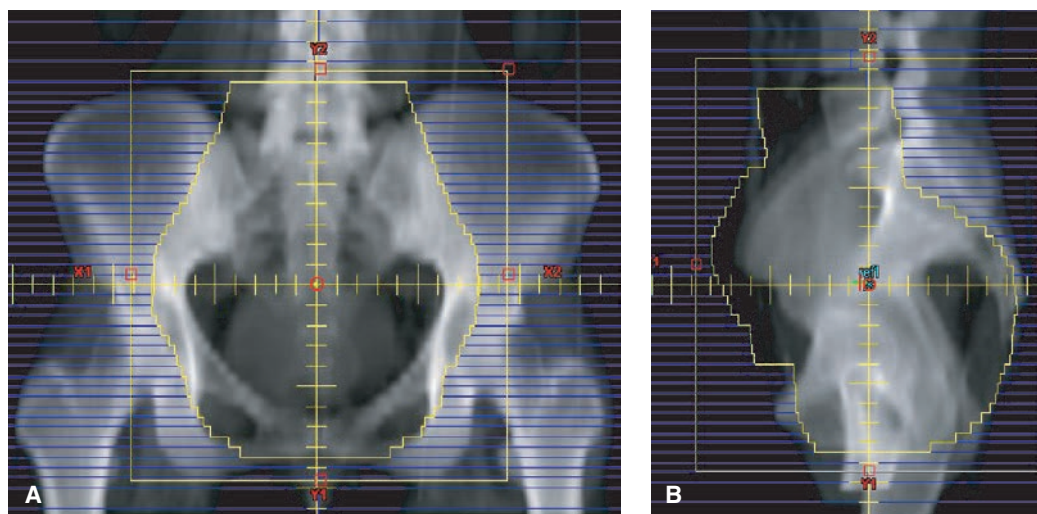


FIGURE 21.13. Standard fields for external beam whole pelvic radiation therapy. **A.** Antero-posterior port. **B.** Lateral port.

routes of local and nodal spread. However, it runs the risk of geographic misses, similar to overly restrictive CT volumes. Bonin et al. analyzed the 2-D simulation films (after lymphangiogram) of 22 patients to determine whether standard pelvic fields as defined by the GOG adequately cover regional nodes (288). They demonstrated that 10 of 22 (45%) patients would have had inadequate nodal irradiation if their fields had been designed according to standard GOG parameters. In all cases, these incompletely irradiated lymph nodes were from the lowest of the lateral external iliac group.

Groin Irradiation

In patients with involvement of the distal third of the vagina, portals should cover the inguinal lymph nodes because of the increased probability of metastases. Understanding the location of the inguinal nodes is best accomplished by measuring the depth of the femoral vessels by cross-sectional imaging. The depth of these nodes averages 6 cm and can vary substantially and be beyond the range of typical electron energies. Dittmer and Randall have published a convenient method of treating inguinal-femoral nodes using AP-PA photons only while limiting the dose to femoral heads and avoiding some of the problems with junctioning fields, for example, electrons (289). Moran et al. reported their institutional clinical experiences of modified segmental boost technique (MSBT), as well as a dosimetric comparison of the MSBT and IMRT (290). Alternatively, IMRT approaches can be used (291).

Use of Midline Shield

Although common practice, there is no consensus regarding the use of MLSs during external beam RT for cervical cancer, resulting in variability in opinions and practice patterns (292,293). The purpose of the MLS is to limit dose to the bladder and rectum in order to permit maximization of the intracavitary dose, while still delivering sufficient doses to gross parametrial disease and microscopic or gross pelvic sidewall disease (nodal or tumor extension). By allowing a greater contribution of dose from the intracavitary portion of the treatment, dose escalation results from the higher doses delivered interior to the typical point A isodose. This form of dose escalation takes advantage of the inverse square law to further limit dose to bladder and rectum.

In general terms, patients with earlier disease (stages I to IIA, or perhaps early IIB) are most likely to benefit from earlier introduction of an MLS (20 to 30 Gy); patients with more advanced disease should not have an MLS placed before 36 to 40 Gy, and possibly not at all. By performing pelvic examinations on a weekly basis in patients receiving primary RT for cervical cancer, the physician might note an early favorable response that might permit earlier use of the MLS. Keeping in mind the purpose of the MLS, a frequent practice is to use a standard-width shield (4 cm), and place it in midline position. Generally, the pelvic dose delivered with the MLS in place is not added to the point A dose, but this dose is added to the nodal (sidewall, point B, point P) dose calculation. Unilateral sidewall boosts should be considered in patients who have only unilateral parametrial or sidewall involvement. Increasing parametrial doses correlates with risk of complications, particularly radiation proctitis.

Although some investigators express objection to the physical/clinical reliability of the use of MLS (294), excellent treatment outcomes have been recently reported, consistent with the long history and positive results from their use (295).

Small Field RT

The pelvis is by far the most frequent site of failure in localized cervical cancer patients, regardless of the initial treatment.

However, in node-negative patients, the risk factors that indicate adjuvant RT following radical surgery are overwhelmingly related to a risk of failure in the central pelvis, including the vaginal vault and paravaginal soft tissues. Given the well-known relationship between radiation volume and complication risk, Kridelka et al. limited the adjuvant pelvic RT to fields smaller than “standard” (296). In 25 patients with a risk of recurrence of at least 40%, as suggested by GOG criteria (101), only one recurrence was noted, with a median follow-up of 32 months. As predicted, morbidity was very limited in quantity and grade.

A similar experience with small field pelvic RT was reported by Ohara et al. in 42 patients with stages I–II node-negative squamous carcinoma of the cervix at significant risk of local recurrence (297). All patients so treated had deep cervical stromal invasion, parametrial extension, and/or positive or close (<5 mm) surgical margins. Only 3 patients treated with small field RT suffered recurrences, all in the pelvis. Serious toxicity was rare. Oike et al. evaluated the potential dosimetric advantage of small pelvic fields excluding common iliac region with 4-field-box technique (M4F). They demonstrated that the M4F plan was significantly better in limiting dose to both small bowel and sacrum (298). Planning CT and MRI images were used to precisely delineate the “small pelvic field” clinical target volume (CTV).

Using the Delgado GOG score (101), Yeo and colleagues developed criteria for tailored adjuvant RT in node-negative stage IB–IIA cervical carcinomas. Patients with a GOG score less than 40 received no RT, while patients with scores of 40 to 120 and greater than 120 received small field RT and standard pelvic RT, respectively. With a median follow-up of 57 months, the 5-year DFS was 98.2% and there were no grade 3 to 4 toxicities. Interestingly, lower limb lymphedema was significantly less with small field RT compared to standard pelvic RT (299).

An alternative approach to limit small bowel dose in the post-operative RT setting is to utilize IMRT approaches, as described in the next section.

Intensity-Modulated External Radiation Therapy

Significant developments in the technology of radiotherapy equipment (e.g., linear accelerators, multileaf collimation, treatment planning systems) have enabled delivery of highly precise external radiotherapy, utilizing a technique known as IMRT. IMRT refers to the delivery of multiple radiation beams with varying intensity patterns that, when summed inside the patient, create a dose distribution in which the target receives the prescribed dose (with some heterogeneity) while tissues that are to be avoided receive much less radiation. Treatment planning is based on 3-dimensional imaging utilizing CT, most commonly. MRI and PET images can also be incorporated into the determination of treatment volume.

Specially configured linear accelerators with multileaf collimators (MLCs) are used to create highly contoured dose distributions utilizing various techniques. “Step and shoot” IMRT uses multiple static fields, typically 5 to 9, with specific dose maps entering the patient from multiple beam angles. “Sliding window” IMRT utilizes an arcing motion of the radiation source along with movements of the MLC leaves. Helical Tomotherapy is a variation of the sliding window technique in which the radiation source is constantly moving around a patient and the patient is translated through the path of the beam while the MLCs rapidly open and close to create the desired dose distribution. Recently, the use of volumetric modulated arc radiotherapy using linear accelerators has been adopted into clinical practice as another IMRT technique.

Potential benefits of IMRT include the ability to preferentially limit the dose of radiation to normal tissues, safely deliver higher

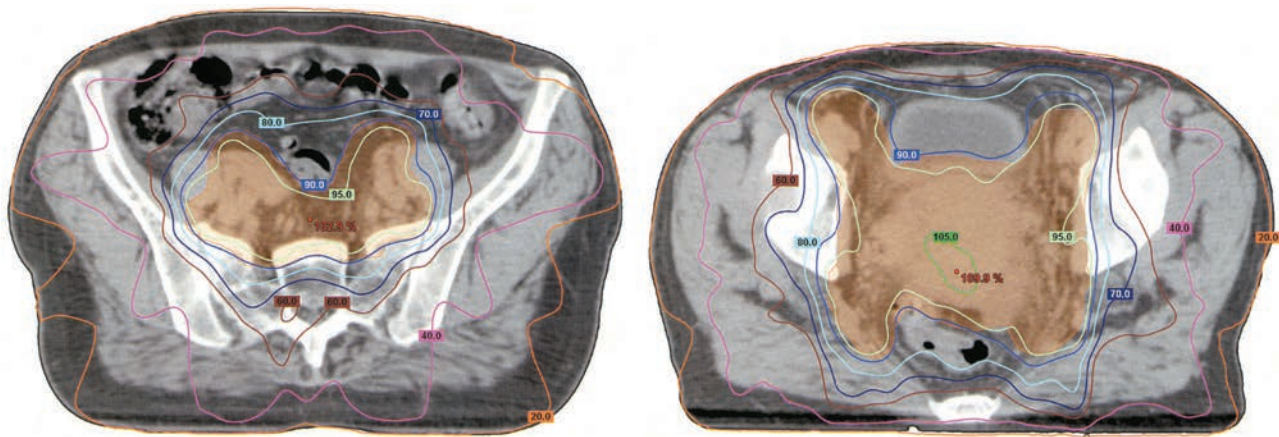


FIGURE 21.14. Typical dose distributions using intensity-modulated RT to deliver pelvic RT in cervical cancer.

tumor doses, and enable treatment and retreatment of tumors that are otherwise less amenable to treatment (Fig. 21.14).

Dose-volume histograms (DVHs) plot the percentage of a certain organ or volume of interest versus the dose received (Fig. 21.15). By looking at a DVH, the radiation oncologist can quickly and quantitatively assess whether the dose delivered to critical structures and tumor volumes is adequate for safety and efficacy of treatment. Furthermore, DVH analysis provides an objective method of comparing different treatment plans. The increasing use of IMRT requires a better understanding of radiation dose-volume relationships than has existed in the past. Although consensus regarding proper dose-volume constraints for most normal tissues is not absolute, continued experience has narrowed the disagreement.

Jhingran has published an extensive review of IMRT use in gynecologic malignancies (291). Data support the ability of IMRT to reduce dose to normal tissues and thereby reduce acute and late toxicities. Treatment of recurrences in or near previous RT fields, dose escalation to grossly involved lymph nodes (Fig. 21.16), and treatment of patients with vesico- or rectovaginal fistulae are

also facilitated. There is debate regarding the ability of IMRT techniques to replace ICBT for treatment of cervical cancer (300,301). To date, the weight of opinion does not support this latter indication (302,303).

Randall and Ibbott have presented a discussion of possible pitfalls and hazards from implementation of IMRT for gynecologic cancers (304). Chief among these concerns is the problem of organ and tissue motion. In addition to respiratory motion, in the pelvis there is considerable motion with varying amounts of distension of the bladder and rectum (305) (Fig. 21.17). In addition, patient and tumor geometry often change during treatment. Beadle et al. evaluated the magnitude of cervix regression and motion during external beam chemoradiotherapy. They demonstrated that cervix regression contributes to marked interfraction variations in the intrapelvic position of the cervical target (306). These geometric uncertainties could require substantial margins around CTVs. As a result, it was felt that the potential value of IMRT was diminished and the risk of missing tumor was increased. To overcome the problem, various adaptive strategies to decrease PTV margins are now under investigation (307,308).

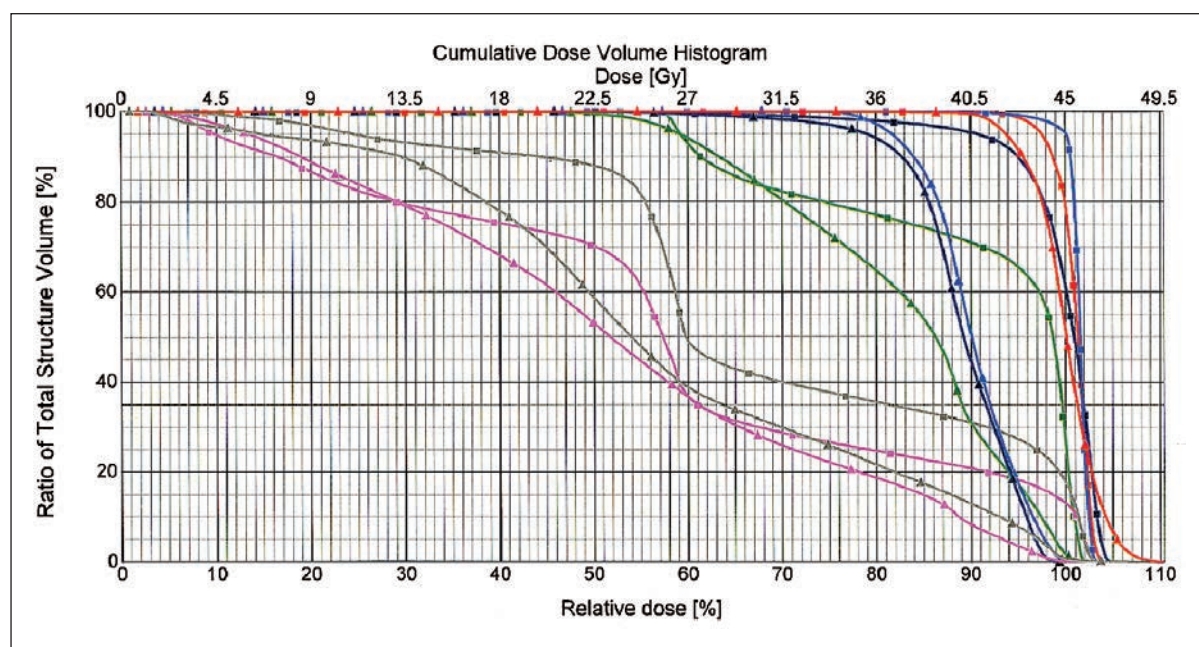


FIGURE 21.15. This dose-volume histogram (DVH) compares a 4-field “box” arrangement (*squares*) with an IMRT plan (*triangles*). The DVH plots doses to the planning target volume (PTV) and the organs at risk (OARs).

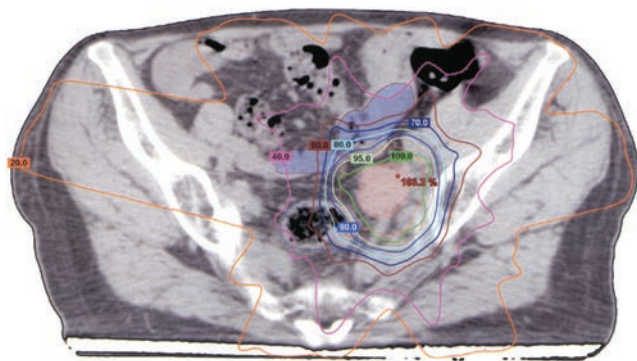


FIGURE 21.16. Intensity-modulated radiation therapy (IMRT) used to treat a pelvic node recurrence after RH.

For proper delivery of IMRT, accurate and reproducible target volume definition is essential in order to minimize the risk of a geographical miss with the tightly conformal fields often used. To minimize the risk of variation for target volume delineations, guidelines have been published. Taylor et al. have presented guidelines for contouring CTV of pelvic lymph nodes for patients undergoing RT, suggesting that a 7-mm margin around iliac vessels presents a reasonable trade-off in terms of maximizing nodal coverage while limiting small bowel dose (309). Consensus guidelines for both pelvic node CTV (310,311) and primary tumor CTV (312,313) have been published by the Gyn IMRT Consortium and the Japan Clinical Oncology Group (Fig. 21.18). In the case of the Gyn IMRT Consortium, an MRI scan was used to create the volumes, in contrast to how treatment planning is most commonly done. Although substantial agreement was seen for the GTV definition, only moderate agreement was seen for volume definitions of cervix, uterus, vagina, and parametrium.

Other concerns with IMRT include an increase in the incidence of secondary radiation-induced malignancies (314,315), limitations of imaging in accurately defining pelvic disease, increased dose heterogeneity, and problems with quality assurance (304). In addition there are concerns regarding deleterious effects of prolonged treatment times on the radiation-induced cell killing (316). Finally, many technical issues are of concern, including the fact that dose distributions are less reproducible and the fact that calculated dosimetry might not reflect what is actually delivered to the patient for many reasons (317). Despite these issues, clinical outcomes of patients with cervical cancer treated with IMRT have been published, especially in

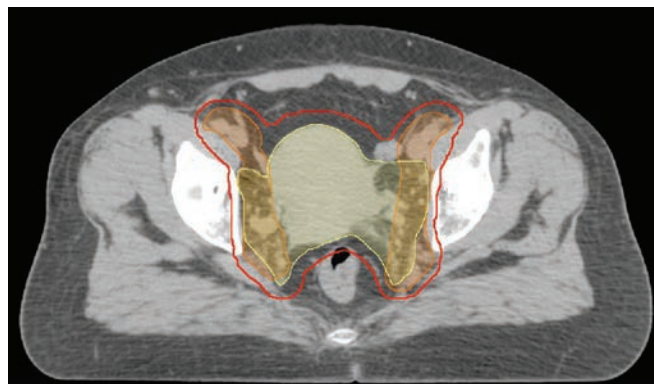


FIGURE 21.18. Contouring of primary tumor CTV (yellow), nodal CTV (orange), and PTV (red) for cervical cancer. PTV is created with 0.5 to 1.5 cm margins for CTV primary and 0.5 cm for CTV node in this case.

the postoperative setting. Promising results have been reported (318–320).

Extended Field RT

The reluctance among some radiation oncologists to utilize extended field radiation therapy (EFRT) either prophylactically or therapeutically in some cases relates to concern over increased acute and late toxicities. This is largely because the paraaortic chain is surrounded by organs of limited radiation tolerance, that is, spinal cord, kidneys, small intestine. The use of opposed anterior and posterior fields is the easiest technique but may deliver a dose that exceeds tolerance to the small bowel if an appropriate dose for microscopic disease is delivered. Various techniques have been utilized in an effort to deliver EFRT, all of which have advantages and disadvantages. A 4-field technique permits continuity with and use of a 4-field approach in the pelvis, spares much of the small intestine, and shields the spinal cord and the vast majority of the kidneys from half of the beams (Fig. 21.19). It is important to perform an IVP or CT to accurately determine the kidneys' location. The dose to the kidneys can be kept within tolerance by preferentially weighting the anterior and posterior beams (e.g., 70:30 AP-PA to laterals). In most cases, this will be adequate to limit kidney doses within tolerance, even when delivering 40 to 45 Gy to the volume. Nevertheless, it is critical to know the kidney doses and the amount of the renal parenchyma receiving this dose when utilizing this technique. IMRT could offer a more favorable dose distribution than extended field RT.

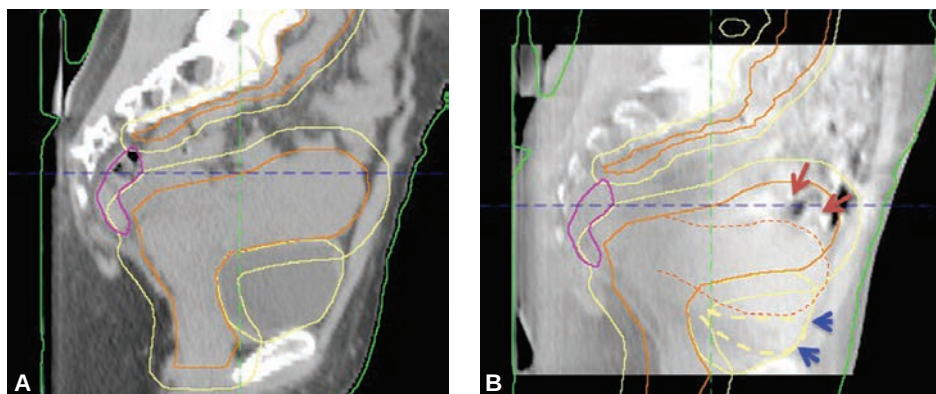


FIGURE 21.17. (A & B) Sagittal reconstructed images of simulation (A) and cone-beam CT (B). Bowel movement to caudal direction (red arrows) is observed on the cone-beam CT image compared with the simulation CT image. Bladder filling affects the position of the uterine body and the bowel (blue arrows).

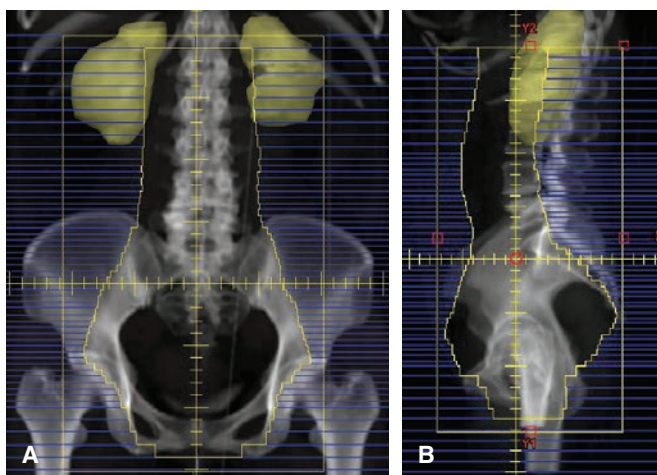


FIGURE 21.19. **A and B:** Portals of extended-field radiation therapy. **A:** Anteroposterior portal, **B:** Lateral portal. Yellow shadows indicate kidneys.

Metastatic involvement of the PANL region in cervical cancer is a somewhat unique situation compared to other malignancies. In the TNM staging systems of AJCC and UICC, this region is considered to be an extra-regional area. Therefore when metastatic disease is detected in the paraaortic region, the patient would be staged as M1 in TNM system or IVB in the FIGO staging system (if the paraaortic involvement is detected clinically). For patients with other primary cancers, elective or therapeutic RT to the extra-regional area with curative intent is unlikely to be indicated. In contrast, RT to extra-regional PANL involvement can be curative in cervical cancer.

Elective Paraaortic Lymph Node Irradiation

Data from the GOG suggests that in patients with stages IB, II, III, and IVA cervical cancer, the disease will have spread to the paraaortic lymph nodes in 5%, 16% to 21%, 25% to 31%, and 13%, respectively (8). Therefore occult involvement of the paraaortic lymph nodes is a potential cause of treatment failure in carcinoma of the cervix. Given the orderly lymphatic spread of cervical carcinoma to pelvic and paraaortic lymph nodes and its frequency in defined patient groups, adjuvant EFRT is a logical treatment strategy that seeks to avoid the risks and treatment delays associated with surgical staging. Its use may be considered in patients with early-stage disease who have undergone appropriate surgical treatment and have risk factors arguing for adjuvant postoperative RT, and in patients for whom RT is the primary treatment.

The European Organization for Research and Treatment of Cancer (EORTC) study reported by Haie et al. (321) included 441 patients with stages I–III disease who did not have surgical staging, but were considered at high risk of undetected paraaortic lymph node involvement. In the study group, the paraaortic area was to receive 45 Gy with EBRT. Significant findings included a higher rate of gastrointestinal toxicity, a significantly lower rate of paraaortic failures in the EFRT group, and a significantly lower rate of distant metastases in patients receiving EFRT and achieving pelvic control. There was no statistically significant difference between the 2 treatment arms with regard to local control, distant metastases, DFS at 4 years, or survival. The incidence of small bowel injury was 0.9% in the pelvic RT and 2.3% in the EFRT groups. A severe complication rate of 9% was observed in patients receiving EFRT, compared with 4.8% in those treated to the pelvis only. Rotman et al. published 10-year results from Radiation Therapy Oncology Group (RTOG) study 79–220 (322). In this study, 367 patients

(stage IIB or stages IB–IIA ≥ 4 cm) were randomized to pelvic RT versus EFRT. OS was 67% at 5 years and 55% at 10 years for the patients receiving elective EFRT, compared with 55% and 44%, respectively, for those treated to the pelvis only ($p = 0.02$). Locoregional failures were similar at 10 years for both arms (pelvic only, 35%; EFRT, 31%). When the first disease failure patterns were examined, more patients failed distally when treated only with pelvic RT compared to those receiving EFRT ($p = 0.053$). The EFRT arm was associated with more grade 4 and 5 complications, particularly in patients with prior abdominal surgery (11% vs. 2%).

Results from RTOG 90–01 showed that pelvic RT combined with platinum-based chemotherapy is superior to adjuvant EFRT in patients with locally advanced disease (323). However, given the apparent ability of EFRT to impact failure rates in the paraaortic chain and the improving therapeutic ratio, EFRT combined with chemotherapy could offer opportunities for improved outcomes in patients at high risk of metastatic paraaortic disease. Possible indications for its consideration include positive PET scans in the paraaortic region; high pelvic lymph nodes involved, for example, common iliac; gross nodal metastases in the pelvis; bilateral positive pelvic lymph nodes; adenocarcinoma histology with any number of positive pelvic lymph nodes; and squamous cell histology with 4 or more positive pelvic lymph nodes. In all cases, the radiation oncologist must determine that the patient is in reasonably good general health, with no or limited risk factors for RT injury. Furthermore, there should be an assessment that there is a good chance of pelvic control (in patients receiving primary RT), since the absence of pelvic control will render paraaortic control meaningless.

Therapeutic Paraaortic Lymph Node Irradiation

Based on a retrospective review of 35 patients treated for documented paraaortic lymph node spread, Stryker and Mortel suggested that EFRT can contribute to cure in approximately 30% of these patients (324). Patients with only microscopic involvement had considerably better outcomes than those with gross disease (42% vs. 26% 5-year survival). Grade 4 morbidity was seen in 8.6%, although in all cases the morbidity was related to the pelvic portion of the treatment rather than the EFRT. Grigsby et al. also reviewed 43 patients with cervical cancer who had biopsy-proven positive paraaortic lymph nodes treated with EFRT (325). The 5-year cause-specific survival rate was 49%. They demonstrated that the majority of failures occurred at distant sites. Compared to most studies showing limited toxicity, Small et al. observed very high acute and late toxicities with therapeutic paraaortic RT. Differences in the treatment regimens included the use of weekly cisplatin at 40 mg/m, more frequent boosting of paraaortic nodes, and high dose-rate brachytherapy in the RTOG study (326). A second phase of this study accrued 18 patients with positive paraaortic or high common iliac lymph nodes. In an effort to limit toxicity, these patients received the radioprotector amifostine along with their RT. Acute toxicity was not decreased, nor was late toxicity significantly diminished (327). Walker et al. reported follow-up data of a phase I/II GOG study on EFRT with concurrent paclitaxel and cisplatin chemotherapy in patients with cervical cancer metastatic to the paraaortic nodes (328). Favorable feasibility and an excellent 5-year survival rate of 45% were demonstrated. However, the incidence of severe late toxicity was unexpectedly high. Based on the nature of the complications observed, it was felt that a high central radiation dose was mostly responsible for the complication rate, rather than the utilization of EFRT or concurrent delivery of chemotherapy.

Therapeutic EFRT in patients with paraaortic metastases appears to be efficacious, resulting in long-term survivals of

25% to 50%. Definable subgroups may have an even higher rate of long-term survival. EFRT can reliably control microscopic disease in the paraaortic chain; however, the curability of the individual patient is more a function of the ability to gain control of the pelvic disease and the likelihood that the patient will develop other metastatic disease, although the incorporation of concurrent chemotherapy into standard management of these patients may decrease systemic failure. Furthermore, the use of “outback” chemotherapy following definitive chemo-RT is under active investigation as a strategy to further decrease systemic failure.

Particle Beam Radiotherapy

There is increasing interest in and availability of proton beam RT, although the reported experience in cervical cancer is limited. Kagei et al. reported 25 patients, stages IIB-IVA, treated with curative intent by photon pelvic RT followed by a proton boost to the primary tumor. No intracavitary RT was given. Long-term survival and complication rates were considered similar to those of conventional photon RT plus ICBT (329). Recently, several techniques for administration of proton RT have been presented to potentially achieve a higher therapeutic ratio. Milby et al. demonstrated that a combination of passive scattering proton therapy (PSPT) + IMRT and intensity-modulated proton therapy (IMPT) + IMRT had a statistically significant dose reduction to the small and large bowel and kidneys compared with IMRT alone, while maintaining excellent PTV coverage (330). Carbon ion RT has some biologic advantages over photons and protons, including a decreased oxygen enhancement ratio. Kato et al. reported a dose escalation study of carbon ion RT for locally advanced carcinoma of the cervix. A promising 5-year local control rate of 69% for stage IVA patients was demonstrated, but 8 out of 44 patients developed major late gastrointestinal complications (331).

Brachytherapy

Brachytherapy refers to the placement of radioactive sources at a short distance from the intended target. Because the anatomy of cervical cancer typically facilitates brachytherapy, and because brachytherapy permits very high doses to be safely delivered, it has long been a major factor in the ability of RT to cure cervical cancer. Several isotopes are available for cervical cancer brachytherapy, although at the present time ^{137}Cs is the most popular for low-dose-rate (LDR) brachytherapy. ^{192}Ir is frequently used for high-dose-rate (HDR) brachytherapy because of its high specific activity. It is also frequently used at lower activities for removable LDR interstitial applications. Brachytherapy can be delivered with intracavitary techniques using applicators typically consisting of an intrauterine tandem and vaginal colpostats or, when necessary, vaginal cylinders. All state-of-the-art applicators are afterloading. Interstitial implants are typically done with removable isotopes such as ^{192}Ir , although there is a role for implants with permanent isotopes, for example, Au-198, Cs-131, especially in small volume vaginal recurrences. Recently, the American Brachytherapy Society provided updated recommendations for brachytherapy for locally advanced cervical cancer (332,333).

Intracavitary Implants

ICBT is generally used in combination with external beam RT, although it may be used alone in very early disease. LDR has been used since the early 1900s, but since its inception the late 1950s with the Cathetron Cobalt-60, HDR brachytherapy has become increasingly utilized (292,334).

Three brachytherapy systems were developed almost simultaneously: the Paris, Stockholm, and Manchester systems. The term

“system” denotes a set of established rules, taking into account the source strength and the geometry, method, and duration of the application in order to obtain suitable dose distributions. In each of these systems, a brachytherapy insertion consisted of an intrauterine component (tandem) and a vaginal applicator. Treatment duration and loadings were developed empirically. Intracavitary treatment prescriptions could be quantified in terms of milligram-hours, that is, the product of the total mass of radium or radium equivalent (e.g., ^{137}Cs) contained in the sources, and the duration of the application in hours.

The classical Manchester system was the first system to use units of radiation exposure (Roentgens) rather than milligram-hours to prescribe dose. The dose (in Roentgens) was prescribed at specific points, termed A and B. Point A was originally defined as a point 2 cm lateral to the center of the uterine canal and 2 cm from the mucous membrane of the lateral fornix in the plane of the uterus. Point A was intended to represent the average dose to the “paracervical triangle.” Point B was defined as 5 cm from the patient’s midline at the same level as point A, and it was intended to quantify the dose received by the regional (obturator) lymph nodes. The various combinations of Manchester system ovoid dimensions and applicator loadings were designed to provide a reasonably constant point A dose rate of 50 to 55 cGy/hour. This approach heavily influenced intracavitary treatment practice patterns in the United States. The widely used Fletcher-Suit applicator system, Fletcher loadings, and the reference points A and B are all derived from this system.

Computer-generated isodose curves provide the best means of determining the doses to point A, point B, bladder, and rectum (Fig. 21.20 A and B). International Commission on Radiation Units and Measurements (ICRU) Report No. 38 (335) defines the dose and volume specifications for reporting intracavitary therapy in gynecologic procedures. ICRU-38 recommended that reference points such as point A not be used, because “such points are located in a region where the dose gradient is high and any inaccuracy in the determination of the distance results in large uncertainties in the absorbed doses evaluated at those points.” Instead, it introduced the concept of reference volume, that is, the tissue volume encompassed by a reference isodose surface, recommending that the dimensions of the 60-Gy isodose surface be specified, including the contribution of EBRT. They proposed that this pear-shaped reference volume be described in terms of its 3 dimensions: height (maximum dimension along the intrauterine sources), width (maximum dimension perpendicular to the intrauterine sources), and thickness (maximum dimension perpendicular to the intrauterine sources in the oblique sagittal plane), measured in the oblique, coronal, and sagittal planes containing the intracavitary sources. Weaknesses of the ICRU-38 recommendations have been pointed out, including the absence of rationale for the choice of 60 Gy. Widespread adoption is, therefore, lacking (336). However, the ICRU definitions of rectal and bladder points are frequently used. Dose prescription at point A is still widely used in clinical practice (337). Point B dose calculation could be optional, because data from 3-D planned brachytherapy revealed point B dose could not be a surrogate for dose to specific nodal group (338).

If the vaginal vault is narrow, making it impossible to insert regular colpostats, miniovoids can be used (usually loaded with 10 mg RaEq sources for LDR implants). When miniovoids cannot be inserted, an option is to use a protruding source in the vaginal vault, which is inserted in the afterloading tandem (usually 20 to 30 mg RaEq) with an overlying plastic sleeve (Delclos ring). Afterloaded vaginal cylinders are used in conjunction with an intrauterine tandem to irradiate the vagina when the disease extends from the uterine cervix along the vaginal walls. Cylinders are available in various diameters (1 to 5 cm) and lengths to fit any vaginal width and length (Fig. 21.11).

For LDR implants, the first intracavitary insertion is generally scheduled after 40 to 45 Gy of EBRT, in order to decrease

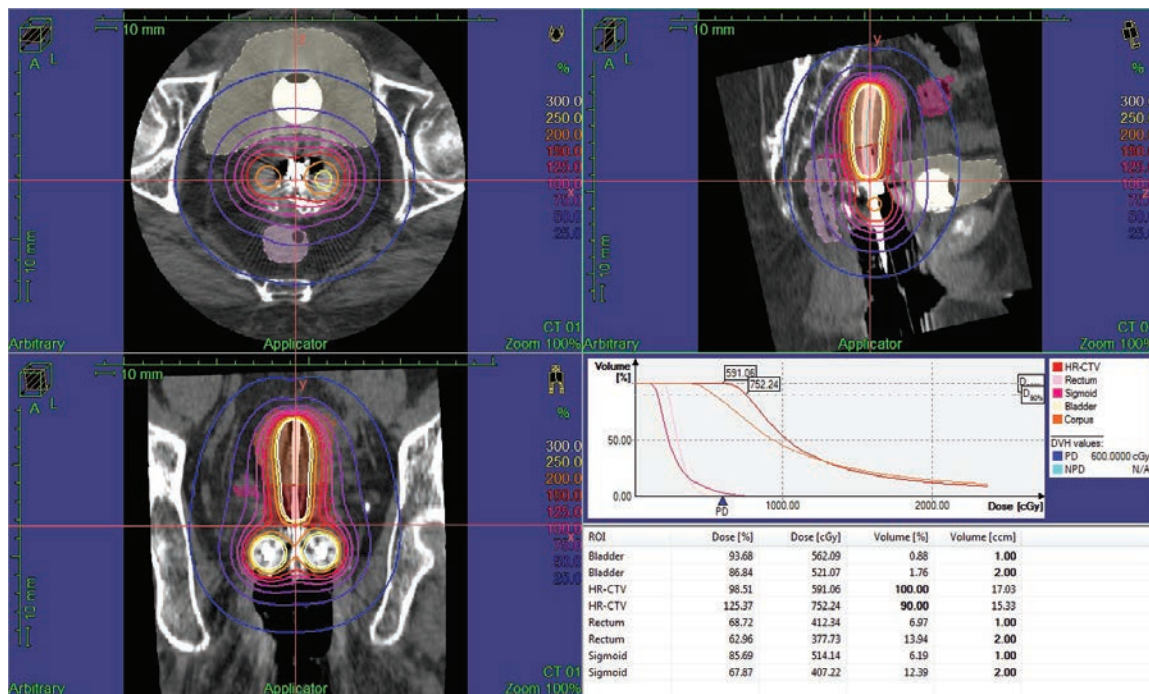


FIGURE 21.21. Image-guided brachytherapy (IGBT) for cervical cancer using CT images. Table (lower right) shows DVH data.

The ICRU defines LDR as exposures between 40 and 200 cGy/hour, medium dose rate (MDR) as between 200 and 1,200 cGy/hour, and HDR as >1,200 cGy/hour (100). All agree that clinically significant differences exist between LDR, MDR, and HDR. In general, as the dose rate is lowered, the biologic effect of the radiation is decreased owing to the ability of tissues to repair sublethal radiation damage and to repopulate. While there is probably no inherent difference in these parameters between tumor and normal tissues, there is apparently a substantial difference when one considers acute-responding (rapidly proliferating) versus late-responding (slowly proliferating) tissues. Late-responding tissues have a greater capability for repair than tumor or early-responding tissues, but this repair does not take place as fully with high dose rates. Therein lies the radiobiologic dilemma: higher dose rate or large doses per fraction cause relatively more severe late damage than tumor cell kill during HDR brachytherapy or external beam therapy.

To a large degree, published data documenting the effectiveness of RT has been obtained with continuous LDR intracavitary techniques, which have been used for nearly a century. However, even within the dose-rate range considered LDR (0 to 200 cGy/hour), a strong dose-rate effect is likely (347,348). Using a slightly higher dose rate (in the low MDR range), Patel et al. suggested, based on analysis of their clinical experience, that a dose reduction factor of approximately 30%, in comparison to a typical LDR range of 50 to 55 cGy/hour, would be required when using a dose rate of 220 cGy/hour at point A (349).

Pulsed LDR brachytherapy has also been investigated as a possible means of preserving the radiobiologic advantages of LDR while taking advantage of dose optimization offered by HDR technology. Swift et al. reported their experience in 65 patients, 42 of whom had cervical cancer (350). Median follow-up was only 15 months. In these patients with cervical cancer, 23 were alive without known disease at the time of the report. The 2-year actuarial survival rate was 65%, and the 2-year actuarial incidence of late complications was 14%. The authors concluded that pulsed LDR was feasible and produced good local control rates. Bachtiary et al. compared outcomes of patients treated with LDR (109 patients) and pulsed dose rate (PDR)

(57 patients). Seventy patients also received concurrent cisplatin. No significant differences were noted in outcomes or toxicities (351). Recently, the ABS published consensus guidelines regarding application of LDR and PDR brachytherapy for cervical cancer (352).

The use of HDR in the curative management of cervical cancer is becoming more accepted, presumably because the outpatient treatment may be more convenient, afterloading LDR machines are no longer manufactured, and Cs-137 sources are difficult to replace as they decay. Other suggested advantages of HDR implants include better stability of the implant and source positions during the short duration of the implant and better ability to optimize dose distributions. The literature reflects considerable inconsistency in terms of whether complication rates are increased with HDR over LDR. Although many retrospective series and a few randomized trials have been reported, results are difficult to interpret. Hareyama et al. published a randomized trial of 132 patients with stage II or IIIB disease (353). External RT doses were identical, and a conversion factor of 0.588 was used to convert LDR to HDR. The 5-year disease-specific survival rates were 69% and 51% with HDR in stages II and III, respectively. This compared with 87% and 60% with LDR. Pelvic recurrence-free survival with HDR was 89% and 73% for stages II and III, versus 100% and 70%, respectively, in the LDR group. Actuarial complication rates ($\geq$ grade 3) at 5 years were 10% with HDR and 13% with LDR. These differences did not reach statistical significance, although stage II patients treated with LDR had a better survival rate than those treated with HDR.

Ferrigno et al. published a retrospective series of 190 patients treated with LDR from 1989 to 1995 and 118 patients treated with HDR from 1994 to 2001. With median follow-ups of 70 and 33 months in the LDR and HDR groups, respectively, no significant differences were seen in OS, DFS, and local control among stage I-II patients. However, for stage III patients, OS and DFS were significantly better in the LDR group, and local control was also better, although not at a statistically significant level (354). Falkenberg et al. reported a single institution study comparing outcomes of 103 patients treated with LDR versus

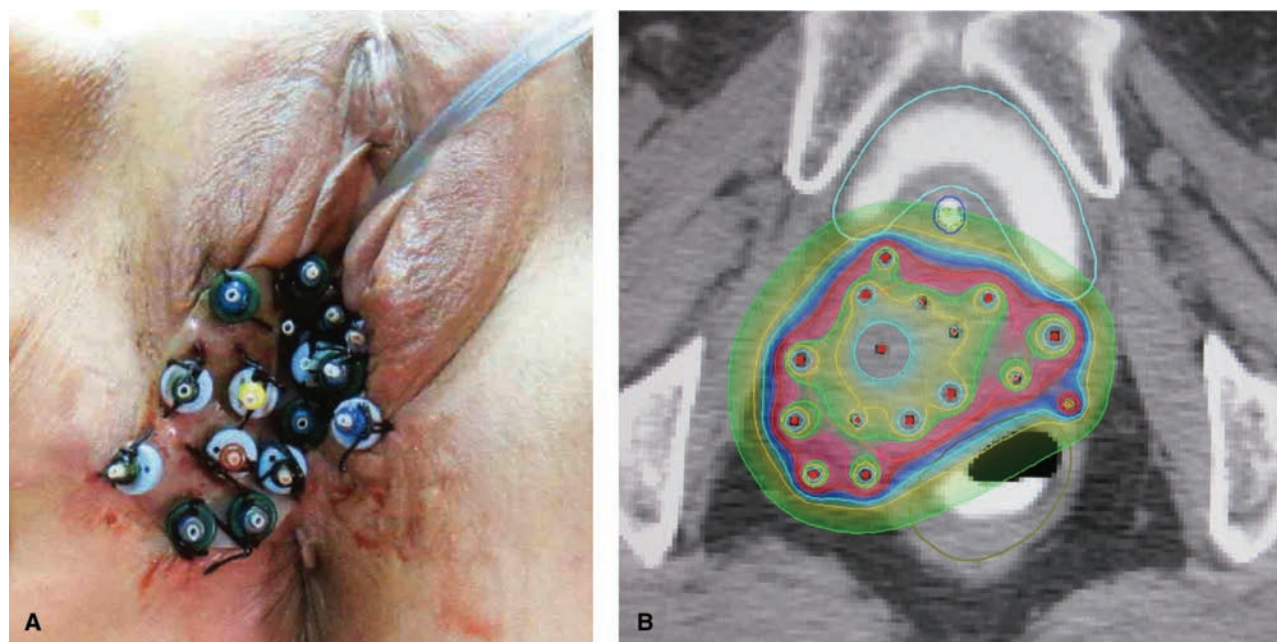


FIGURE 21.22. A and B: High-dose-rate interstitial brachytherapy for vaginal stump recurrence. **A:** External view of the application. Vinyl template applicators are used in this case. **B:** Dose distribution curves superimposed on a relevant CT image. Red line: 100% prescribed isodose line. Orange line: CTV (Special courtesy of Dr. K. Yoshida, Department of Radiology, Osaka National Hospital).

57 patients treated with HDR. No significant differences were seen in any stage in this series (355). Stewart and Viswanathan nicely reviewed current controversies in the dose rate issues (356). They acknowledged are challenges in using HDR for patients with stage III disease who exhibit poor response to EBRT.

To facilitate multiple insertions, intrauterine stents can be used so that applicators can be placed quickly, without cervical dilatation, using little or no sedation. In some institutions, treatment planning is performed on the initial insertion and is duplicated for all subsequent fractions by verifying the applicator position with fluoroscopy or radiographs. In the event that specifics of the implant change (e.g., tandem length), treatment planning must be redone to account for the change. In addition to fractionation, clinical experience has demonstrated that some method of increasing the distance from the HDR sources to the rectal wall is mandatory to keep rectal doses and subsequent sequelae at acceptable levels. Various techniques, including rectal retractors, vaginal speculums, gauze packing, and intravaginal Foley catheter balloons, are used to achieve this goal. Technical details for HDR application are described in the ABS guidelines (337,338).

Interstitial Implants

Interstitial implants are an option when intracavitary implants are impossible. Implants are typically planned and facilitated using perineal templates such as the Syed-Neblett Interstitial Template (Fig. 21.22). The use of endorectal MR coils and transrectal ultrasound can facilitate needle placement by improving visualization of tumor and normal tissues in relation to needle position. In some cases, this is done in conjunction with open laparotomy or laparoscopy. Image-guided interstitial implants with MRI could be a promising alternative for patients whose tumors are considered difficult to cover by conventional ICBT (357). Combined intracavitary/interstitial brachytherapy has also been described as technically feasible for these patients. Promising treatment outcomes have been reported (358).

Patients are typically selected for interstitial therapy on the basis of practical difficulties that preclude intracavitary therapy;

thus, they may not be comparable to patients treated in a more conventional manner. However, until further improvements and better data supporting the efficiency and safety of this technique are available, its use in locally advanced cervical cancer should be only in exceptional circumstances, and by experienced brachytherapists. Furthermore, IMRT is likely to prove to be an effective alternative to interstitial therapy in patients who are not candidates for intracavitary therapy. However one should keep in mind that there are some unresolved issues with regard to delivering appropriate IMRT for intact cervical cancers, as mentioned above (304).

Doses of Irradiation

When RT is used as curative intent treatment for primary cervical cancer, radiation dose will almost always be quite heterogeneous due to the need to deliver much higher doses to the cervical mass and its gross extensions (GTV) and grossly involved regional lymph nodes as compared to elective treatment of clinically uninvolved regional nodes. Typically, this dose gradient is created with a combination of external beam pelvic RT with intracavitary therapy, used to escalate the dose to the primary tumor. Some institutions use lower doses of pelvic RT (e.g., 20 to 36 Gy with the addition of parametrial doses to complete external beam therapy utilizing a MLS. Many institutions in the US prefer higher doses of pelvic external irradiation (usually 40 to 45 Gy), delivered by 4-field box or IMRT technique. If utilizing LDR brachytherapy techniques, approximately 40 to 55 Gy to point A is added with 1 or 2 LDR intracavitary insertions, depending on tumor stage, volume, and doses delivered to critical structures. Usual doses to point A from both the external irradiation to the pelvis and the LDR intracavitary brachytherapy can range from 70 Gy for small (≤ 1 cm) stage IB tumors to 90 to 95 Gy for stage IIB or IIIB tumors, if normal tissue doses permit. An additional parametrial boost is administered in some patients with IIB, III, or IVA tumors (factoring in the dose delivered to the sidewall by the brachytherapy component). In patients with only unilateral parametrial involvement, consideration should be given to boosting only the involved side.

Table 21.5 Suggested Schedules of HDR-ICBT in the United States

EBRT	HDR-ICBT (Point A)	EQD2 (Point A)
45 Gy/25 fx	7 Gy × 4	83.9 Gy
	6 Gy × 5	84.3 Gy
	5.5 Gy × 6	79.8 Gy
	5 Gy × 6	81.8 Gy

Note: For tandem and ovoid or tandem and ring applicators.

HDR-ICBT, high dose-rate intracavitary brachytherapy; EBRT, external beam radiotherapy; EQD2, normalized therapy dose.

When using HDR brachytherapy, it is necessary to use multiple HDR fractions and to decrease, as much as possible, the dose to late-responding tissues to decrease the likelihood of increased late effects. Peterit and Pearcey (359) used 45 Gy/25 fractions of external beam irradiation to the pelvis, combined with 5 HDR fractions (5.5 to 6 Gy per fraction), or 4 fractions of HDR brachytherapy (6.5 to 7 Gy in each fraction). The equivalent LDR brachytherapy at point A is 80 Gy, with 67 Gy delivered to the bladder or the rectum, assuming that these tissues receive 70% of the prescribed point A dose. Table 21.5 shows examples of regimens popularly used in the US for tandem and ovoid or ring applicator brachytherapy presented by ABS (333).

Clinical outcomes of patients treated with the US schedules have been reported. Anker et al. retrospectively evaluated local control and toxicity of 65 cervical cancer patients who received external beam RT and HDR (360). With a median BED at point A of 101 Gy₁₀ (EQD2 = 84 Gy), excellent 3-year local control of 97% was reported. On the other hand, actuarial 3-year Grade 3 or greater toxicity was 17%. Almost all patients received concurrent chemotherapy. Forrest et al. (361) presented an analysis of patients who received pelvic radiotherapy of 45 Gy with parametrial boosts of 5.4 or 9 Gy and HDR of 30 Gy in 5 fractions to point A (EQD2 = 85 Gy), which was a former standard radiotherapy schedule of the GOG. Although pelvic control was favorable (overall pelvic failure rate of 14%), the actuarial grade 3/4 toxic effect rate at 2 years was 14%.

Based on a perceived and observed escalation in complication rates compared to the LDR techniques used in earlier clinical trials, the GOG amended the standard HDR brachytherapy prescription to deliver a pelvic dose of 41.4 to 45 Gy to be followed by an HDR prescription dose of 5.3 to 6 Gy for 5 fractions for a total dose of 70 to 75 Gy.

Favorable local control outcomes with low levels of late toxicity were reported in Japanese prospective multi-institutional studies of definitive RT with lower doses of HDR brachytherapy compared to the doses typically used in the United States (295). Whether this observation can be explained by anatomic variation, different tumor biology, or other reasons is not clear at this time. More clinical data with DVH parameters of IGBT, close observation, and extended follow-up are needed to establish optimum brachytherapy treatment schedules using HDR brachytherapy.

Altered Fractionation

Conventional RT schedules typically employ fraction sizes of 180 to 200 cGy, given 5 days per week over a number of weeks. Altered fractionation refers to the use of nonstandard dose and fractionation schedules. Radiobiologic research and modeling suggest that these different fractionation schedules could favorably impact control rates, complication rates, or both. Examples include hypofractionation (larger doses per fraction, lower total dose), hyperfractionation (smaller doses per fraction given more

frequently, e.g., 2 to 3 fractions per day, to a slightly higher total dose), accelerated fractionation (standard fraction sizes given more frequently, e.g., twice daily), and concomitant boost techniques (a larger volume is treated in standard fashion, while part of the volume, typically gross tumor, is treated with an additional smaller fraction on the same day, separated by 4 to 6 hours). The development of IMRT techniques, described earlier, has made it possible to create dose gradients to escalate dose to gross disease, for example, enlarged lymph nodes, while maintaining standard fractionation to areas of potential microscopic disease, a form of concomitant boost.

Ohno et al. reported the toxicity and outcomes of an accelerated hyperfractionated RT for locally advanced cervical cancer (362). They conducted a multi-institutional prospective study among 8 Asian countries. Protocol treatment consisted of whole pelvis RT of 30 Gy, 1.5 Gy/fraction twice daily, followed by 20 Gy of pelvic RT with central shielding at a dose of 2-Gy fractions daily and HDR of 18 to 20 Gy/3 to 4 fractions or LDR of 45 to 60 Gy/2 fractions. The median overall treatment time was 35 days. The 5-year pelvic control and OS rate for all patients were 84% and 70%, respectively. The 5-year actuarial rate of Grade 3 to 4 late toxicity at any site was 5%. This treatment strategy could be a treatment option, for example, in patients who cannot receive CCRT.

Overall Treatment Time

Owing to the radiobiologic phenomena of tumor cell repopulation and accelerated repopulation, clinicians have long assumed that treatment prolongation, beyond some reasonable point, would have a deleterious effect on outcome in patients treated with RT. Several studies have supported this assumption by demonstrating lower pelvic tumor control and survival rates after definitive RT in invasive carcinoma of the cervix when the overall treatment time is prolonged.

Combining the published results, largely from the prechemoRT era, one can suggest that pelvic control will suffer at an approximate rate of 1% per day that treatment extends beyond 52 to 55 days. This impact will be potentially seen in all stages of localized disease, and survival will be negatively affected. Erridge et al. have pointed out that there is probably a limit to the relationship between treatment time and outcome (363). In a cohort of patients, almost all of whom completed treatment within 7 weeks, no impact of overall treatment time was observed. However, grade 4 toxicities were more common among patients completing treatment on a compact schedule of 29 to 32 days.

Monk et al. suggested that prolonged overall treatment times negatively impact outcomes for patients with locally advanced cervical carcinoma treated with weekly cisplatin and pelvic RT (364). They reviewed data from 335 women who participated in GOG studies and demonstrated that a prolonged course of RT was associated with poorer PFS and OS.

Feddock et al. reviewed curative intent treatment of 227 patients with cervical cancer, separating them into 2 groups based on overall treatment time of less than 8 weeks versus ≥8 weeks. With a median follow-up of 38 months, there was a decrement in cause-specific survival with prolonged treatment time in patients managed with LDR brachytherapy. However, a similar decrement was not observed in patients managed with HDR brachytherapy (365).

Palliative or Emergent Irradiation

The radiation or gynecologic oncologist is often faced with treating a patient who requires palliation of pelvic pain, obstruction, or bleeding. If vaginal bleeding is the main concern, bleeding can be controlled by vaginal packing, followed by the immediate institution of EBRT. It can be appropriate, particularly in

noncurative situations such as metastatic disease, to treat a slightly smaller pelvic volume. Doses per fraction slightly higher than standard, for example, 250 to 300 cGy will more quickly result in hemostasis while still allowing patients with localized disease to be approached with curative intent, without an excessive risk of complications. As an alternative strategy, a single intracavitary implant with tandem and colpostats can be used. Again, this does not preclude curative intent treatment for patients with localized disease.

Patients with stage IVB or incurable recurrent carcinoma often require palliation of pelvic pain or bleeding, and their general condition may not warrant a prolonged course of external irradiation. Spanos et al. (366) reported an RTOG phase 3 study of accelerated split-course palliative irradiation in 284 patients. Patients received 3 courses of 14.8 Gy in 4 fractions over 2 days, with a rest of 2 to 4 weeks between courses, up to 44.4 Gy total dose. There were 136 patients randomized to rest periods of 2 or 4 weeks. There was a trend toward increased acute toxicity in patients with shorter rest periods (5 of 68, versus 0 of 68; $p = 0.07$). Late toxicity was not significantly different in the 2 groups, although length of follow-up was not sufficient to accurately assess it. Pelvic tumor response was comparable in both. More patients in the 2-week rest period group completed the 3 courses of therapy, but the most significant predictor for completion of therapy was Karnofsky performance status of 80 or higher. This schedule offers significant logistic benefits and has been shown to result in good tumor regression and excellent palliation of symptoms.

CHEMOTHERAPY

Chemotherapy is an integral part of the multidisciplinary approach to the treatment of cervical cancer. While chemotherapy is most often given concurrently with radiation in the setting of locally advanced disease, it is also administered in the neoadjuvant setting prior to surgery or radiation and in the recurrent and metastatic disease setting as palliative therapy (367). When administered concurrently with radiation, the most commonly used chemotherapeutic agent is single agent cisplatin, though other agents used alone or in various combinations include capecitabine, carboplatin, epirubicin, 5-fluorouracil, hydroxyurea, irinotecan, mitomycin, nedaplatin, topotecan, and vinorelbine (367,368). In the neoadjuvant, recurrent, or metastatic settings, capecitabine, carboplatin, cisplatin, epirubicin, gemcitabine, ifosfamide, irinotecan, paclitaxel, pegylated liposomal doxorubicin, topotecan, and vinorelbine are used as single agents or in various combinations. More recently, biologic agents such as bevacizumab and cetuximab and hypoxic cell sensitizers such as tirapazamine are being used as single agents or in combination with chemotherapy in the treatment of cervix cancer (367,368).

COMBINED MODALITY TREATMENT

Adjuvant Hysterectomy after Radiation Therapy

Multiple retrospective series have been reported comparing preoperative RT plus adjuvant hysterectomy postradiation therapy (AHPRT) with curative intent RT or chemo-RT without AHPRT. Most commonly, no improvement in tumor control or survival is noted, although other series report improved pelvic control rates and possibly improved survival. Given the retrospective nature of these series, the authors acknowledge likely biases in patient selection, limiting the ability to draw conclusions.

A randomized trial to address this question was performed by the GOG. Keys et al. reported 256 patients with cervical cancers greater than 4 cm in size who were randomized to curative doses of pelvic RT with brachytherapy versus preoperative doses of RT and brachytherapy plus AHPRT. The relapse rate was significantly lower in the AHPRT arm versus RT alone (27% vs. 14%). The incidence of progression was somewhat higher in the RT alone group at 46% versus 37% ($p = 0.07$) in the AHPRT group. However, no OS advantage was seen, and the toxicities were similar in both groups. Pathologic evaluation of hysterectomy specimens revealed 48% with no residual disease, 40% with microscopic disease, and 12% with grossly positive tumor. Patients with grossly positive tumors had a death rate seven times higher than those with negative specimens (179).

The main impetus for AHPRT is to decrease the incidence of pelvic recurrence; however, its use remains controversial because OS appears to be unaffected. Patients who could potentially benefit include those with bulky endocervical lesions greater than 4 cm in size and patients with difficult anatomy that limits appropriate placement of brachytherapy applicators. Patients with persistent disease after RT may benefit from planned hysterectomy.

Adjuvant Postoperative Pelvic RT

The most common failure pattern following radical surgery for cervical carcinoma is pelvic relapse. Based on an extensive GOG clinico-pathologic study, Delgado et al. proposed separate intermediate- and high-risk groups as well as a “GOG score” (171). These risk group definitions have become generally accepted and incorporated into the design of both prospective trials and retrospective reports. Intermediate-risk criteria relate to tumor size, depth of stromal invasion, and LVSI; these are presented in Table 21.6. High-risk criteria include positive pelvic nodes, close or positive margins, and parametrial extension. Retrospective and prospective data suggest that adjuvant pelvic RT significantly improves pelvic control rates and DFS in patients with risk factors for recurrence who have completed radical surgery. The role of chemotherapy, particularly in high-risk patients, has also become established.

Intermediate Risk, Node Negative

The GOG conducted a phase 3 trial comparing RH alone with RH and postoperative pelvic RT in patients with node-negative stage IB cervical carcinomas, with prognostic features correlated with an intermediate risk of recurrence (GOG 92) (369). Eligibility criteria for this study are given in Table 21.6. There were 277 patients randomized after RH: 137 to pelvic RT, and 140 to no further therapy. RT consisted of 46 to 50.4 Gy to a whole pelvic field. No brachytherapy was used.

The RT arm had a 46% reduction in the risk of recurrence compared to the observation arm ($p = 0.007$) and a reduction in the risk of progression or death ($p = 0.009$). Particularly striking was the impact of postoperative RT in patients with adenocarcinoma or adenosquamous histologies: among this subset, only

Table 21.6 GOG 92 Eligibility Criteria

Capillary Lymphatic Space Involvement	Stromal Invasion	Tumor Size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2 cm
Positive	Superficial 1/3	≥5 cm
Negative	Deep or middle 1/3	≥4 cm

8.8% recurred in the RT arm, versus 44% in the observation arm. There was a strong trend toward improved survival in the RT arm, but this did not reach statistical significance ($p = 0.074$).

Several reasons have been suggested for the inability of this study to conclusively demonstrate a survival benefit in the presence of such a strong impact on recurrence rate. For example, a number of patients randomized to the RT arm did not receive RT and additional patients had protracted treatment or inadequate doses. However, the strongest factor is probably that the study was powered for its primary end point, which was disease-free interval, and was not sufficiently powered to demonstrate a survival benefit.

A retrospective series from the Netherlands looked at 51 patients with intermediate-risk, node-negative tumors. Of these, 34 received RT and 17 did not. The 5-year DFS was 86% in the group receiving RT, compared to 57% in the observation group (370). Ryu et al. retrospectively reviewed treatment outcomes of 172 cervical cancer patients with intermediate risk factors (371). A statistically significant difference was observed in 3-year recurrence-free survival rate among the no adjuvant treatment, postoperative RT, and postoperative CCRT groups (67.5%, 90.5%, and 97.5%, respectively; $p < 0.05$). A prospective trial to investigate whether postoperative CCRT improves survival of intermediate-risk patients compared with RT alone is now underway (GOG 263).

As mentioned previously, Yeo and colleagues used the Delgado GOG score (171) to tailor adjuvant RT in node-negative stage IB-IIA cervical carcinomas. Patients with GOG scores less than 40 were observed, while patients with scores of 40 to 120 and greater than 120 received small-field RT and standard pelvic RT, respectively. The 5-year DFS was 98.2%, and no grade 3 to 4 toxicities were observed (299).

Management of patients with stage IB2 tumors is somewhat controversial, in that some favor initial surgery followed by adjuvant chemo-RT, while others recommend curative intent chemo-RT, avoiding the use of 2 local modalities. This topic is discussed earlier in the chapter.

Node-Positive/High-Risk Patients

Metastatic disease in the pelvic lymph nodes is a poor prognostic sign, as this is associated with a higher risk of both local and distant recurrence. Pelvic nodal metastases may be associated with lesion size, deep stromal invasion, and involvement of capillary or lymphatic vascular spaces. Postoperative RT has been advocated for patients with pelvic nodal metastases, although results vary in different series. A practice-changing intergroup study was conducted by the Southwest Oncology Group (SWOG), GOG, and RTOG in women with FIGO stages IA2, IB, or IIA carcinoma of the cervix found to have metastatic disease in the pelvic lymph nodes, positive parametrial involvement, or positive surgical margins at time of primary RH, and total pelvic lymphadenectomy with confirmed negative paraaortic lymph nodes (142). One hundred twenty-seven patients were randomized between pelvic external beam radiation therapy with 5-FU infusion and cisplatin, and 116 were treated with pelvic external beam irradiation alone. The median follow-up for survivors was 43 months. The 3-year survival on the adjuvant cisplatin/5-FU and irradiation arm was 87%, compared with 77% on the pelvic irradiation arm. The difference is statistically significant. Chemotherapy appeared to reduce both pelvic and extrapelvic recurrences. Acute toxicities were more common in the chemo-therapy arm.

Largely as a result of this study, adjuvant chemo-RT is a standard treatment for these patients. It should be noted that, in this study, a combination of cisplatin 70 mg per m^2 and a 96-hour infusion of fluorouracil 1,000 mg per m^2 for 4 cycles were administered with the RT, which is different from the more commonly used chemotherapy regimen weekly 40 mg per m^2

cisplatin for 5 to 6 weeks. Additional long-term follow-up data are needed regarding late complications with this regimen.

Monk et al. reviewed the data from this randomized intergroup trial to assess the benefit of adjuvant therapies in definable subgroups of patients and to better understand histologic and clinical risk factors for recurrence (143). With a median follow-up of 5.2 years, the survival rates were 80% and 66% for the chemo-RT and RT alone groups, respectively. In a univariate analysis, the benefit of chemotherapy was not significant in patients with tumor ≤ 2 cm and 1 nodal metastasis. Although retrospective, a large and well-analyzed series of patients receiving postoperative RT was presented by Kim et al. (372). Death and recurrence rates increased with the number of positive lymph nodes. Five-year DFS was 89% if no nodes were positive, decreasing to 85%, 74%, and 56% in patients with 1, 2, 3, and 4 or more positive nodes, respectively. Similar data were reported by Uno et al. (373).

Close or Positive Margins/Parametrial Involvement

Eighty-five percent of patients accrued on the SWOG/GOG/RTOG Intergroup study were eligible based on pelvic node involvement. Only 5% of patients accrued to this intergroup study had positive margins, probably because of the reluctance of clinicians to put these patients on a trial that did not allow brachytherapy boosts. Nevertheless, patients with positive or close margins and/or parametrial involvement are also considered to be at high risk and, based on this randomized trial, should be considered for adjuvant chemoradiation. Other data might suggest that some patients, particularly close or positive margin patients, might be adequately treated with only postoperative RT.

Espace et al. retrospectively analyzed 51 patients with close vaginal surgical margins following RH (defined as ≤ 5 mm) (374). Twenty-three patients with negative nodes and close vaginal margins were studied. Although the 16 patients receiving RT had a preponderance of other risk factors, recurrence rates (12.5% vs. 85.7%) and 5-year survival rates (81.3% vs. 28.6%) significantly favored the group receiving adjuvant pelvic RT.

Kim et al. (375) described results for 38 patients receiving postoperative RT after RH for close surgical margins and/or metastatic pelvic lymph nodes. Patients with close surgical margins were treated with intracavitary vaginal ovoid insertions. Patients with positive margins fell into 2 groups: those with positive parametrial margins and those with involved vaginal margins. All 5 patients with involved parametrial margins treated with only cuff brachytherapy suffered local failures, compared with no pelvic failure in similarly treated patients with only vaginal margins positive for tumor.

Uno et al. analyzed 117 patients with parametrial invasion who had undergone radical surgery and received adjuvant RT. Of 51 node-negative patients, only 6 developed extrapelvic recurrence, and the 5-year OS and recurrence-free survivals were 89% and 83%, respectively. Patients with positive nodes fared much worse (373). Similarly, Kodama et al. found excellent outcomes among parametrium-positive patients who were treated with RH and adjuvant RT if lymph node metastasis and vaginal invasion were not present (approximately 90% 5-year survival) (108).

Radiation Therapy Dose and Technique

Vaginal intracavitary RT alone can be appropriate for patients with carcinoma *in situ* with minimally invasive carcinoma at the vaginal margin of resection as the only risk factor. Outpatient HDR brachytherapy is commonly employed because it prevents the prolonged immobilization required for LDR brachytherapy. A commonly utilized treatment regimen consists of 7 Gy per fraction prescribed at 0.5 cm depth; 3 weekly fractions are typically given. The upper 3 to 5 cm of the vagina should be targeted.

ABS recently developed consensus guidelines for adjuvant vaginal brachytherapy (376). Details of technical recommendation are described in the guidelines.

When external RT is used, patients generally should not receive more than 45 Gy to the whole pelvis. Doses up to 50.4 Gy are acceptable when treating fields that limit the amount of small bowel treated, whether this is done by using smaller fields or by IMRT techniques. Brachytherapy or small-field external beam boosts can be given, within tolerance, to increase dose to the central pelvis. The impact of concurrent chemotherapy on complication rates appears to be limited.

The use of IMRT with chemotherapy has been reported to maintain excellent pelvic control rates, with better acute tolerance and fewer chronic toxicities compared to conventional 4-field box RT (377).

CHEMOTHERAPY IN COMBINATIONS FOR LOCALIZED CARCINOMA OF THE CERVIX

Neoadjuvant Chemotherapy Followed by Radiotherapy

While surgery and radiation therapy are the primary treatment options for early-stage cervical cancer, NACT followed by radiotherapy has largely been abandoned in favor of concurrent chemoradiation for locally advanced cervical cancer (378–380). Concurrent chemoradiation therapy is supported by the results of 5 randomized clinical trials prompting the US National Cancer Institute's Clinical Alert in 1999, the long-term follow-up of 3 of these trials, and several meta-analyses including one published in 2010 (142,189,190,191,323,381–387). Nevertheless, a meta-analysis was performed on 18 randomized trials with 2,074 women receiving NACT followed by radiation compared to radiation alone (388). The heterogeneity of the various trials was a major drawback to the analysis. When separate analyses of groups of trials were performed, the 5-year survival improved when shorter chemotherapy cycles and higher dose intensity of chemotherapy were used, even though there was no statistically significant difference in survival when all trials were analyzed together (388). Given the lack of data from randomized trials comparing NACT followed by radiation to concurrent chemoradiation, NACT followed by radiation is not recommended in the routine care of women with localized carcinoma of the cervix outside of participation in a clinical trial.

Neoadjuvant Chemotherapy Followed by Surgery

Surgery and radiation therapy are the treatment options for early-stage cervical cancer and concurrent chemoradiation is the standard of care for locally advanced disease (378,379). Nonetheless, adjuvant chemotherapy (NACT) followed by surgery may have a role in this disease. It has been suggested that NACT may reduce tumor volume and decrease micrometastatic disease, improving resectability and survival, respectively (378,379). A meta-analysis of 5 trials and 872 patients evaluating NACT followed by surgery revealed a 14% absolute improvement in survival at 5 years when compared with radiotherapy alone (388). These results should be interpreted with caution, as the total number of patients was small and the 5 trials were heterogeneous. This heterogeneity consisted of patients treated with different stages of disease (early-stage versus locally advanced), administered different chemotherapeutic regimens, and given adjuvant pelvic radiotherapy following NACT and surgery (388).

A more recent meta-analysis of 6 trials and 1,072 patients revealed a statistically significant PFS but no statistically significant benefit in OS in patients treated with NACT followed by surgery when compared with patients treated with surgery alone (389). Moreover, many of the patients treated with NACT followed by surgery also received adjuvant radiotherapy.

While it remains unclear if NACT followed by surgery is better than surgery alone, 2 randomized Phase III trials are presently ongoing which will address whether NACT prior to surgery is comparable to chemoradiation in this disease. These trials, sponsored by the European Organization for Research and Treatment of Cancer (EORTC 55994, NCT00039338) and the Tata Memorial Hospital in Mumbai, India (NCT00193739), are comparing the overall and PFS of patients with Stage IB2 to IIB cervical cancer treated with neoadjuvant platinum-based chemotherapy followed by RH versus concurrent cisplatin-based chemoradiation (390,391). If, at surgery, women are found to have risk factors for recurrence, adjuvant radiotherapy or chemoradiotherapy is administered.

At this time, NACT followed by surgery is not recommended in the routine care of women with locally advanced cervical cancer outside of the special circumstances. Such circumstances may include sexually active women with bulky Stage IB–IIB cervical cancer interested in avoiding the long-term complications of radiation and wishing to undergo FSS. These women must have no risk factors for recurrence to avoid adjuvant radiation following NACT and surgery. In addition, NACT followed by surgery is appropriate care for women with locally advanced cervical cancer where radiation facilities are limited or not available.

Preoperative Chemoradiation in Advanced Disease

Concurrent chemoradiation is considered the standard of care for locally advanced cervical cancer (142,189,190,191,323,381–386). With 5-year OS of approximately 70% for women receiving this treatment (189), completion surgery following chemoradiation has been performed with the expectation of improving local control and increasing survival. In support of this concept, women with Stage IB2 tumors were randomized to hysterectomy versus no surgery following primary radiotherapy without chemotherapy (179). Results of this study revealed that adjuvant surgery provided no additional benefit in the 5-year OS of these women though the 5-year recurrence rate in the pelvic region was significantly lower (15% with surgery versus 27% without surgery). In addition, the 5-year OS was statistically significant in subset analyses in women with tumors less than 7 cm in size who underwent surgery following radiation therapy (179).

There have been many series published over the last several years reporting institutional experiences with chemoradiation followed by surgery (392–406). Comparison of these studies is difficult given their heterogeneity with respect to disease stage, chemotherapy regimen, external beam radiation dose, brachytherapy administration, and type of surgery. Nonetheless, the pelvic recurrence rate, DFS, and OS appear to be comparable to those of women receiving chemoradiation in several of these studies. Importantly, complications related to the genitourinary tract, gastrointestinal tract, and lymphatics may be increased especially in those women who underwent a radical rather than simple (extrafascial) hysterectomy (403,404). Recently, the results of the French GYNECO 02 randomized trial were published (407). Begun in 2003, this trial was closed prematurely due to poor accrual after only enrolling 61 of the anticipated 320 patients by 2006. Given the limited size, this study was underpowered. Nonetheless, women with Stage IB2–II disease with a clinical and radiographic complete response following chemoradiation were randomized to hysterectomy or no further treatment. Though this

study was underpowered given its limited size, there was no significant difference in the 3-year event-free or OS with a median follow-up of 3.8 years (407). Therefore, given these results and given that there appears to be a higher incidence of complications with surgery following chemoradiation, state of the art chemoradiation remains the standard of care in women with locally advanced cervical cancer (408).

Adjuvant Chemotherapy

The use of adjuvant chemotherapy for women with cervical cancer has been studied in both early-stage disease and locally advanced disease (409,410). In early-stage disease, adjuvant therapy with radiation, often in combination with chemotherapy, has been administered to women who are at intermediate or high risk for recurrence following surgery (409). In locally advanced disease with a 5-year OS of 66%, adjuvant chemotherapy after chemoradiation has been administered with the aim of decreasing distant metastases and increasing survival (410,193). Presently, the role of adjuvant chemotherapy in early stage and locally advanced cervical cancer is also being investigated in ongoing clinical trials.

In early-stage IA2, IB1, and IIA cervical cancer, a meta-analysis of 3 randomized controlled trials compared radiotherapy versus cisplatin-based chemoradiation after RH in women with at least 1 of the following risk factors for recurrence: (a) lymph node metastasis; (b) positive surgical margin; or (c) microscopic involvement of the parametrium; (d) deep stromal invasion (>10 mm); (e) LVSI; or (f) nonsquamous histology (411). Although these studies were small with limited follow-up, the results suggested a clinical benefit from the addition of chemotherapy to radiotherapy. Two of the trials in this meta-analysis compared chemoradiation versus radiotherapy alone in 325 women and found that adjuvant cisplatin-based chemotherapy significantly reduced the risk of death and disease progression. The trial by Peters et al. consisted of 268 of the 325 patients and has been considered the definitive trial for the use of cisplatin-based chemoradiation for patients with early-stage cervical cancer at high risk for recurrence (142).

There are currently 3 ongoing randomized trials further investigating the role of adjuvant chemotherapy in early-stage disease (412–414). In women with Stage I–IIA cervical cancer and intermediate risk of recurrence, a randomized controlled trial (Korean GOG 1008/GOG 0263, NCT 01101451) is comparing postoperative adjuvant chemoradiotherapy with radiation therapy alone after treatment with RH (412). In women with high risk of recurrence, the addition of adjuvant chemotherapy is now being explored in two randomized controlled trials. The first, NCT00980954 (Radiation Therapy Oncology Group/GOG 0724), is comparing adjuvant paclitaxel and carboplatin after chemoradiotherapy versus chemoradiation in women with Stage IA2, IB, or IIA disease (413). The second, NCT 00806117 (Sun Yat-sen University, China), is a 3-arm study comparing radiotherapy versus chemoradiation versus sequential therapy (paclitaxel and cisplatin, followed by radiation therapy, and then adjuvant paclitaxel and cisplatin) in women with Stage IB–IIA disease. Results of these prospective trials will help determine the benefit of adjuvant therapy following RH for women with early-stage disease at risk for recurrence (414).

Adjuvant chemotherapy has also been used following concurrent chemoradiation in locally advanced cervical cancer, although supporting data have been limited (142,193,415). Within the meta-analysis that reviewed 18 trials comparing chemoradiotherapy to radiotherapy alone for primary treatment of locally advanced carcinoma of the cervix, 2 trials examined the addition of chemotherapy following chemoradiotherapy and found a greater survival advantage in this group (142,193,415). Recently, Dueñas-González et al. completed a Phase III trial in women with Stage IIB–IVA carcinoma of the cervix comparing

the standard concurrent chemoradiation with cisplatin versus chemoradiotherapy with cisplatin and gemcitabine followed by adjuvant cisplatin and gemcitabine (416). Patients in both groups received brachytherapy following chemoradiotherapy. Survival outcomes were improved in the adjuvant chemotherapy group and the increased toxicity was clinically manageable.

There are currently 2 ongoing trials further investigating the role of adjuvant chemotherapy in locally advanced cervical cancer. An international collaborative Phase III randomized trial (The Outback Trial, ANZGOG 0902, NCT 01414608) is examining the role of adjuvant carboplatin and paclitaxel chemotherapy following chemoradiotherapy (417). In this multicenter study, patients are stratified by stage (IB/IIA vs. IIB vs. IIIB/IVA), pelvic or common iliac nodal involvement, requirement for extended-field radiotherapy, age, and hospital/site. Patients with paraaortic lymph nodes above the common iliac nodes are excluded. However, a Phase I trial (GOG 9926, NCT 01295502) establishing the maximum tolerated dose and dose-limiting toxicities of adjuvant carboplatin (AUC 4 vs. 5) and paclitaxel chemotherapy following concurrent cisplatin-based chemoradiotherapy, includes women with Stage IB–IVA cervical cancer with positive paraaortic lymph nodes (418).

In summary, adjuvant chemotherapy has a role both in early-stage disease and locally advanced disease. Current clinical trials of adjuvant chemoradiation following radical surgery in early-stage disease and of adjuvant chemotherapy following chemoradiation in locally advanced disease will define its role in cervical cancer.

TREATMENT OF RECURRENT CARCINOMA OF THE CERVIX

General Considerations

The main cause of death among women with cervical cancer is uncontrolled disease in the pelvis. However, a subset of patients with recurrent disease confined to the pelvis following definitive therapy, whether that therapy is surgery or RT, are potentially curable. Treatment selection and the likelihood of success are functions of the primary therapy, extent of disease at presentation, site of recurrence, local extent of the recurrence, disease-free interval, performance status, and comorbidities.

When curative intent salvage treatment is contemplated, the local recurrence should be biopsy proven, and the patient should be evaluated for regional and distant metastasis by physical examination and imaging. A clinical diagnosis of pelvic sidewall involvement can almost always be made in the presence of a triad of sciatic pain, leg edema, and hydronephrosis. PET scanning may be the most accurate test in terms of assessing metastasis prior to embarking on local salvage therapy.

Generally, patients with pelvic or regional recurrences after definitive surgery alone are managed with RT or chemoradiation. Salvage options for patients with central recurrence after definitive or adjuvant RT are limited to radical, usually exenterative, surgery, and in selected patients, re-irradiation using interstitial radiation implants or highly conformal EBRT or IMRT. Chemotherapy-responsive patients can obtain meaningful palliation in many cases.

Salvage Treatment After Definitive Radiation Therapy: Interstitial Re-irradiation

Recurrent cervical carcinoma following definitive RT within previously irradiated areas presents a difficult management problem.

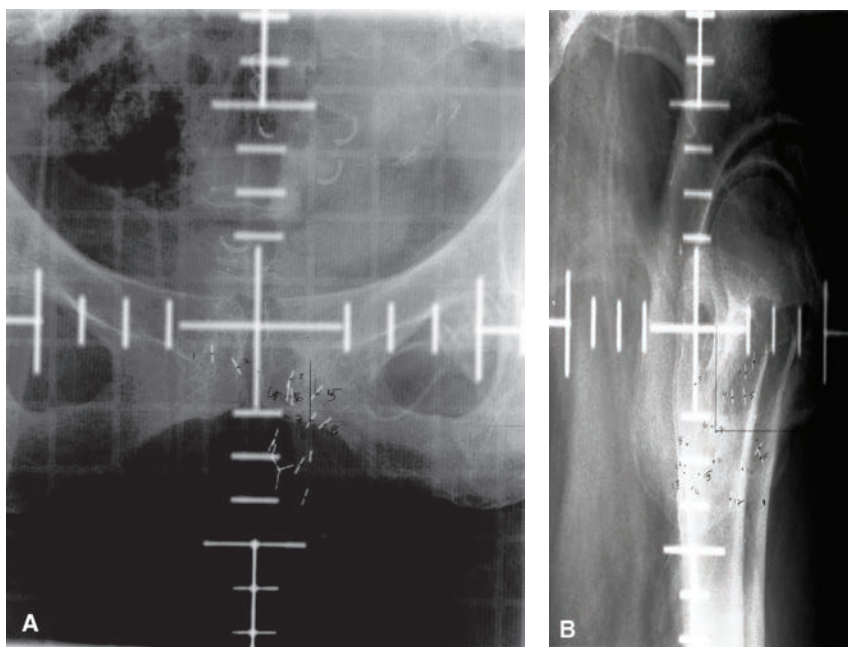


FIGURE 21.23. **A and B:** Anterior-posterior and lateral views of a permanent interstitial implant done with Cs^{131} for a patient with locally recurrent cervical cancer several years after previous RT.

Although salvage surgery, usually exenterative, can be offered to patients with limited, centrally recurrent lesions if age and general condition permit, radical surgery following RT is accompanied by operative mortality in some, severe morbidity in many, and substantial loss of structure and function in all. Therefore, the applicability of salvage surgery is limited by physician and patient acceptance, as well as by clinical parameters. Even among patients meeting rigorous preoperative criteria, salvage surgery will be aborted in about one-fourth of patients.

Previously irradiated tissues do not have the same tolerance as unirradiated tissues. Therefore, severe late effects have been observed in the re-irradiation setting, particularly in older series that predominantly used external beam techniques in poorly selected patients. More recently, evidence has been presented to suggest that re-irradiation can be curative in a significant percentage of patients with small-volume central recurrences, particularly when there has been a long disease-free interval since the earlier diagnosis and treatment.

Randall et al., in a series of 13 patients, observed a 69% complete response rate and a 46% NED (no evidence of disease) rate with a minimum 2-year follow-up, and median follow-up of 59 months (419). Interstitial re-irradiation (IRI) doses of 30 to 55 Gy were employed, with low-dose-rate permanent and temporary implants. Patients with squamous histology did significantly better than patients with adenocarcinoma histology. Other predictors for improved outcomes included smaller tumor volumes, higher implant doses, and vaginal wall/suburethra versus vaginal cuff location. Late morbidity was limited to one recto-vaginal fistula in a patient who also had recurrent tumor.

Brabham and Cardenes reported the Indiana University experience of 19 patients who underwent interstitial re-irradiation with gold-198 as salvage treatment for recurrent gynecologic cancers after previous RT. With a median follow-up of nearly 2 years, the complete response rate was 95% and the local control was 63%. Over half the patients were alive with NED at the time of the analysis. Only one self-limited toxicity was observed. The control rate did not seem to be affected by histology or tumor volume (420).

Although gold-198 has excellent properties as a permanent interstitial isotope for re-irradiation, its major drawback is its high energy, resulting in some radiation exposure for staff. An alternative permanent seed isotope, Cesium-131, has recently been introduced. This isotope has a short half-life (9.69 days) and low mean

energy (30 keV). It has been shown that similar dose distributions are achievable with both isotopes, although Cs^{131} results in significantly enhanced radiation safety (421) (Fig. 21.23).

Jhingran has described the use of external beam IMRT in the re-irradiation setting (291). In particular, IMRT can treat pelvic recurrences that cannot be treated with brachytherapy, because of size, location, or other factors.

Compared to exenterative surgery, re-irradiation is better tolerated acutely, has little operative mortality, and often preserves structure and function of pelvic organs. When contemplating re-irradiation, it is important to analyze the techniques used in the initial treatment (beam energy, volume, doses delivered with external or intracavitary irradiation). The period of time between the 2 treatments must be taken into consideration.

Re-irradiation, in particular IRI, is under-utilized in the management of locally recurrent cervical cancer. As chemotherapy does not have curative potential and many patients will not be candidates for exenterative surgery or will refuse such surgery, re-irradiation, in many cases, will be the only feasible curative intent therapy. Patient selection and careful brachytherapy technique are crucial to successful re-irradiation.

Recurrence in the Paraortic Chain

Although unusual, recurrences limited to the PANL region are reported following primary surgery or RT. Grigsby et al. reported a 100% salvage rate in patients with isolated paraortic recurrences if the recurrences were asymptomatic and discovered by imaging follow-up, and received full-dose (>45 Gy) salvage RT combined with chemotherapy (422). This observation was confirmed by the experience reported by Kim et al. (423). These investigators treated 12 patients with isolated paraortic failures following RT with concurrent chemotherapy (mostly paclitaxel) and hyperfractionated RT. In patients who relapsed within 24 months of their initial treatment, the median survival following attempted salvage was 13 months. In contrast, patients having a disease-free interval greater than 24 months had a median survival of 45 months with this therapy. Niibe et al. conducted a multi-institutional retrospective analysis of 84 patients with isolated paraortic node recurrences treated with RT. The 3- and 5-year OS rates were 50% and 31%, respectively (424). A significant difference in 3-year OS was observed between symptom-positive and symptom-negative

patients, 28% versus 56%, respectively ($p = 0.018$). Three-year OS rates were 43% for patients treated with ≤ 50 Gy and 58% for those with ≥ 51 Gy ($p = 0.07$).

Salvage Treatment After Definitive Radiation Therapy: Radical Surgery

Pelvic Exenteration

Advances in perioperative and postoperative care and better techniques of pelvic, urinary, and GI reconstruction have led to much improved outcomes and enhanced quality of life compared to early experiences with pelvic exenteration (PE). Survival rates have increased from 20% to about 60% with an average of 40% to 50% 5-year survival in reported series of patients completing the procedure.

Despite these advances, PE is still a very morbid operation with acute and late complications reported as high as 50% to 60% and a mortality rate of 5% to 7%. The procedure is most commonly used in patients with recurrent central pelvic disease after treatment with pelvic RT. Historically, one-third of patients explored for PE will have the procedure abandoned. In some cases patients with stage IVA disease may be offered primary PE, although modern chemoradiotherapy is probably preferred.

In patients undergoing PE, Marnitz et al. noted the importance of margin status: 5-year survival was 55% with negative margins compared to 10% if margins were positive (425). Given this fact and the potential morbidity and mortality from the procedure, proper patient selection requires that all efforts be made to assure that there is no site of metastatic disease and the isolated central recurrence can be resected with negative margins. Additional negative prognostic factors include disease-free interval less than 1 year, size of recurrence greater than 3 cm, lymphatic spread, and parametrial and sidewall involvement. Patients with positive nodes have a survival rate of 20% or less. The presence of grossly positive lymph nodes during exploration is a poor indicator for survival and should be considered a contraindication to exenteration. The use of PET/CT technology may assist in detecting occult metastatic disease prior to consideration of TPE (286).

Berek et al. reported 75 patients older than 45 years who underwent PE at a single institution. The operative time averaged 7.76 hours, the mean estimated blood loss was 2.5 liters, and the median length of stay was 23 days. Morbidities included intestinal fistulae in 15%, urinary fistulae in 8%, early bowel obstruction in 11%, and late bowel obstruction in 22%. When a J-pouch was used for colonic re-anastomosis, there was no reported fistula. Survival for patients with cervical and vaginal cancers was 73% at 1 year, 57% at year 3, and 54% at 5 years (426).

A recently published large series with long follow-up found 1-, 2-, and 4-year survivals to be 64%, 44%, and 34%, respectively (427). As in most series, the 54 patients in this series included only those patients who actually had an exenteration, excluding those in whom it was attempted but not performed. A larger series of 106 patients was reported from Italy. With a median follow-up of less than 2 years, the OS for the cervical cancer subgroup was 52%. The overall morbidity rate was 66%, with nearly half of patients experiencing early and late complications. Among the complications, 70% were urinary tract and 25% were gastrointestinal, including bowel obstructions and fistulae (428). It appears that overweight and obese patients experience longer operative times and higher rates of wound separation than patients with normal weight, but the overall outcomes appear equivalent to normal-weight women (429).

Pelvic Reconstruction

In 1950, Bricker described a novel approach to diversion of urinary flow that involved isolating a segment of ileum, implanting

the ureters into this segment, and bringing an open end to the abdominal wall as a separate urostomy (430). This technique was a major advancement and significantly reduced complications compared to the wet colostomy (reimplantation of ureters in the colostomy that diverts the fecal stream). This form of urinary conduit is incontinent, where the urine drains continuously to an external reservoir. The other option is to create an internal reservoir using bowel wall with a continent mechanism that allows for self-catheterization, which negates the need for an ostomy bag and affords more control to a motivated patient. The most common complications of continent reservoirs are acute and chronic pyelonephritis, ureteral stricture, urinary leak, fistula, stone formation, and, rarely, renal failure.

The choice between continent and incontinent pouches depends most heavily on the surgeon's preference and the status of the distal ileum after RT. Penalver et al. reported complications in a series of patients undergoing construction of a Miami pouch. The early complication rate in 66 patients was 53% and included 10 ureteral stricture/obstructions, 4 anastomotic leaks, and 4 fistulae. An additional 5 had difficulty with catheterization, and 10 had pyelonephritis. Most complications were managed conservatively with antibiotics, percutaneous drainage, and nephrostomies. The operative mortality was 9%. The late complication rate was 37%. Out of 25 patients, 6 had strictures, 8 were incontinent, 7 had difficulty with catheterization, and 4 developed urinary stones. Again, most complications were managed conservatively (431). In a similar series from M. D. Anderson Cancer Center, 65% had postoperative complications related to the Miami pouch. Most complications were managed conservatively, and 90% retained normal continent conduit function (432).

Ungar and Palfalvi reported 29 patients who underwent orthotopic urinary reconstruction using ileocecal ascending colon reservoirs (the Budapest pouch). Although 77% of patients were able to void voluntarily without the need for self-catheterization, 23% to 47% had some incontinence (433). This is an attractive option as patients can potentially be free of any ostomies. However, only a select group of patients are candidates for these procedures.

The other component of pelvic reconstruction following PE is creation of a neovagina. Formation of a neovagina is an important component of reconstruction in several respects. For example, it fills the pelvis with well-perfused tissue and can significantly decrease the rate of pelvic infection and fistula formation. It also may restore some sense of normalcy in patients who are able to resume sexual activity after PE. Many options are available for construction of a neovagina. These include the following flaps: gracilis myocutaneous, anterolateral thigh fasciocutaneous, bulbocavernosus myocutaneous, transverse rectus abdominis musculoperitoneal (TRAMP) or myocutaneous (TRAM), vertical rectus abdominis musculocutaneous (VRAM), femoris myocutaneous, tensor fasciae latae myocutaneous, inferior gluteal, and omental J-flap. Portions of sigmoid colon have also been used. Myocutaneous flaps are favored due to better blood supply, ease of procedure, and functionality.

McCraw et al. first described the use of gracilis muscle for vaginal reconstruction (434). Ratliff et al. evaluated sexual adjustment in these patients and found that 52.5% never resumed sexual activity even though 70% were thought to have adequate and functional neovagina length on examination. Self-consciousness about urostomy and colostomy was the most common reason cited for avoiding sexual activity (435). Soper et al. reported on a "short gracilis" flap based on the terminal branches of the obturator artery and found no difference between the traditional and "short gracilis" flaps (436).

O'Connell et al. reported a 100% success rate with no fistula formation, bowel obstruction, or pelvic infection using VRAM flaps. Almost 50% of women reported sexual activity after VRAM (437). Soper et al. reported that 62% of women reported sexual activity within 12 months after VRAM or TRAM flap

reconstruction, concluding that both techniques give similar results and complication rates (438). Previous ligation of the inferior epigastric artery is an absolute contraindication of use of rectus flaps.

Sood et al. reported a modification to the VRAM using a smaller flap size anteriorly with a full-thickness skin graft placed posteriorly. One of 18 patients had a partial flap loss that resolved with conservative management, and 8 of 18 remained sexually active (439). This technique allows for a smaller abdominal wall defect with minimal compromise of the neovagina. Soper et al. compared gracilis muscle versus rectus abdominis flaps for vaginal reconstruction. Flap-specific complications and flap loss were significantly greater in gracilis muscle flaps. The authors have adopted rectus abdominis flaps as their preferred choice for vaginal reconstruction (440).

Re-anastomosis following rectosigmoid resection depends on many factors and is an option in patients undergoing suprallevator PE. Factors associated with anastomotic integrity include the length of remaining rectum/anus (<4 cm having a higher incidence of leaks versus >7 cm), blood supply to the region, and tension on the anastomosis. The use of low rectal anastomosis is controversial. Mirhashemi et al. found a 35% versus 7.5% rate of fistula formation or anastomotic breakdown in patients with previous RT compared to those who were radiation naïve. Protective colostomy was not associated with an improved outcome (441). Husain et al. reported a 54% anastomotic leak after low rectal anastomosis (442). This may be decreased by using a J-pouch instead of an end-to-end re-anastomosis (426). However, some patients have difficulty emptying the pouch, particularly with shorter pouch lengths.

No method of pelvic reconstruction is clearly superior to others or appropriate in all cases. The surgeon has many choices and should individualize according to each patient.

Radical Hysterectomy

Patients with very small central recurrences (<2 cm) after RT may be candidates for a less radical approach than PE, specifically RH. Maneo et al. evaluated the role of RH in patients with persistent or recurrent disease in 34 patients. They reported grade 3 to 4 toxicities in 44%, including 5 who developed fistulae. The overall 5-year survival was 49%, and 59% recurred with an average time to recurrence of 37 months. Patients with smaller tumors and lack of involvement of parametrium or vagina had better outcomes (443). Coleman et al. studied 50 patients treated with RH for persistent or recurrent central disease after RT. All patients with positive nodes died within 13 months. Severe toxicities occurred in 42%, and 28% developed either a GI or GU fistula. An additional 22% had ureteral injuries with 20% having severe long-term bladder dysfunction. The 5- and 10-year survival rates were 72% and 60%, respectively. Tumor size less than 2 cm was associated with a significantly greater survival compared to larger tumors. Overall recurrence rate was 48% (444).

RH may be a reasonable option for selected patients with persistent or recurrent central disease less than 2 cm with no extension to the parametrium or vagina. However, significant morbidity rates are relatively high.

Salvage Treatment After Previous Surgery—Definitive RT or Chemoradiation

Patients with pelvic recurrences after surgery alone are potentially curable. In particular, when recurrences are small and limited to the vagina and paravaginal tissues, salvage rates can be quite favorable, approaching 70% (445,446).

Concurrent chemotherapy with RT has proven beneficial in locally advanced cervical cancer. Several studies also suggest

a possible benefit in patients with recurrent disease. Grigsby reported a prospective trial of 22 patients with pelvic recurrences of cervical cancer following hysterectomy who received concurrent RT with 5-FU and cisplatin chemotherapy (447). None had received prior RT. The 10- and 15-year OS rates were 35%. Acute toxicity was limited; however, late toxicity was significant in some survivors, leading the author to recommend consideration of other chemotherapy regimens or RT alone.

In RT-naïve patients, pelvic RT of 40 to 50 Gy to the primary tumor and regional lymphatics is indicated. Inguinofemoral lymph node regions should be included in patients with involvement of the distal third of the vagina. The entire vagina should be treated in most patients with vaginal recurrences following hysterectomy. A vaginal dose of 60 to 65 Gy from external RT, with or without brachytherapy, is desirable. The gross tumor volume should receive additional radiation; doses of 15 to 30 Gy are administered with single, double-plane, or volume implants, or with intensity-modulated external RT. High-dose-rate brachytherapy techniques are also possible with appropriate dose modifications. Kotsuma et al. reported with the use of image-guided HDR interstitial brachytherapy for postoperative recurrences of 15 uterine cancers (including 9 cervical cancers) (448). The 3-year local control and survival rates were 78% and 77%, respectively. Two of 7 patients treated with a combination of EBRT and brachytherapy developed late complications.

Salvage Treatment—Intraoperative Radiation Therapy

Patients with microscopically positive or close margins have a poor prognosis after salvage surgery. Intraoperative RT (IORT) has been used in this situation to potentially sterilize residual disease after tumor debulking. IORT allows direct visualization of the target volume, and displacement and/or shielding of the surrounding normal tissues. The IORT dose is generally limited because of prior RT, proximity of critical normal structures, and the single fraction nature of the treatment.

IORT has been used for treatment of locally advanced and recurrent carcinoma of the cervix. Most of this experience is based on the treatment of isolated central and nodal recurrences, generally amenable to surgical excision. Limitations in evaluating IORT include small patient numbers, short follow-up, and widely varying patient selection criteria. The available data seem to indicate that IORT, although feasible, does not dramatically improve prognosis and is associated with significant incidence of long-term complications. Patients with limited central recurrences who are candidates for pelvic exenteration but are found to have unfavorable prognostic factors for local recurrence, such as close positive margins, LVSI, or perineural invasion, may benefit from IORT (449) or intraoperative interstitial brachytherapy (450).

SALVAGE TREATMENT – ROLE OF CHEMOTHERAPY AND TARGETED AGENTS

At this time, the role of chemotherapy and targeted agents in metastatic cervical cancer is palliative. While it is known that salvage treatment may prolong PFS, there are no randomized trials that compare systemic therapy with best supportive care and demonstrate that systemic therapy improves OS. However, given that systemic treatment does prolong PFS and may improve quality of life, women with good performance status should be offered further treatment.

There are several chemotherapeutic agents that are active as single agents in metastatic cervical cancer (367,368,451,452,453).

Over the past 3 decades, cisplatin has been the mainstay for treatment of metastatic disease with response rates of 18% to 38% depending on the dose and schedule, and with time to progression and median survival of less than 3 and less than 7 months, respectively (reviewed in 451,453). However, the frequent use of cisplatin as concurrent treatment with radiation in patients with locally advanced disease or as adjuvant treatment following radiation or surgery in patients at high risk of recurrence has contributed to a lower response rate when used in the salvage setting and suggested the need for nonplatinum agents (454,455). Other chemotherapeutic agents including capecitabine, carboplatin, docetaxel, 5-fluorouracil, gemcitabine, ifosfamide, irinotecan, oxaliplatin, mitomycin C, paclitaxel, pegylated liposomal doxorubicin, pemetrexed, topotecan, and vinorelbine have shown activity as single agents without a significant increase in objective response rates, and may be used in this setting (367,368,451–453).

To further evaluate the role of chemotherapy in metastatic disease, combination chemotherapy regimens have been investigated to improve the response rate and OS. In 2007, Hirte et al. published a systematic review identifying 15 randomized controlled trials of chemotherapy for women with recurrent, metastatic, or persistent cervical cancer (456). The data were unable to be pooled for a meta-analysis because of the clinical heterogeneity between trials, especially regarding the use of cisplatin in the primary treatment regimen. Outcomes were reviewed from 7 trials comparing single-agent versus combination cisplatin-based chemotherapy, 2 trials comparing combination cisplatin-based chemotherapy with nonplatinum agents, 3 trials evaluating regimens of other platinum-containing agents, and 3 trials evaluating nonplatinum agents. Their review showed that overall combination cisplatin-based chemotherapy was more effective than single-agent cisplatin. In particular, a Phase II randomized study demonstrated a survival benefit of cisplatin and topotecan over single-agent cisplatin in a population in which 57% of patients had previously been treated with cisplatin-based chemoradiation (455). Although there was increased toxicity with this regimen, it was not associated with poorer quality of life. Other reviews confirmed this analysis demonstrating a response advantage or improvement in PFS with combination chemotherapy when compared to single-agent cisplatin chemotherapy (367,368,451–453). Interestingly, Moore pooled data from 3 Phase III studies comparing single-agent cisplatin to cisplatin in combination with ifosfamide (GOG 110), paclitaxel (GOG 169), or topotecan (GOG 179) and performed a multivariate analysis to identify factors predictive of response and survival (453). The following 5 factors were identified as independently predictive of poor response: African American race, performance status greater than 0, pelvic disease, prior treatment with radiosensitizer, recurrence ≤ 1 year. Risk groups were determined according to the number of risk factors present (0 to 1 factors for low risk, 2 to 3 factors for mid-risk, 4 to 5 factors for high risk). Patients in the high risk groups had a predicted treatment response of only 13% and median PFS and OS of 2.8 and 5.5 months, respectively. The model was externally validated using the database on GOG 149, a study comparing cisplatin and ifosfamide with or without bleomycin (457). Nonetheless, they recommend further validation and pointed to a current Phase III GOG study (GOG 0240 NCT 00803062) as a source for this validation (458).

In 2007, the GOG established cisplatin and paclitaxel as the reference combination chemotherapeutic regimen for their future trials in the treatment of women with Stage IVB, recurrent, or persistent cervical cancer when they closed their Phase III randomized study (GOG 204, NCT 00064077) comparing cisplatin combined with either paclitaxel, topotecan, vinorelbine or gemcitabine to patient entry (459). After enrollment of 513 patients, a planned interim analysis by the Data Monitoring Committee recommended early closure for futility. The response rates were 29.1%, 25.9%, 22.3%, and 23.4% for the cisplatin

combinations with paclitaxel, vinorelbine, gemcitabine, and topotecan, respectively. The 3 cisplatin combinations were not superior to the control arm of cisplatin and paclitaxel with respect to OS, and there was a positive trend favoring the cisplatin and paclitaxel arm not only for response rate but also for progression-free, and OS (459). There was no difference in quality-of-life (QoL) outcomes between the cisplatin and paclitaxel arm and the other 3 combinations during treatment (460). While several retrospective studies have shown activity of carboplatin and paclitaxel, the results of the Japan Clinical Oncology Group's prospective, randomized Phase III study of cisplatin and paclitaxel versus carboplatin and paclitaxel (JCOG0505, NCT 00295789) presented at the American Society of Clinical Oncology Annual Meeting in 2012 and verified the equivalence of these regimens (461–466).

In this trial, paclitaxel 135 mg per m² over 24 hours and cisplatin 50 mg per m² were administered intravenously on days 1 and 2, respectively, as given in GOG 204, and compared with paclitaxel 175 mg per m² over 3 hr and carboplatin AUC 5, both administered intravenously on day 1. With a median follow-up of 17.6 months, this trial confirmed the noninferiority of carboplatin and paclitaxel to cisplatin and paclitaxel with respect to median OS (17.5 vs. 18.3 months, HR 0.994, noninferiority one-sided $p = 0.032$) and confirmed its tolerability and feasibility in the outpatient setting. In a subset analysis, this trial demonstrated that the combination of carboplatin and paclitaxel was particularly preferable to the combination of cisplatin and paclitaxel in patients with prior platinum-free intervals of ≥ 6 months.

The need to increase the response rate and OS in metastatic cervical cancer, particularly in women previously treated with platinum-based chemoradiation in the locally advanced cancer setting, has led to the investigation of nonplatinum doublets (467–469). Several Phase II trials nonplatinum doublet trials including paclitaxel in combination with topotecan and docetaxel in combination with gemcitabine have shown the response rates of 54% (7/13) and 28% (5/18), respectively (467,469). The results of Germany's Arbeitsgemeinschaft Gynäkologische Onkologie study (AGO-Zervix-1, NCT 01405235) randomized Phase III study investigating paclitaxel and topotecan versus cisplatin and topotecan are pending (470).

Several classes of targeted agents are also being investigated in metastatic cervical cancer (367,368,471,472). Epidermal growth factor receptor (EGFR) inhibitors have been of significant interest, given the ubiquitous presence of EGFR and its association with a negative prognosis in this disease (reviewed in 367,473). The EGFR inhibitor, gefitinib, was found to have minimal activity with only stable disease in 20% (6/28) of patients (474). Furthermore, the results of Phase II trials with other EGFR inhibitors, cetuximab and erlotinib, administered as single agents, revealed a PFS of 6 months or greater in 14.2% (5/35) and 3.6% (1/28) of patients, respectively, and again there were no responses (475,476). Even more disappointing was the response rate of 11.6% (8/69) with the combination of cetuximab with cisplatin (477). Though the response rate of cetuximab, topotecan, and cisplatin was 32% (6/19), the study was stopped prematurely due to excessive toxicity, including 3 treatment-related deaths (478). The results of the randomized Phase II study, Mito Cervix-2 (NCT 00997009), assessing the role of cetuximab with paclitaxel and carboplatin, are pending (479).

Anti-angiogenesis agents have also been investigated as targeted agents and have shown more promise than the EGFR inhibitors in metastatic or persistent cervical cancer. Single-agent bevacizumab demonstrated activity in this setting with a response rate of 10.9% (5/46) and a PFS of 6 months or greater in 23.9% of patients (480). Consistent with the activity of bevacizumab, the National Institute of Canada's Clinical Trials Group study with sunitinib (NCT 00389974), the multitargeted receptor tyrosine kinase inhibitor (TKI) of VEGF, platelet-derived growth factor receptor (PDGFR), c-kit, and FLT3, had a PFS of 6 months

or greater in 31.6% (6/19) of patients but had no objective responses. However, 5 patients (4 on-study and 1 3.5 months following discontinuation of study) developed a fistula (481). All 5 patients had received previous chemoradiation and the fistula occurred in the previously radiated field. A randomized Phase II study of lapatinib, the dual TKI of EGFR and HER2, versus pazopanib, the multitargeted receptor TKI of VEGF, PDGFR, and the c-kit, noted a response rate of 5.1% (4/78) with lapatinib and 9.5% (7/74) with pazopanib (482,483). Treatment with lapatinib in combination with pazopanib was the third treatment arm in this randomized study, but was discontinued due to an interim analysis which demonstrated increased toxicity and similar efficacy to lapatinib. Presently, a Phase II trial with brivanib, a potent dual inhibitor of VEGF and fibroblast growth factor receptor, is actively recruiting patients (484). In addition, a randomized Phase II study with cediranib, a VEGF inhibitor, in combination with carboplatin and paclitaxel is also actively recruiting patients (485).

The PARP inhibitors are another class of targeted agents actively being investigated in this disease. There are no single agent studies reported. Combination therapy trials with the PARP inhibitors, veliparib, and topotecan (NCT 01266447) or paclitaxel and carboplatin (NCT 01281852) and olaparib with carboplatin (NCT 01237067) are ongoing (486–488).

Utilizing platinum and nonplatinum doublets together with a targeted agent, the current Phase III randomized trial, GOG 240 (NCT 00803062) employed a 2×2 factorial design to investigate the doublets cisplatin and paclitaxel versus topotecan and paclitaxel, with or without bevacizumab. Interim analysis performed by the Data Safety Monitoring Board concluded that topotecan was not a superior substitute for cisplatin with paclitaxel chemotherapy by OS in this group. This study is closed to accrual at this time, and the final results concerning the tolerability and efficacy of these regimens are pending (458). Given the poor prognosis of patients with metastatic or recurrent cervical cancer and the limited efficacy with the presently available treatments, it is anticipated that randomized studies such as GOG 240 which include platinum and nonplatinum doublets with targeted agents will improve the response rate, PFS, and OS in women with this disease.

COMPLICATIONS AND SEQUELAE OF TREATMENT

Surgery Related

The most common complications with conization include infection, bleeding, damage to surrounding structures (bladder, rectum, vagina), and cervical incompetence with predisposition to preterm labor in future pregnancies. RH and lymphadenectomy may result in additional and somewhat unique complications. Urologic complications such as ureteral injuries and vesicovaginal or ureterovaginal fistulas are reported in 1% to 2% of cases, and this can be increased in patients requiring postoperative RT. Most vesicovaginal fistulas can be diagnosed with a voiding cystogram or clinically by infusion of a diluted methylene blue solution into the bladder and observation of leakage into the vaginal vault (commonly known as the “tampon test”). The majority will heal spontaneously with continuous bladder drainage for 6 to 8 weeks and treatment of any underlying infection. Ureterovaginal fistulas may be more difficult to diagnose. An IVP or CT scan may be indicated and demonstrate such a fistula in a patient with symptoms suggestive of a urinary fistula with a negative clinical exam or cystogram. Conservative management can include ureteral stenting and drainage of the urinary system via percutaneous nephrostomy, which may lead to healing of the fistula. Repeat imaging should be done prior to removal of

the stent to assure ureteral healing. Repair of a persistent vesicovaginal fistula can be attempted vaginally, depending on the site of injury. The fistulous tract is excised and repaired in multiple layers, followed by continuous bladder drainage and repeat cystogram to ensure surgical success. Ureteral fistulas that do not resolve with conservative management may require reimplantation of the ureter into the bladder (ureteroneocystostomy). Fistulas that occur following pelvic RT are less likely to heal with conservative management and may require earlier surgical treatment. As surgical repair after RT has a lower success rate, urinary diversion may be required as definitive treatment.

Averette et al. published their experience with RH in 978 patients over 25 years. The surgical mortality was 1.4%, and the urinary fistula rate was 1.4% (489). Artman et al. published their experience with RH in 275 patients over 21 years. The average blood loss was 1,800 cc. The urinary fistula rate was 2.6%, and the surgical mortality rate was 0.7% (490). Lee et al. reported a fistula rate of 2.4% and an operative mortality of 0.4% in a series of 954 patients. Lymphocyst formation is about 1.6% and the lymphedema rate is about 3.6% following PLD (491).

Located over the sacral promontory, the hypogastric plexus contains sympathetic fibers that fuse with parasympathetic fibers located in the parametrium and allows for bladder contraction and compliance. Surgical disruption of this plexus results in bladder atony and dysfunction in about 5% of patients, possibly requiring continuous or intermittent drainage for a few weeks (283).

Ralph et al. performed urologic evaluations in 40 patients at 2 weeks, 6 months, and 1 year after RH. At 2 weeks all had impaired bladder sensation and 68% had residual urine after voiding. At 1 year, 63% had impaired bladder sensation. Bladder capacity was lowest at 2 weeks (180 mL) and returned to baseline between 6 to 12 months. By 1 year, patients had residual urine after voiding. However, 62% had abnormal compliance and 85% used abdominal straining to void (492).

Rectal function can also be impacted by RH. Changes include altered relaxation of the internal sphincter, increased distention required to trigger relaxation, chronic straining, constipation, and decreased rectal sensation. Rectal dysfunction is frequently reported.

Levrant et al. evaluated the effects of obesity and age on RH outcomes. They reported no difference in survival or complications in obese versus nonobese patients. Similarly, age did not affect long-term complications and survival. However, patients older than 65 did have a higher incidence of postoperative ileus (493). Cohn et al. reported on 48 obese women (median body mass index [BMI] of 36 kg/m²) who underwent RH. Median blood loss was 800 cc, and the median number of lymph nodes obtained was 26. Margins were uninvolved in 98%. This study also confirmed the safety and efficacy of RH in selected obese patients (494).

Methods to decrease postoperative complications following RH have been suggested. Franchi et al. evaluated the role of pelvic drains following RH with LND in a randomized trial of pelvic drainage versus none. No difference was noted in lymphocyst formation or postoperative complications, suggesting that drains can be safely omitted following RH (495). The omental J-flap has been used in gynecologic oncology for pelvic reconstruction. Patsner and Hackett evaluated 140 patients who had an omental J-flap placed following RH. No urinary complications or infections were noted, even in patients who received postoperative RT (496). These data suggest that an omental J-flap may decrease postoperative complication rate, although there was no control arm for comparison.

Radiation Therapy-Related

Acute effects during external pelvic RT most typically include diarrhea and bladder irritation. These are usually self-limited

and can be managed effectively with conservative measures. Toita et al. reported the incidence of acute toxicity for patients entered in the prospective multi-institutional study (295). The only severe toxicities observed were 3 patients who experienced grade 3 leukopenia and 1 with grade 3 diarrhea. Physicians should keep in mind the risk of reduced locoregional control in patients who experience treatment delay caused by acute toxicity. Low-dose-rate (and pulsed LDR) implants require hospitalization and bed rest. At typical dose rates of 50 to 60 cGy per hour, implants typically last 2 to 3 days. During this time, there is the potential for acute problems related to or during the hospital stay. Jhingran and Eifel reviewed 7,662 implants in 4,043 patients, finding fatal or life-threatening complications to be exceptionally rare (497).

Commonly reported late sequelae of pelvic RT involve the rectosigmoid, small intestine, genitourinary tract, and vagina. Rarer sequelae include lymphedema, lumbosacral plexopathy, and pelvic insufficiency fractures. In contrast to acute effects, late sequelae are often permanent or require some intervention to improve. These complications usually occur within the first 3 years after RT. There is approximately a 5% rate of major late sequelae in patients with stage I cervical carcinoma treated with RT, and approximately 10% in patients with stages II–IVA disease. Grade 2 complications are seen in 10% to 15% of patients with all stages treated with RT alone (498,499). The risk is related to a number of factors, mainly dose and volume treated.

Perez et al. reported a less than 2% risk of severe small bowel toxicity when the pelvic sidewall dose was less than 50 Gy, and a 5% incidence with doses >greater than 60 Gy (164). In a multivariate analysis, Perez et al. found total doses to rectal and bladder points to significantly impact morbidity (499). Many investigators have found a significant relationship between radiation dose and complications. A greater incidence of pelvic complications has been consistently observed in patients treated with higher doses to the whole pelvis (above 40 to 50 Gy). Intracavitary dose does not correlate closely with severe complications.

Injury to the gastrointestinal tract is the most frequent late complication of RT for cervical cancer. A report by Eifel et al. (500) on 1,784 patients with stage IB carcinoma of the cervix indicates that the greatest risk is in the first 3 years after therapy. The risk of rectal complications declined after the first 2 years of follow-up to 0.06% per year. Nakano et al. reported long-term follow-up results for patients treated with definitive radiotherapy using HDR-ICBT (187). The median follow-up for surviving patients was 22 years. They demonstrated that the 10-year actuarial rates of major (grade 3–5) complications were 4.4% in the rectosigmoid colon, 0.9% in the bladder, and 3.3% in the small intestines. They showed that the incidence of major rectosigmoid complications moderately increased with follow-up beyond 5 years. The 5-year, 10-year, and 20-year actuarial rates of major rectosigmoid complications were 3.8%, 4.4%, and 5.3%, respectively. The rate of small intestinal complications also continually increased with longer follow-ups. The 5-year, 10-year, and 20-year actuarial rates of major complications involving the small intestine were 2.6%, 3.3%, and 8.3%, respectively (187).

Rectosigmoid complications include chronic proctosigmoiditis, rectal stricture, rectal bleeding, and rectal ulcer. Complications involving the small intestine include partial or complete obstruction, food intolerances, and malabsorption syndrome. Predisposing factors for injury, particularly to small bowel, include a history of abdominopelvic surgery and pelvic inflammatory disease. Accurate diagnosis is essential to proper management. It does not appear that specific symptoms have a reliable relationship to the underlying process (501). Major complications include intestinal obstruction, fistula formation, severe bleeding, and intractable diarrhea. Fortunately, these sequelae are relatively infrequent. These injuries generally result from fibrosis and ischemia secondary to the effect of RT on the small blood vessels and connective tissue. Conservative management might include a low residue diet,

antidiarrheal medications, and steroid or sucralfate enemas. Some cases of partial small bowel obstruction can be managed by bowel rest, decompression, and diet modification. Obstruction refractory to conservative management may require surgery involving intestinal resection or anastomoses.

Chronic urinary symptoms (urgency, incontinence, and frequency) are occasionally seen following RT. Genitourinary toxicity includes chronic cystitis, bladder contracture, and urethral stricture. Parkin et al. (502) reported a 26% incidence of these symptoms in patients treated with RT alone for cervical carcinoma. The authors found that the mean volume of full bladder sensation was significantly lower in the post-RT group than in the pretreatment group, as was the mean maximum cystometric capacity. Severe genitourinary toxicities secondary to RT include hemorrhagic cystitis and fistula, but these are rare. The latency period between RT and symptom onset is considerably longer for genitourinary than for gastrointestinal sequelae. In the longitudinal study by Eifel et al. (500), the risk of major urinary tract complications for survivors continued at 0.3% per year beyond 20 years. At 20 years, the actuarial risk of major complications was 14.4%. Nakano et al. also reported a similar time course (187). Lajer et al. prospectively gathered data regarding urologic morbidity in 177 consecutive patients treated curatively with RT (503). The 5-year actuarial incidences of grades 1 + 2 + 3, 2 + 3, and 3 were 62%, 32%, and 5%, respectively. In the long-term recurrence-free survivors, there was evidence of some reversibility of grade 1 and 2 morbidities.

Late sequelae involving the vagina include vaginal stenosis/fibrosis, dyspareunia, vault necrosis, and rectovaginal or vesicovaginal fistulae. Vaginal function can be affected by both radical surgery and RT. Surgery will shorten the functional length of the vagina, but pliability and transudative lubrication are often preserved. Radiation therapy can reduce length, caliber, and lubrication of the vagina; however, these symptoms can be alleviated in some patients with hormonal replacement and vaginal dilatation. Although some gynecologists feel that radical pelvic surgery may affect vaginal function to a lesser degree than RT, a large Swedish study found that the type of treatment had virtually no effect on the prevalence of vaginal changes and sexual distress (504). Huh et al. also demonstrated that there was no difference in sexual dysfunction between surgery and radiotherapy (505).

Postradiation fistula rate is about 2%. Fistulae can be difficult to manage, as most will not heal spontaneously, and local corrective procedures may prove unsuccessful (506). Patients with large fistulae may require diversion. Factors that may increase the rate of fistula are combined treatment (surgery and RT), advanced stage of disease, high rectal dose, smoking, thin habitus, inflammatory bowel diseases, diabetes, and other vasculopathies. Feddock et al. reviewed 24 patients with fistulae in the setting of cervical cancer, out of a 495 patient cohort. Six were present at diagnosis, 6 were in the setting of recurrent disease, and 12 developed following treatment. Among these 12 patients, 9 (75%) developed the fistula following a biopsy that was negative for tumor, with a median time to fistulization of 4.5 months (507). Postradiation biopsies should be taken only in the setting of a high index of suspicion, when the results will affect management, and with appropriate caution.

Although extremely rare, lumbosacral plexopathy has been occasionally reported in patients treated for pelvic tumors with doses of 60 to 68 Gy. Characteristically, these patients have lower motor neuron weakness of the legs combined with loss of deep reflexes and muscular fasciculation. Separating lumbosacral plexopathy from recurrent tumor is sometimes difficult. Generally, weakness is more prominent in radiation-related plexopathy, and pain is more frequently seen in tumor-related cases. Muscular weakness, numbness, and paresthesias are common in both groups.

Insufficiency fracture occurs with normal stress in bone with diminished elastic flexibility, a condition that can exist in irradiated bones. The usual presenting symptom is moderate to severe pelvic pain. Differential diagnosis can include metastatic disease,

tumor recurrence, second malignancy, and benign causes. Because symptoms can resolve with conservative management, proper diagnosis is important. Ikushima et al. reviewed 158 patients with gynecologic malignancies who received whole-pelvis RT. Eighteen patients (11%) developed insufficiency fractures in the irradiated field (508). Oh et al. retrospectively evaluated the incidence, clinical characteristics, and risk factors of pelvic insufficiency fractures after whole-pelvis RT in 557 patients with cervical cancer (509). The 5-year cumulative incidence of fracture was 19.7%, most commonly involving the sacroiliac joint. Multivariate analysis demonstrated that age ≥ 55 years, body weight less than 55 kg, curative treatment, and dose ≥ 50.4 Gy were statistically associated with the development of insufficiency fractures.

High doses of RT cause obliterative endarteritis, reactive fibrosis, and decreased vascularity and oxygenation. As a result, soft-tissue injury can occur, and this can be particularly problematic in the treatment of cervical cancer extending to the distal vagina. Careful attention to radiation planning and dosimetry, careful blocking, and avoidance of unnecessary dose to the perineum during both external beam RT and brachytherapy will make these complications less common. Although these injuries can cause pain that can be difficult to distinguish clinically from recurrent disease, the possibility of radiation injury should be kept in mind, because it is advisable to try to avoid deep biopsies or other trauma to tissues in which perfusion is compromised (507). For refractory radiation-related ulceration and necrosis of the vagina, vulva, and soft tissues, hyperbaric oxygen therapy has been used with some success (510,511).

Combined Modality Related

Irradiation Followed by Surgery

In a GOG study reported by Keys et al., 256 patients with stage IB carcinomas of the cervix ≥ 4 cm confined to the cervix were treated with either external RT and intracavitary

irradiation, or with external RT and a lower dose of intracavitary irradiation followed by an extrafascial hysterectomy. The toxicities were similar in both groups, with grade 3 and 4 toxicities of about 10% in each arm (179). Meticulous, sharp dissection is recommended in the performance of extrafascial hysterectomy following preoperative RT.

Coleman et al. studied 50 patients managed with RH for persistent or recurrent disease limited to the cervix after pelvic RT. Severe toxicities occurred in 42%, and 28% developed GI or GU fistulae (444).

Surgery Followed by Irradiation

Radical pelvic operations commonly result in intestinal adhesions to denuded surfaces in the pelvis. When postoperative RT is given, complications are more likely. A significant increase in grade 2 to 4 late complications following RT is seen among patients undergoing pre-RT surgical staging, particularly with a transperitoneal approach compared with a retroperitoneal approach. Pretreatment laparotomy increased the rate of fistula formation (5.2% vs. 2.9%) as well as small bowel obstruction (14.5% vs. 3.7%) (500). An extraperitoneal approach to lymph node staging purposes lessens these complications.

In a randomized study of postoperative RT versus no further treatment (NFT) after RH, Sedlis et al. found that grade 3 to 4 GU toxicities occurred in 3.1% in the RT versus 1.4% in the NFT arm. Grade 3 to 4 GI toxicities were 3.1% versus 0.8%, respectively. The overall grade 3 to 4 toxicity was 6% in the RT group versus 2.1% in the NFT arm (369). Kim et al. presented an analysis of 800 patients with stages IB-IIIB cervical cancer who received postoperative RT following RH and bilateral salpingo-oophorectomy (BSO). With a median follow-up of 100 months, the incidence of late injuries (grade 3 to 4) were 1.6%, 1.4%, and 1.0% for rectum, bladder, and small bowel, respectively (372).

Methods to decrease the volume of small bowel irradiated will further lessen enteric morbidity. Figures 21.24 and 21.25

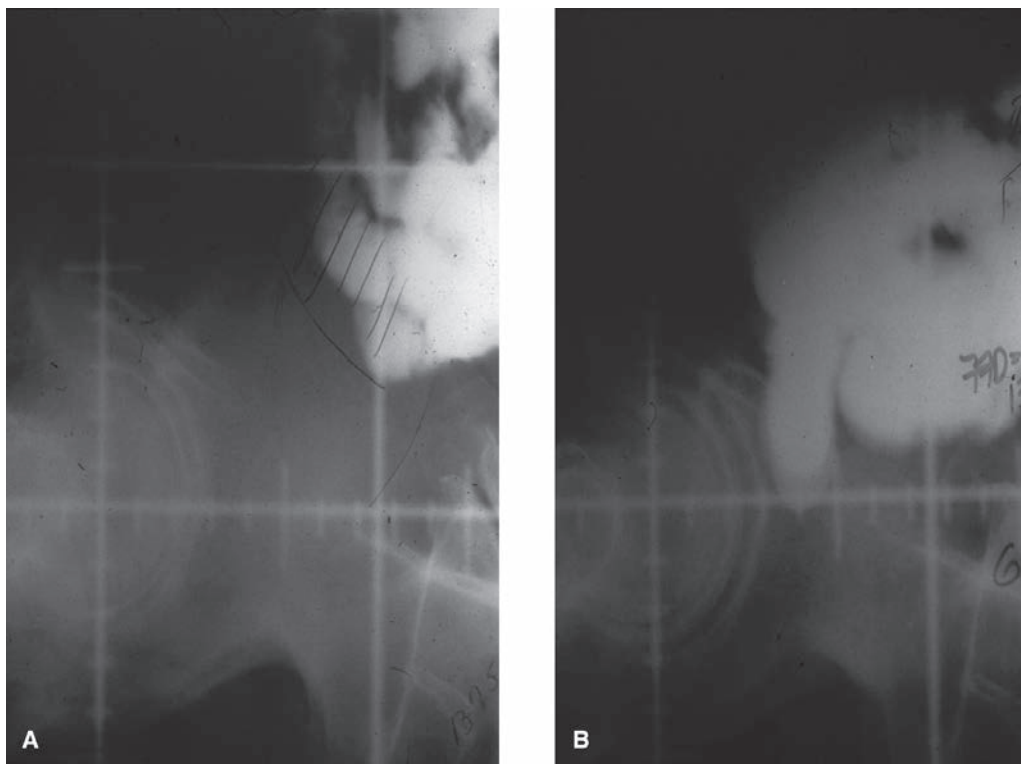


FIGURE 21.24. Lateral radiographs with and without bladder distention in a patient with contrast in small intestine.

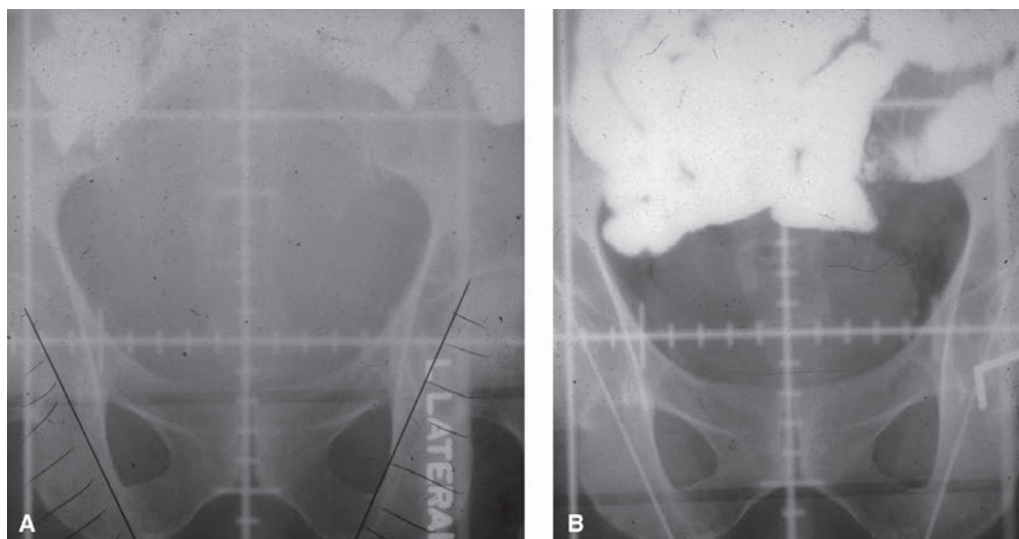


FIGURE 21.25. A and B: Anterior–posterior radiographs with and without bladder distention in a patient with contrast in small intestine.

show the effect of treating patients in the prone position with a full bladder as a means of limiting the volume of small bowel irradiated. Similarly, IMRT techniques can also be used to limit doses to normal tissues (Figs. 21.14 and 21.16) (291).

Concurrent Chemoradiation

The concurrent administration of chemotherapy and radiotherapy for women with locally advanced cervical cancer results in both acute and late complications. In 2005, a meta-analysis compared the effectiveness of concurrent chemoradiation to radiotherapy in 24 randomized trials involving 4,921 women treated in the 1980s and 1990s (512). Acute toxicities were analyzed on data from 17 trials, of which 15 were published and 2 unpublished. In all trials, the reported number of deaths from acute toxicities was 7. Six of these occurred in the women treated with chemoradiation (1 neutropenic sepsis and 5 unspecified treatment-related deaths). Four deaths occurred on 1 unpublished trial and were felt to be related to the chemotherapy dose which was modified. In review of both the hematologic and nonhematologic toxicities, there were statistically significant increases in all grades of toxicities in the chemoradiation arm compared to the radiation arm. The nonhematologic toxicities included gastrointestinal (nausea, vomiting, and diarrhea), skin, and neurologic toxicities. Most commonly, these toxicities were self-limiting or amenable to medical treatment. Late toxicities, defined as toxicity that occurred or persisted 3 months (90 days) after the start of radiation therapy, were reported in 12 of the 24 trials. There were eight deaths due to late toxicities. Four deaths in the chemoradiation arm were due to 1 patient each with small bowel obstruction and perforation, bilateral ureteral obstruction and fibrosis and 1 renal failure, late gastrointestinal event, and unspecified toxicity. Four deaths in the radiation arm were due to 3 patients with bowel late events and 1 with radiotherapy-related fistula. The most commonly reported late toxicities involved the gastrointestinal or genitourinary tract (512).

In 2010, the meta-analysis reported in 2005 was superseded by an updated meta-analysis of these data by the Chemotherapy for Cervical Cancer Meta-analysis Collaboration (387). While 18 trials were used in this meta-analysis for various outcomes, only data from 16 and 7 trials were used for the acute and chronic toxicity analyses, respectively. For patients receiving chemoradiation therapy, there was a significant increase in white blood cell and gastrointestinal toxicities. Few serious

events were recorded for acute toxicity in hemoglobin or platelet values and genitourinary or skin toxicities. As a result, no formal analyses were performed. While data on late toxicities were available, insufficient data were available to assess whether serious late toxicity was affected by the type of treatment (387).

An audit by the Royal College of Radiologists in the United Kingdom was performed to compare the survival and late complications among women treated with chemoradiotherapy and radiotherapy (513,514). During 2001–2002, 1,243 patients from 42 centers were treated with radical chemoradiation (472), radical radiation alone (355), surgery with postoperative radiotherapy (249), or nonradical treatment (168) for locally advanced cervical cancer. Death due to complications from treatment was noted in 6 women treated with chemoradiotherapy and no women in the radiotherapy group. There was no difference in the grade 3 and 4 gastrointestinal and genitourinary late complications in women receiving chemoradiotherapy (10%) versus women receiving radiotherapy alone (8%). Of interest was the timing in both groups for development of these serious late complications. Within the first 3 years after treatment, approximately 50% of the bowel toxicity and 60% of the bladder toxicity had occurred in patients receiving chemoradiotherapy, whereas nearly all the bowel and bladder toxicity had occurred in the radiotherapy alone group. Furthermore, serious complications developed up to 7 years after treatment in the chemoradiation group. Despite this, these authors reported that there was no apparent increase in overall late complications in women receiving chemoradiotherapy compared with radiotherapy alone (513).

Several case reports of unusual late complications including subacute neurologic toxicity, uterine necrosis, and multiple bowel stenoses with perforation have been reported in women following chemoradiation (515–518). In addition, a case report of acute myelogenous leukemia occurring 5 years after treatment with cisplatin-based chemoradiation has been reported (519).

Thromboembolic Complications

The incidence of venous thromboembolic complications in women with cervical cancer varies from 0% to 34% (520–522). Risk factors for venous thromboembolism are attributed to the classic Virchow triad of hypercoagulability, venous stasis, and endothelial injury. Barbera and Thomas have written a comprehensive review on venous thromboembolism in cervical cancer

and divided the risk factors further into patient, tumor, and treatment-related factors (520). They reported that many of these factors related to Virchow's triad.

There are no published reports of patient-related risk factors in cervix cancer (520). However, in other cancers, these risk factors may include age, body mass index, immobilization, previous venous thromboembolism, and Factor V Leiden deficiency or prothrombin 2010A gene mutation (520,522). Tumor-related risk factors include histologic cell type, tumor production of prothrombotic substances, and cancer stage (520). Stage has been associated with venous thrombosis because stage in cervical cancer is defined by extent of tumor spread to the pelvic sidewall or parametrium, and this extension may cause compression of the pelvic veins and venous stasis. However, the most common risk factors for venous thromboembolism are treatment-related risk factors associated with surgery, radiotherapy, chemotherapy, and biologic therapy (520–522).

In reviewing treatment-related risk factors for venous thromboembolism, surgery has accounted for up to 17% incidence (520,522). EBRT is also felt to be a risk factor for venous thromboembolism, though it has not been as well studied as the incidence with brachytherapy, which ranges from 0% to 17% (520).

In addition, women undergoing low-dose rate brachytherapy may also be at risk due to bed rest and immobilization required for this therapy. Chemotherapy alone or in combination with radiotherapy has been associated with venous thromboembolism (520–522). Erythropoietin-stimulating agents administered with radiotherapy or concurrent chemoradiation have been thought to increase the risk of venous thromboembolism and are not encouraged (121,122,523–526). In a randomized trial of chemoradiation with or without erythropoietin-stimulating agent for patients with locally advanced cervical cancer and hemoglobin levels less than 14 g/dL, the trial was closed prematurely with less than 25% of the planned accrual due to concerns of a potential increased risk of VTE with the use of erythropoietin-stimulating agents (122). At the time of study closure, the incidence was 7.7% (n = 52) in the control group and 19.3% (n = 57) in the erythropoietin-treated group, with an overall incidence of 13.8%. There was no significant increase in the treated group. Finally, anti-angiogenesis agents are known to increase the incidence of venous thromboembolism in patients with cancer (472,527). Several of these agents are presently under investigation and are demonstrating promising activity in treatment of cervical cancer (472).

REFERENCES

1. Siegel R, Naishadham MA, Jemal A, et al. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10–29.
2. ACOG Practice Bulletin. Clinical management guidelines for obstetricians-gynecologists. Human papillomavirus. *Obstet Gynecol*. 2005;105(6):905.
3. Holowaty P, Miller AB, Rohan T, et al. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst*. 1999;91:252–258.
4. Melnikow J, Nuovo J, Willan AR, et al. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol*. 1998;92:727–735.
5. McIndoe WA, McLean MR, Jones RW, et al. The invasive potential of carcinoma in situ of the cervix. *Obstet Gynecol*. 1984;64:451–458.
6. Samlal RA, van der Velden J, Ten Kate FJ, et al. Surgical pathologic factors that predict recurrence in stage IB and IIA cervical carcinoma patients with negative pelvic lymph nodes. *Cancer*. 1997;80:1234–1240.
7. Havrilesky LJ, Leath CA, Huh W, et al. Radical hysterectomy and pelvic lymphadenectomy for stage IB2 cervical cancer. *Gynecol Oncol*. 2004;93:429–434.
8. Berman ML, Keys H, Creasman W, et al. Survival and patterns of recurrence in cervical cancer metastatic to periaortic lymph nodes (a Gynecologic Oncology Group study). *Gynecol Oncol*. 1984;19:8–16.
9. Vasilev SA, Schlaerth JB. Scalene lymph node sampling in cervical carcinoma: a reappraisal. *Gynecol Oncol*. 1990;37:120–124.
10. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med*. 2000;132:810–819.
11. Hutchinson ML, Zahniser DJ, Sherman ME, et al. Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. *Cancer*. 1999;87:48–55.
12. Sulik SM, Kroeger K, Schultz JK, et al. Are fluid-based cytologies superior to the conventional Papanicolaou test? A systematic review. *J Fam Pract*. 2001;50:1040–1046.
13. ACOG Practice Bulletin. Clinical management guidelines for obstetricians-gynecologists. Cervical cytology screening. *Obstet Gynecol*. 2003;45:417–427.
14. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guidelines for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin*. 2002;52:342–362.
15. American College of Obstetricians and Gynecologists Practice Bulletin No. 61. Clinical management guidelines for obstetricians-gynecologists. Human papillomavirus. *Obstet Gynecol*. 2005;105:905–918 (reaffirmed 2009).
16. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society of Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*. 2012;62:147–172.
17. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda system: terminology for reporting results of cervical cytology. *JAMA*. 2002;287:2114–2119.
18. Solomon D, Schiffman M, Tarone R, et al. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst*. 2001;93:293–299.
19. Cox JT, Schiffman M, Solomon D, et al. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. *Am J Obstet Gynecol*. 2003;188:1406–1412.
20. Ancheta E, Perry J, Bernard-Pearl L, et al. Participants at the ASCCP 2000 biennial meeting adhere to published guidelines in their management of atypical squamous cells and atypical glandular cells on Pap test. *J Low Genit Tract Dis*. 2003;7:279–284.
21. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst*. 2003;95:46–52.
22. Clavel C. Value of cervical screening by HPV DNA testing. It is legitimate to type HPV for the primary screening of cervix neoplasms. *Gynecol Obstet Fertil*. 2002;30:896–898.
23. Castle PE, Stoler MH, Wright TC Jr, et al. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. *Lancet Oncol*. 2011;12(9):880–890.
24. Carozzi FM, Del Mistro A, Confortini M, et al. Reproducibility of HPV DNA testing by hybrid capture 2 in a screening setting. *Am J Clin Pathol*. 2005;124:716–721.
25. Mathevet P, Chemali E, Roy M, et al. Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP. *Eur J Obstet Gynecol Reprod Biol*. 2003;106:214–218.
26. Gadducci A, Tana R, Cosio S, et al. The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: a review of the literature. *Crit Rev Oncol Hema*. 2008;66:10–20.
27. Noordhuis MG, Eusink JH, Roossink F, et al. Prognostic cell biological markers in cervical cancer patients primarily treated with (chemo) radiation: a systematic review. *Int J Radiation Oncology Biol Phys*. 2011;79:325–334.
28. Huang EY, Huang YJ, Chanchien CC, et al. Pre-treatment carcinoembryonic antigen level is a risk factor for para-aortic lymph node recurrence in addition to squamous cell carcinoma antigen following definitive concurrent chemoradiotherapy for squamous cell carcinoma of the uterine cervix. *Radiat Oncol*. 2012;7:13.
29. Kotowicz B, Fuksiewicz M, Kowalska M, et al. The value of tumor marker and cytokine analysis for the assessment of regional lymph node status in cervical cancer patients. *Int J Gynecol Cancer*. 2008;18(6):1279–1284.
30. Sheng X, Du X, Zhang X, et al. Clinical value of serum HMGB1 levels in early detection of recurrent squamous cell carcinoma of uterine cervix: comparison with serum SCCA, CYFRA21-1, and CEA levels. *Croat Med J*. 2009;50(5):455–464.

31. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynecol Obstet*. 2009;105:107–108.
32. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obstet*. 2009;105:103–104.
33. Pecorelli S. Corrigendum to “Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium” [*Int J Gynecol Obstet*. 2009;105:103–104]. *Int J Gynecol Obstet*. 2010;108:176.
34. Liyanage SH, Roberts CA, Rockall AG. MRI and PET scans for primary staging and detection of cervical cancer recurrence. *Womens Health*. 2010;6:251–269.
35. Bell DJ, Pannu HK. Radiologic assessment of gynecologic malignancies. *Obstet Gynecol Clin N Am*. 2011;38:45–68.
36. Kitajima K, Murakami K, Kaji Y, et al. Established, emerging and future applications of FDG-PET/CT in the uterine cancer. *Clin Radiol*. 2011;66:297–307.
37. Gaffney D, Mundt A, Schwarz J, et al. Advances in clinical research in gynecologic radiation oncology: an RTOG symposium. *Int J Gynecol Cancer*. 2012;22 [Epub ahead of print].
38. Hricak H, Gatsonis C, Chi DS, et al. Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. *J Clin Oncol*. 2005;23:9329–9337.
39. Mitchell DG, Snyder B, Coakley F, et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 intergroup study. *J Clin Oncol*. 2006;24:5687–5694.
40. Hricak H, Gatsonis C, Coakley FV, et al. Early invasive cervical cancer: CT and MR imaging in preoperative evaluation-ACRIN/GOG comparative study of diagnostic performance and interobserver variability. *Radiology*. 2007;245:491–498.
41. Mitchell DG, Snyder B, Coakley F, et al. Early invasive cervical cancer: MRI and CT predictors of lymphatic metastases in the ACRIN 6651/GOG 183 intergroup study. *Gynecol Oncol*. 2009;112:95–103.
42. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. *J Clin Oncol*. 2010;28:2108–2113.
43. Choi HJ, Ju W, Myung SK, et al. Diagnostic performance of computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with cervical cancer: meta-analysis. *Cancer Sci*. 2010;101:1471–1479.
44. Kang S, Kim S-K, Chung D-C, et al. Diagnostic value of 18F-FDG PET for evaluation of paraaortic nodal metastasis in patients with cervical carcinoma: a metaanalysis. *J Nucl Med*. 2010;51:360–367.
45. Kim SK, Choi HJ, Park SY, et al. Additional value of MR/PET fusion compared with PET/CT in the detection of lymph node metastases in cervical cancer patients. *Eur J Cancer*. 2009;45:2103–2109.
46. Mayr NA, Yuh WTC, Jajoura D, et al. Ultra-early predictive assay for treatment failure using functional magnetic resonance imaging and clinical prognostic parameters in cervical cancer. *Cancer*. 2010;116:903–912.
47. Mayr NA, Wang JZ, Lo SS, et al. Translating response during therapy into ultimate treatment outcome: a personalized 4-dimensional MRI tumor volumetric regression approach in cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010;76:719–727.
48. Kidd EA, Siegel BA, Dehdashti F, et al. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. *Cancer*. 2007;117:1738–1744.
49. Ramirez PT, Jhingran A, Macapinlac HA, et al. Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer: a prospective correlation of surgical findings with positron emission tomography/computed tomography findings. *Cancer*. 2011;117:1928–1934.
50. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. *J Clin Oncol*. 2010;28:2108–2113.
51. Gold MA, Tian C, Whitney CW, et al. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. *Cancer*. 2008;112:1954–1963.
52. Fagotti A, Fanfani F, Longo R, et al. Which role for pre-treatment laparoscopic staging? *Gynecol Oncol*. 2007;107:S101–S105.
53. Leblanc E, Narducci F, Frumovitz M, et al. Therapeutic value of pretherapeutic extraperitoneal laparoscopic staging of locally advanced cervical carcinoma. *Gynecol Oncol*. 2007;105:304–311.
54. Lai CH, Huang KG, Hong JH, et al. Randomized trial of surgical staging (extraperitoneal or laparoscopic) versus clinical staging in locally advanced cervical cancer. *Gynecol Oncol*. 2003;89:160–167.
55. Thompson JF, Uren RF. What is a “sentinel” lymph node? *Eur J Surg Oncol*. 2000;26:103–104.
56. Levenback C, Coleman RL, Burke TW, et al. Lymphatic mapping and sentinel node identification in patients with cervix cancer undergoing radical hysterectomy and pelvic lymphadenectomy. *J Clin Oncol*. 2002;20:688–693.
57. Plante M, Renaud MC, Tetu B, et al. Laparoscopic sentinel node mapping in early-stage cervical cancer. *Gynecol Oncol*. 2003;91:494–503.
58. Roy M, Bouchard-Fortier G, Popa I, et al. Value of sentinel node mapping in cancer of the cervix. *Gynecol Oncol*. 2011;122:269–274.
59. Lécuru F, Mathevet P, Querleu D, et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J Clin Oncol*. 2011;29:1686–1691.
60. Diaz JP, Gemignani ML, Pandit-Taskar N, et al. Sentinel lymph node biopsy in the management of early-stage cervical carcinoma. *Gynecol Oncol*. 2011;120:347–352.
61. Altgassen C, Hertel H, Brandstädt A, et al. Multi-center validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. *J Clin Oncol*. 2008;26:2943–2951.
62. Frumovitz M, Ramirez PT, Levenback CF. Lymphatic mapping and sentinel lymph node detection in women with cervical cancer. *Gynecol Oncol*. 2008;110:S17–S20.
63. Malpica A, Matisis JP, Van Niekirk D, et al. Kappa statistics to measure interrater and intrarater agreement for 1790 cervical biopsy specimens among twelve pathologists: qualitative histopathologic analysis and methodologic issues. *Gynecol Oncol*. 2005;99:S38–S52.
64. Bean SM, Kurtycz DFL, Colgan TJ. Recent developments in defining microinvasive and early invasive carcinoma of the uterine cervix. *J Lower Genital Tract Dis*. 2011;15:146–157.
65. Kristensen GB, Abeler VM, Risberg B, et al. Tumor size, depth of invasion and grading of the invasive tumor front are the main prognostic factors in early squamous cell cervical carcinoma. *Gynecol Oncol*. 1999;74:245–251.
66. Grayson W, Cooper K. A reappraisal of “basaloid carcinoma” of the cervix, and the differential diagnosis of basaloid cervical neoplasms. *Adv Anat Pathol*. 2002;9:290–300.
67. Kashimura M, Tsukamoto N, Matsukuma K, et al. Verrucous carcinoma of the uterine cervix: report of a case with follow-up of 6 1/2 years. *Gynecol Oncol*. 1984;19:204–215.
68. Randall ME, Andersen WA, Mills SE, et al. Papillary squamous cell carcinoma of the uterine cervix: a clinicopathologic study of nine cases. *Int J Gynecol Pathol*. 1986;5:1–10.
69. Koenig C, Turnicky RP, Collins FK, et al. Papillary squamotransitional cell carcinoma of the cervix: a report of 32 cases. *Am J Surg Pathol*. 1997;21:915–921.
70. Drew PA, Hong B, Massoll NA, et al. Characterization of papillary squamotransitional cell carcinoma of the cervix. *J Lower Genital Tract Dis*. 2005;9:149–153.
71. Kurman RJ, Norris HJ, Wilkinson E. Tumors of the cervix, vagina, and vulva. In: *Atlas of Tumor Pathology*. 3rd Series, Fascicle 4. Washington, DC: Armed Forces Institute of Pathology; 1992.
72. Tseng CJ, Pao CC, Tseng LH, et al. Lymphoepithelioma-like carcinoma of the uterine cervix: association with Epstein-Barr virus and human papillomavirus. *Cancer*. 2000;80:91–97.
73. Martorell MA, Julian JM, Calabuig C, et al. Lymphoepithelioma-like carcinoma of the uterine cervix. A clinicopathologic study of 4 cases not associated with Epstein-Barr virus, human papillomavirus, or simian virus 40. *Arch Pathol Lab Med*. 2002;126:1501–1505.
74. Noel J, Lespagnard L, Fayt I, et al. Evidence of human papilloma virus infection but lack of Epstein-Barr virus in lymphoepithelioma-like carcinoma of uterine cervix: report of two cases and review of the literature. *Hum Pathol*. 2001;32:135–138.
75. Saylam K, Anaf V, Fayt I, et al. Lymphoepithelioma-like carcinoma of the cervix with prominent eosinophilic infiltrate: an HPV associated case. *Acta Obstet Gynecol Scand*. 2002;81:564–566.
76. Bais AG, Kooi S, Teune TM, et al. Lymphoepithelioma-like carcinoma of the uterine cervix: absence of Epstein-Barr virus, but presence of a multiple human papillomavirus infection. *Gynecol Oncol*. 2005;97:716–718.
77. Zaino RJ. Symposium part I: adenocarcinoma *in situ*, glandular dysplasia, and early invasive adenocarcinoma of the uterine cervix. *Int J Gynecol Pathol*. 2002;21:314–326.
78. Young RH, Clement PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. *Histopathology*. 2002;41:185–207.
79. McCluggage WG. Endocervical glandular lesions: controversial aspects and ancillary techniques. *J Clin Pathol*. 2003;56:164–173.
80. Gien LT, Beauchemin MC, Thomas G. Adenocarcinoma: a unique cervical cancer. *Gynecol Oncol*. 2010;116:140–146.
81. Pirog EC, Kleter B, Olgac S, et al. Prevalence of human papillomavirus DNA in different histological subtypes of cervical adenocarcinoma. *Am J Pathol*. 2000;157:1055–1062.
82. Hart WR. Special types of adenocarcinoma of the uterine cervix. *Int J Gynecol Pathol*. 2002;21:327–346.
83. An HJ, Kim KR, Kim IS, et al. Prevalence of human papillomavirus DNA in various histological subtypes of cervical adenocarcinoma: a population-based study. *Mod Pathol*. 2005;18:528–534.

84. Fadare O, Zheng W. Well-differentiated papillary villoglandular adenocarcinoma of the uterine cervix with a focal high-grade component: is there a need for reassessment? *Virchows Arch*. 2005; 447:883–887.
85. Macdonald RD, Kirwan J, Hayat K, et al. Villoglandular adenocarcinoma of the cervix: clarity is needed on the histological definition for this difficult diagnosis. *Gynecol Oncol*. 2006;100:192–194.
86. Silver SA, Devouassoux-Shisheboran J, Mezzetti TP, et al. Mesonephric adenocarcinomas of the uterine cervix: a study of 11 cases with immunohistochemical findings. *Am J Surg Pathol*. 2001; 25:379–387.
87. Ordi J, Nogales FF, Palacin A, et al. Mesonephric adenocarcinoma of the uterine corpus: CD10 expression as evidence of mesonephric differentiation. *Am J Surg Pathol*. 2001;25:1540–1545.
88. Tambouret R, Bell DA, Young RH. Microcystic endocervical adenocarcinomas: a report of eight cases. *Am J Surg Pathol*. 2000;24:369–374.
89. Wang SS, Sherman ME, Silverberg SG, et al. Pathological characteristics of cervical adenocarcinoma in a multi-center U.S.-based study. *Gynecol Oncol*. 2006;103:541–546.
90. Parwani AV, Sehdev AES, Kurman RJ, et al. Cervical adenoid basal tumors comprised of adenoid basal epithelioma associated with various types of invasive carcinoma: clinicopathologic features, human papillomavirus DNA detection, and P16 expression. *Hum Pathol*. 2005;36:82–90.
91. Albores-Saavedra J, Gersell D, Gilks B, et al. Terminology of endocrine tumors of the uterine cervix. Results of a workshop sponsored by the College of American Pathologists and the National Cancer Institute. *Arch Pathol Lab Med*. 1997;121:34–39.
92. Gilks CB, Young RH, Gersell DJ, et al. Large cell carcinoma of the uterine cervix: a clinicopathologic study of 12 cases. *Am J Surg Pathol*. 1997; 21:905–914.
93. Horn LC, Hentschel B, Bilek K, et al. Mixed small cell carcinomas of the uterine cervix: prognostic impact of focal neuroendocrine differentiation but not of Ki-67 labeling index. *Ann Diagn Pathol*. 2006;10:140–143.
94. McCluggage WG. Mullerian adenosarcoma of the female genital tract. *Adv Anat Pathol*. 2010;17:122–129.
95. Sharma NK, Sorosky JI, Bender D, et al. Malignant mixed müllerian tumor (MMMT) of the cervix. *Gynecol Oncol*. 2005;97:442–445.
96. Grayson W, Taylor LF, Cooper K, et al. Carcinosarcoma of the uterine cervix: a report of eight cases with immunohistochemical analysis and evaluation of human papillomavirus status. *Am J Surg Pathol*. 2001;25:338–347.
97. Wright JD, Rosenblum K, Huettner PC, et al. Cervical sarcomas: an analysis of incidence and outcome. *Gynecol Oncol*. 2005;99:348–351.
98. Chan JK, Loizzi V, Magistis A, et al. Clinicopathologic features of six cases of primary cervical lymphoma (review). *Am J Obstet Gynecol*. 2005;103:866–872.
99. Malpica A, Moran CA. Primitive neuroectodermal tumor of the cervix: a clinicopathologic and immunohistochemical study of two cases. *Ann Diagn Pathol*. 2002;6:281–287.
100. Khalbuss WE, Bui M, Loya A. A 19-year-old woman with a cervicovaginal mass and elevated serum CA 125: desmoplastic small round cell tumor. *Arch Pathol Lab Med*. 2006;130:e59–e61.
101. Delgado G, Bundy B, Zaino R, et al. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1990;38:352–357.
102. Horn L-C, Fischer U, Raptis G, et al. Tumor size is of prognostic value in surgically treated FIGO stage II cervical cancer. *Gynecol Oncol*. 2007;107:310–315.
103. Rutledge TL, Kamelle SA, Tillmanns TD, et al. A comparison of stages IB1 and IB2 cervical cancers treated with radical hysterectomy. Is size the real difference? *Gynecol Oncol*. 2004;95:70–76.
104. Perez CA, Grigsby PW, Chao KSC, et al. Tumor size, irradiation dose, and long-term outcome of carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1998;41:307–317.
105. Eifel PJ, Morris M, Wharton JT, et al. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1994;29:9–16.
106. Chung HH, Kim JW, Han KH, et al. Prognostic value of metabolic tumor volume measured by FDG-PET/CT in patients with cervical cancer. *Gynecol Oncol*. 2011;120:270–274.
107. Viswanathan AN, Lee H, Hanson E, et al. Influence of margin status and radiation on recurrence after radical hysterectomy in stage IB cervical cancer. *Int J Radiat Oncol Biol Phys*. 2006; 65:1501–1507.
108. Kodama J, Seki N, Nakamura K, et al. Prognostic factors in pathologic parametrium-positive patients with stage IB-IBB cervical cancer treated by radical surgery and adjuvant therapy. *Gynecol Oncol*. 2007;105:757–761.
109. Fyles AW, Pintilie M, Kirkbride P, et al. Prognostic factors in patients with cervix cancer treated by radiation therapy: results of a multiple regression analysis. *Radiother Oncol*. 1995;35:107–117.
110. Stehman FB, Bundy BN, DiSaia PH, et al. Carcinoma of the cervix treated with irradiation therapy. I. A multi-variate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer*. 1991;67:2776–2785.
111. Creasman WT, Kohler MF. Is lymph vascular space involvement an independent prognostic factor in early cervical cancer? *Gynecol Oncol*. 2004;92:525–529.
112. Marchiolo P, Buenerd A, Benchaib M, et al. Clinical significance of lymphovascular space involvement and lymph node micrometastases in early-stage cervical cancer: a retrospective case-control surgico-pathological study. *Gynecol Oncol*. 2005;97:727–732.
113. Juretzka MM, Jensen KC, Longacre TA, et al. Detection of pelvic lymph node micrometastases in stage IA2-IB2 cervical cancer by immunohistochemical analysis. *Gynecol Oncol*. 2004; 93:107–111.
114. Chernofsky MR, Felix JC, Mderspach LI, et al. Influence of quantity of lymph node vascular space invasion on time to recurrence in women with early-stage squamous cancer of the cervix. *Gynecol Oncol*. 2006;100:288–293.
115. Milam MR, Frumovitz M, dos Reis R, et al. Preoperative lymphovascular space invasion is associated with nodal metastases in women with early-stage cervical cancer. *Gynecol Oncol*. 2007; 106:12–15.
116. Ferrandina G, Distefano M, Smaniotto D, et al. Anemia in patients with locally advanced cervical carcinoma administered preoperative radiochemotherapy: association with pathological response to treatment and clinical outcome. *Gynecol Oncol*. 2006;103:500–505.
117. De Los Santos JE, Thomas GM. Anemia correction in malignancy management: threat or opportunity? *Gynecol Oncol*. 2007;105:517–529.
118. Fyles AW, Milosevic M, Pintilie M, et al. Anemia, hypoxia and transfusion in patients with cervix cancer: a review. *Radiother Oncol*. 2000; 57:13–19.
119. Fyles M, Milosevic M, Hedley D, et al. Tumor hypoxia has independent predictor impact only in patients with node-negative cervix cancer. *J Clin Oncol*. 2002;20:680–687.
120. Fuso L, Mazzola S, Marocco F, et al. Pretreatment serum hemoglobin as a predictive factor of response to neoadjuvant chemotherapy in patients with locally advanced squamous cervical carcinoma: a preliminary report. *Gynecol Oncol*. 2005;99:S187–S191.
121. Lavey RS, Liu PY, Greer BE, et al. Recombinant human erythropoietin as an adjunct to radiation therapy and cisplatin for stage IIB-IVA carcinoma of the cervix: a Southwest Oncology Group study. *Gynecol Oncol*. 2004;95:145–151.
122. Thomas G, Ali S, Hoebbers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs. above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol*. 2008;108:317–325.
123. Santin AD, Bellone S, Palmieri M, et al. Effect of blood transfusion during radiotherapy on the immune function of patients with cancer of the uterine cervix: role of interleukin-10. *Int J Radiat Oncol Biol Phys*. 2002;54:1345–1355.
124. DiSilvestro P, Ali S, Craighead P, et al. A Gynecologic Oncology Group phase III randomized trial of weekly cisplatin and radiation versus cisplatin and tirapazamine and radiation in stage IB2, IIA, IIIB, and IVA cervical carcinoma limited to the pelvis. *Gynecol Oncol*. 2012; 125:S3–S4 (abstract #2).
125. Xue F, Lin LL, Dehdashti F, et al. F-18 fluorodeoxyglucose uptake in primary cervical cancer as an indicator of prognosis after radiation therapy. *Gynecol Oncol*. 2006;101:147–151.
126. Yen TC, See LC, Lai CH, et al. Standardized uptake value in para-aortic lymph node is a significant prognostic factor in patients with primary advanced squamous cervical cancer. *Eur J Nucl Med Mol Imaging*. 2008;35:493–501.
127. Grigsby PW, Siegel BA, Dehdashti F, et al. Posttherapy [F18] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. *J Clin Oncol*. 2004; 22:2167–2171.
128. Schwarz JK, Siegel BA, Dehdashti F, et al. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA*. 2007;298:2289–2295.
129. Semple SI, Harry VN, Parkin DE, et al. A combined pharmacokinetic and radiologic assessment of dynamic contrast-enhanced magnetic resonance imaging predicts response to chemoradiation in locally advanced cervical cancer. *Int J Radiation Oncol Biol Phys*. 2009;75:611–617.
130. Zahra MA, Tan LT, Priest AN, et al. Semiquantitative and quantitative dynamic contrast-enhanced magnetic resonance imaging measurements predict radiation response in cervix cancer. *Int J Radiat Oncol Biol Phys*. 2009;74:766–773.
131. Anderson EKE, Hole KH, Lund KV, et al. Dynamic contrast-enhanced MRI of cervical cancers: temporal percentile screening of contrast enhancement identifies parameters for prediction of chemoresistance. *Int J Radiat Oncology Biol Phys*. 2010;77:502–508.
132. Donaldson SB, Buckley DL, O'Connor JP, et al. Enhancing fraction measured using dynamic contrast-enhanced MRI predicts disease-free survival in patients with carcinoma of the cervix. *Br J Cancer*. 2010;102:23–26.

133. McVeigh PZ, Syed AM, Milosevic M, et al. Diffusion-weighted MRI in cervical cancer. *Eur Radiol*. 2008;18:1058–1064.
134. Harry VN, Semple SI, Gilbert FJ, et al. Diffusion-weighted magnetic resonance imaging in the early detection of response to chemoradiation in cervical cancer. *Gynecol Oncol*. 2008;111:213–220.
135. Liu Y, Bai R, Sun H, et al. Diffusion-weighted imaging in predicting and monitoring the response of uterine cervical cancer to combined chemoradiation. *Clin Radiol*. 2009;64:1067–1074.
136. Chen J, Yun Z, Biling L, et al. The utility of diffusion-weighted MR imaging in cervical cancer. *Eur J Radiol*. 2010;74:e101–e106.
137. Ma DJ, Zhu J-M, Grigsby PW. Change in T2 saturation MRI correlates with outcome in cervical cancer patients. *Int J Radiation Oncology Biol Phys*. 2011;81:e707–e712.
138. Kasamatsu T, Onda T, Sawada M, et al. Radical hysterectomy for FIGO stage I–IIB adenocarcinoma of the uterine cervix. *Br J Cancer*. 2009;100:1400–1405.
139. Katanyoo K, Sanguanrungsirikul S, Manusirivithaya S. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma in locally advanced cervical cancer. *Gynecol Oncol*. 2012;125:292–296.
140. Galic V, Herzog TJ, Lewin SN, et al. Prognostic significance of adenocarcinoma histology in women with cervical cancer. *Gynecol Oncol*. 2012;125:287–291.
141. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys*. 2006;65:169–176.
142. Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*. 2000;18:1606–1613.
143. Monk BJ, Wang J, Im S, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. *Gynecol Oncol*. 2005;96:721–728.
144. Landoni F, Maneo A, Colombo A, et al. Randomized study of radical surgery versus radiotherapy for stage IB–IIA cervical cancer. *Lancet*. 1997;350:535–540.
145. Alfsen CG, Kristensen GB, Skovlund E, et al. Histologic subtype has minor importance for overall survival in patients with adenocarcinoma of the uterine cervix. A population-based study of prognostic factors in 505 patients with nonsquamous cell carcinomas of the cervix. *Cancer*. 2001;92:2471–2483.
146. Alonso I, Torne A, Puig-Tintore LM, et al. Pre- and post-conization high-risk HPV testing predicts residual/recurrent disease in patients treated for CIN 2–3. *Gynecol Oncol*. 2006;103:631–636.
147. Verguts J, Bronselaer B, Donders G, et al. Prediction of recurrence after treatment for high-grade cervical intraepithelial neoplasia: the role of human papillomavirus testing and age at conization. *Br J Obstet Gynecol*. 2006;113:1303–1307.
148. Kolstad P. Follow-up study of 232 patients with stage IA1 and 411 patients with stage IA2 squamous cell carcinoma of the cervix (microinvasive carcinoma). *Gynecol Oncol*. 1989;33:265–272.
149. Luesley DM, Cullimore J, Redman CW, et al. Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears. *Br Med J*. 1990;300:1690–1693.
150. Martin-Hirsch PL, Paraskevaidis E, Kitchener H. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev*. 2000;(2):CD001318.
151. Temkin SM, Hellmann M, Lee YC, et al. Dysplastic endocervical curettings: a predictor of cervical squamous cell carcinoma. *Am J Obstet Gynecol*. 2007;196:469.e1–469.e4.
152. Lu CH, Liu FS, Kuo CJ, et al. Prediction of persistence or recurrence after conization for cervical intraepithelial neoplasia III. *Obstet Gynecol*. 2006;107:830–835.
153. Case AS, Rocconi RP, Straughn JM Jr, et al. Cervical intraepithelial neoplasia in adolescent women: incidence and treatment outcomes. *Obstet Gynecol*. 2006;108:1369–1374.
154. Grigsby PW, Perez CA. Radiotherapy alone for medically inoperable carcinoma of the cervix: stage IA and carcinoma in situ. *Int J Radiat Oncol Biol Phys*. 1991;21:375–378.
155. Takeshima N, Yanoh K, Tabata T, et al. Assessment of the revised International Federation of Gynecology and Obstetrics staging for early invasive squamous cervical cancer. *Gynecol Oncol*. 1999;74:165–169.
156. Creasman WT. Stage IA cancer of the cervix: finally some resolution of definition and treatment? *Gynecol Oncol*. 1999;74:163–164.
157. Hou J, Goldberg GL, Qualls C, et al. Risk factors for poor prognosis in microinvasive adenocarcinoma of the uterine cervix (IA1 and IA2): a pooled analysis. *Gynecol Oncol*. 2011;121:135–142.
158. Covens A, Rosen B, Murphy J, et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? *Gynecol Oncol*. 2002;84:145–149.
159. Smrkolj S, Pogacnik RK, Slabe N, et al. Clinical outcome of patients with FIGO stage IA2 squamous cell carcinoma of the uterine cervix. *Gynecol Oncol*. 2012;124:68–71.
160. Bisseling K, Bekkers R, Rome R, et al. Treatment of microinvasive adenocarcinoma of the uterine cervix: a retrospective study and review of the literature. *Gynecol Oncol*. 2007;107:424–430.
161. Hamberger AD, Fletcher GH, Wharton JT. Results of treatment of early stage I carcinoma of the uterine cervix with intracavitary radium alone. *Cancer*. 1978;41:980–985.
162. Schorge JO, Lee KR, Flynn CE, et al. Stage IA1 cervical adenocarcinoma: definition and treatment. *Obstet Gynecol*. 1999;93:219–222.
163. Bull-Phelps SL, Garner EI, Walsh CS, et al. Fertility-sparing surgery in 101 women with adenocarcinoma in situ of the cervix. *Gynecol Oncol*. 2007;107:316–319.
164. Shin CH, Schorge JO, Lee KR, et al. Conservative management of adenocarcinoma in situ of the cervix. *Gynecol Oncol*. 2000;79:6–10.
165. Lea JS, Shin CH, Sheets EE, et al. Endocervical curettage at conization to predict residual cervical adenocarcinoma in situ. *Gynecol Oncol*. 2002;87:129–132.
166. Salani R, Puri I, Bristow RE. Adenocarcinoma in situ of the uterine cervix: a meta-analysis of 1278 patients evaluating the predictive value of conization margin status. *Am J Obstet Gynecol*. 2009;200:182.e1–e5.
167. Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB–IIA cervical cancer: a prospective randomized study. *Gynecol Oncol*. 2001;80:3–12.
168. Nam JH, Kim JH, Kim DY, et al. Comparative study of laparoscopic–vaginal radical hysterectomy and abdominal radical hysterectomy in patients with early cervical cancer. *Gynecol Oncol*. 2004;92:277–283.
169. Jensen PT, Groenvold M, Klee MC, et al. Early-stage cervical carcinoma, radical hysterectomy, and sexual function. *Cancer*. 2004;100:97–106.
170. Frumovitz M, Sun CC, Schmeler KM, et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. *Obstet Gynecol*. 2009;114:93–99.
171. Delgado G, Bundy BN, Fowler WC, et al. A prospective surgical pathological study of stage I squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1989;35:314–320.
172. Dargent D. Radical trachelectomy: an operation that preserves the fertility of young women with invasive cervical cancer. *Bull Acad Natl Med*. 2001;185:1295–1304; discussion 1305–1306.
173. Plante M, Renaud MC, Hoskins IA, et al. Vaginal radical trachelectomy: a valuable fertility-preserving option in the management of early-stage cervical cancer. A series of 50 pregnancies and review of the literature. *Gynecol Oncol*. 2005;98:3–10.
174. Boss EA, van Golde RJ, Beerendonk CC, et al. Pregnancy after radical trachelectomy: a real option? *Gynecol Oncol*. 2005;99:S152–S156.
175. Marchiole P, Benchaib M, Buenerd A, et al. Oncological safety of laparoscopic-assisted vaginal radical trachelectomy (LARVT or Dargent's operation): a comparative study with laparoscopic-assisted vaginal radical hysterectomy (LARVH). *Gynecol Oncol*. 2007;106:132–141.
176. Ungar L, Palfalvi L, Hogg R, et al. Abdominal radical trachelectomy: a fertility-preserving option for women with early cervical cancer. *Br J Obstet Gynecol*. 2005;112:366–369.
177. Nick AM, Frumovitz MM, Soliman PT, et al. Fertility sparing surgery for treatment of early-stage cervical cancer: open vs. robotic radical trachelectomy. *Gynecol Oncol*. 2012;124:276–280.
178. Schneider A, Erdemoglu E, Chiantera V, et al. Clinical recommendation radical trachelectomy for fertility preservation in patients with early-stage cervical cancer. *Int J Gynecol Cancer*. 2012;22:659–666.
179. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol*. 2003;89:343–353.
180. Darius CJ, Callahan MB, Nguyen Q-N, et al. Chemoradiation with and without adjuvant extrafascial hysterectomy for IB2 cervical carcinoma. *Int J Gynecol Cancer*. 2008;18:730–735.
181. Zivanovic O, Alektiar K, Sonoda Y, et al. Treatment patterns of FIGO stage IB2 cervical cancer: a single-institution experience of radical hysterectomy with individualized postoperative therapy and definitive radiation therapy. *Gynecol Oncol*. 2008;111:265–270.
182. Kamelle SA, Rutledge TL, Tillmanns TD, et al. Surgical-pathologic predictors of disease-free survival and risk grouping for IB2 cervical cancer: do the traditional models still apply? *Gynecol Oncol*. 2004;94:249–255.
183. Ackerman A. FIGO Stage IB2 cervix cancer and putting all your eggs in one basket. *Gynecol Oncol*. 2004;94:245–246.
184. Stehman FB. A thousand several tongues. *Gynecol Oncol*. 2004;94:247–248.
185. Eddy GL, Bundy BN, Creasman WT, et al. Treatment of (“bulky”) stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: A phase III trial of the

- Gynecology Oncology Group. *Gynecol Oncol*. 2007;106:362–369.
186. Trimble EL, Harlan LC, Gius D, et al. Patterns of care for women with cervical cancer in the United States. *Cancer*. 2008;113:743–749.
 187. Nakano T, Kato S, Ohno T, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer*. 2005;103:92–101.
 188. Leung AR, Amdur RJ, Morris CG, et al. Long-term outcome after radiotherapy for FIGO stage IIB and IVA carcinoma of the cervix. *Int J Radiat Oncol Biol Phys*. 2007;67:1445–1450.
 189. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of Radiation Therapy Oncology Group trial (RTOG) 90-01. *J Clin Oncol*. 2004;22:872–880.
 190. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007;25:2804–2810.
 191. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol*. 1999;17:1339–1348.
 192. Eifel PJ. Chemoradiotherapy in the treatment of cervical cancer. *Semin Radiat Oncol*. 2006;16:177–185.
 193. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol*. 2008;26:5802–5812.
 194. National Comprehensive Cancer Network. Cervical Cancer, Version 1.2012. Available online: http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf.
 195. Mancini N, Marchetti C, Di Tucci C, et al. A prospective phase II study of topotecan (Hycamtin®) and cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer. *Gynecol Oncol*. 2011;122(2):285–290.
 196. Sardi JE, Sananes CE, Giaroli AA, et al. Neoadjuvant chemotherapy in cervical carcinoma stage IIB: a randomized controlled trial. *Int J Gynecol Cancer*. 1998;8:441–450.
 197. Katsumata N, Yoshikawa H, Hirakawa T, et al. Phase III randomized trial of neoadjuvant chemotherapy (NAC) followed by radical hysterectomy (RH) versus RU for bulky stage I/II cervical cancer (JCOG 0102). *Proc ASCO*. 2006; 24(Pt 1):18S (5013).
 198. Lanciano RM, Martz K, Coia LR, et al. Tumor and treatment factors improving outcome in stage III-B cervix cancer. *Int J Radiat Oncol Biol Phys*. 1991;20:95–100.
 199. Matsuura K, Tanimoto H, Fujita K, et al. Early clinical outcomes of 3D-conformal radiotherapy using accelerated hyperfractionation without intracavitary brachytherapy for cervical cancer. *Gynecol Oncol*. 2007;104:11–14.
 200. Park HC, Shimizu S, Yonesaka A, et al. High dose three-dimensional conformal boost using the real-time tumor tracking radiotherapy system in cervical cancer patients unable to receive intracavitary brachytherapy. *Yonsei Med J*. 2010;51:93–99.
 201. Georg D, Kirisits C, Hillbrand M, et al. Image-guided radiotherapy for cervix cancer: high-tech external beam therapy versus high-tech brachytherapy. *Int J Radiat Oncol Biol Phys*. 2008;71:1272–1278.
 202. Sakuragi N. Up-to-date management of lymph node metastasis and the role of tailored lymphadenectomy in cervical cancer. *Int J Clin Oncol*. 2007;12:165–175.
 203. Chou HH, Chang TC, Yen TC, et al. Low value of [18F]-fluoro-2-deoxy-D-glucose positron emission tomography in primary staging of early-stage cervical cancer before radical hysterectomy. *J Clin Oncol*. 2006;24:123–128.
 204. Whitney C, Stehman FB. The abandoned radical hysterectomy: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2000;79:350–356.
 205. Leath CA, Straughn JM Jr, Estes JM, et al. The impact of aborted radical hysterectomy in patients with cervical carcinoma. *Gynecol Oncol*. 2004;95:204–207.
 206. Suprasert P, Srisomboon J, Charoenkwan K, et al. Outcomes of abandoned radical hysterectomy in patients with stages IB–IIA cervical cancer found to have positive nodes during the operation. *Int J Gynecol Cancer*. 2005;15:498–502.
 207. Richard SD, Krivak TC, Castleberry A, et al. Survival for stage IB cervical cancer with positive lymph node involvement: a comparison of completed vs. abandoned radical hysterectomy. *Gynecol Oncol*. 2008;109:43–48.
 208. Kupets R, Thomas GM, Covens A. Is there a role for pelvic lymph node debulking in advanced cervical cancer? *Gynecol Oncol*. 2002;87:163–170.
 209. Tammela J, Bundy B, Odunsi K. Reassessment of pelvic lymph node debulking in advanced cervical cancer. *Gynecol Oncol*. 2004;92:1014–1015.
 210. Lim MC, Bae J, Park JY, et al. Experiences of pretreatment laparoscopic surgical staging in patients with locally advanced cervical cancer: results of a prospective study. *J Gynecol Oncol*. 2008;19:123–128.
 211. Cheung TH, Lo KW, Yim SF, et al. Debulking metastatic pelvic nodes before radiotherapy in cervical cancer patients: a long-term follow-up result. *Int J Clin Oncol*. 2011;16:546–552.
 212. Grigsby PW, Singh AK, Siegel BA, et al. Lymph node control in cervical cancer. *Int J Radiat Oncol Biol Phys*. 2004;59:706–712.
 213. Hsu W-L, Shueng P-W, Jen Y-M, et al. Long-term treatment results of invasive cervical cancer patients undergoing inadvertent hysterectomy followed by salvage radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;59:521–527.
 214. Smith KB, Amdur RJ, Yeung AR, et al. Postoperative radiotherapy for cervix cancer incidentally discovered after a simple hysterectomy for either benign conditions or noninvasive pathology. *Am J Clin Oncol*. 2010;33:229–232.
 215. Munstedt K, Johnson P, von Georgi R, et al. Consequences of inadvertent, suboptimal primary surgery in carcinoma of the uterine cervix. *Gynecol Oncol*. 2004;94:515–520.
 216. Leath CA, Straughn JM, Bhoala SM, et al. The role of radical parametrectomy in the treatment of occult cervical carcinoma after extrafascial hysterectomy. *Gynecol Oncol*. 2004;92:215–219.
 217. Buda A, Pellegrino A, Vitobello D, et al. Total laparoscopic radical parametrectomy, partial colectomy, and pelvic lymphadenectomy in patients with occult cervical cancer. *Int J Gynaecol Obstet*. 2009;107:73–76.
 218. Park JY, Kim DY, Kim JH, et al. Management of occult invasive cervical cancer found after simple hysterectomy. *Ann Oncol*. 2010;21:994–1000.
 219. Kavadi VS, Eifel PJ. FIGO stage IIIA carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1992;24:211–215.
 220. Kazumoto T, Kato S, Tabushi K, et al. High dose-rate intracavitary brachytherapy for cervical carcinomas with lower vaginal infiltration. *Int J Radiat Oncol Biol Phys*. 2007;69:1157–1166.
 221. Ambros RA, Park JS, Shah KV, et al. Evaluation of histologic, morphometric, and immunohistochemical criteria in the differential diagnosis of small cell carcinomas of the cervix with particular reference to human papillomavirus types 16 and 18. *Mod Pathol*. 1991;4:586–593.
 222. Chen J, Macdonald OK, Gaffney DK. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. *Obstet Gynecol*. 2008;111:1394–1402.
 223. Viswanathan AN, Deavers MT, Jhingran A, et al. Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. *Gynecol Oncol*. 2004;93:27–33.
 224. Zivanovic O, Leitao MM Jr, Park KJ, et al. Small cell neuroendocrine carcinoma of the cervix: Analysis of outcome, recurrence pattern and the impact of platinum-based combination chemotherapy. *Gynecol Oncol*. 2009;112:590–593.
 225. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. *Am J Obstet Gynecol*. 2010;203:347.e1–e6.
 226. Garavaglia E, Taccagni G, Montoli S, et al. Primary stage I–III non-Hodgkin's lymphoma of the uterine cervix and upper vagina: evidence for a conservative approach in a study on three patients. *Gynecol Oncol*. 2005;97:214–218.
 227. Dursun P, Gultekin M, Bozdag G, et al. Primary cervical lymphoma: report of two cases and review of the literature. *Gynecol Oncol*. 2005;98:484–489.
 228. Kendrick JE IV, Straughn JM Jr. Two cases of non-Hodgkin's lymphoma presenting as primary gynecologic malignancies. *Gynecol Oncol*. 2005;98:490–492.
 229. Heredia F, Bravo M, Pierotic M, et al. Neoadjuvant combined chemotherapy followed by external whole pelvic irradiation in two cases of primary extranodal non-Hodgkin's lymphoma of the uterine cervix. *Gynecol Oncol*. 2005;97:285–287.
 230. Sandvei R, Lote K, Svendsen E, et al. Successful pregnancy following treatment of primary malignant lymphoma of the uterine cervix. *Gynecol Oncol*. 1990;38:128–131.
 231. Fadare O. Uncommon sarcomas of the uterine cervix: a review of selected entities. *Diagn Pathol*. 2006;1:30.
 232. Gitau GM, Shepherd JH, Hughes G, et al. Alveolar soft part sarcoma of the uterine cervix. *Int J Gynecol Oncol*. 2008;18:853–856.
 233. Wright JD, Rosenblum K, Huettner PC, et al. Cervical sarcomas: an analysis of incidence and outcome. *Gynecol Oncol*. 2005;99:348–351.
 234. Pathak B, Bruchim I, Brisson M-L, et al. Granulocytic sarcoma presenting as tumors of the cervix. *Gynecol Oncol*. 2005;98:493–497.
 235. Barillor I, Horiot JC, Cuisenier J, et al. Carcinoma of the cervical stump: a review of 213 cases. *Eur J Cancer*. 1993;29A:1231–1236.
 236. Hopkins MP, Morley GW. The prognosis and management of cervical cancer associated with pregnancy. *Obstet Gynecol*. 1992;80:9–13.
 237. Economos K, Perez Veridiano N, Delke I, et al. Abnormal cervical cytology in pregnancy: a 17-year experience. *Obstet Gynecol*. 1993;81:915–918.
 238. Marnitz S, Schmittl A, Bolbrinker J, et al. The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer,

- following laparoscopic staging and chemotherapy, with an emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum. *Fertil Steril*. 2009;92:1748.e1-e4.
239. Awerette HE, Nasser N, Yankow SL, et al. Cervical conization in pregnancy: analysis of 180 operations. *Am J Obstet Gynecol*. 1970;106:543-549.
 240. Hannigan EV, Whitehouse HH 3rd, Atkinson WD, et al. Cone biopsy during pregnancy. *Obstet Gynecol*. 1982;60:450-455.
 241. Goldberg GL, Altaras MM, Block B. Cone cerclage in pregnancy. *Obstet Gynecol*. 1991;77:315-317.
 242. Robinson WR, Webb S, Tirpack J, et al. Management of cervical intraepithelial neoplasia during pregnancy with LOOP excision. *Gynecol Oncol*. 1997;64:153-155.
 243. Lacour RA, Garner EI, Molpus KL, et al. Management of cervical adenocarcinoma *in situ* during pregnancy. *Am J Obstet Gynecol*. 2005;192:1449-1451.
 244. Marnitz S, Köhler C, Oppelt P, et al. Cisplatin application in pregnancy: first *in vivo* analysis of 7 patients. *Oncology*. 2010;79:72-77.
 245. Benhaim Y, Haie-Meder C, Lhomme C, et al. Chemoradiation therapy in pregnant patients treated for advanced-stage cervical carcinoma during the first trimester of pregnancy: report of two cases. *Int J Gynecol Cancer*. 2007;17:270-274.
 246. Ostrom K, Ben-Arie A, Edwards C, et al. Uterine evacuation with misoprostol during radiotherapy for cervical cancer in pregnancy. *Int J Gynecol Cancer*. 2003;13:340-343.
 247. Morice P, Uzan C, Gouy S, et al. Gynaecological cancers in pregnancy. *Lancet*. 2012;3379:558-569.
 248. Amant F, Van Calsteren K, Halaska MJ, et al. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. *Int J Gynecol Cancer*. 2009;19:S1-S12.
 249. Morice P, Narducci F, Mathevet P, et al. On the Behalf of the French Working Group on Gynecological Cancers in Pregnancy, Société Française d'Oncologie Gynécologique (SFOG), Société Française de Chirurgie Pelvienne (SFCP), and the Collège National des Gynécologues Obstétriciens Français (CNGOF). *Int J Gynecol Cancer*. 2009;19:1638-1641.
 250. Abu-Rustum NR, Tal MN, DeLair D, et al. Radical abdominal trachelectomy for stage IB1 cervical cancer at 15-week gestation. *Gynecol Oncol*. 2010;116:151-152.
 251. van de Nieuwenhof HP, van Ham MA, Lotgering FK, et al. First case of vaginal radical trachelectomy in a pregnant patient. *Int J Gynecol Cancer*. 2008;18:1381-1385.
 252. Sood AK, Sorosky JI, Mayr N, et al. Cervical cancer diagnosed shortly after pregnancy: prognostic variables and delivery routes. *Obstet Gynecol*. 2000;95:832-838.
 253. Maiman M, Fruchter RG, Clark M, et al. Cervical cancer as an AIDS-defining illness. *Obstet Gynecol*. 1997;89:76-80.
 254. Ahdieh L, Klein RS, Burk R, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis*. 2001;184:682-690.
 255. Harris TG, Burk RD, Palefsky JM, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. *JAMA*. 2005;293:1471-1476.
 256. Koshiol JE, Schroeder JC, Jamieson DJ, et al. Time to clearance of human papillomavirus infection by type and human immunodeficiency virus serostatus. *Int J Cancer*. 2006;119:1623-1629.
 257. Viscidi RP, Schiffman M, Hildesheim A, et al. Seroreactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection: results from a population-based study in Costa Rica. *Cancer Epidemiol Biomarkers Prev*. 2004;13:324-327.
 258. Viscidi RP, Snyder B, Cu-Uvin S, et al. Human papillomavirus capsid antibody response to natural infection and risk of subsequent HPV infection in HIV-positive and HIV-negative women. *Cancer Epidemiol Biomarkers Prev*. 2005;14:283-288.
 259. Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2005;97:577-586.
 260. Clifford GM, Goncalves MA, Franceschi S, et al. Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS*. 2006;20:2337-2344.
 261. Anderson JR, Paramsothy P, Heilig C, et al. Accuracy of Papanicolaou test among HIV-infected women. *Clin Infect Dis*. 2006;42:562-568.
 262. Duerr A, Paramsothy P, Jamieson DJ, et al. Effect of HIV infection on atypical squamous cells of undetermined significance. *Clin Infect Dis*. 2006;42:855-861.
 263. Paramsothy P, Duerr A, Heilig CM, et al. Abnormal vaginal cytology in HIV-infected and at-risk women after hysterectomy. *J Acquir Immune Defic Syndr*. 2004;35:484-491.
 264. Massad LS, Xie X, Greenblatt RM, et al. Effect of human immunodeficiency virus infection on the prevalence and incidence of vaginal intraepithelial neoplasia. *Obstet Gynecol*. 2012;119:582-589.
 265. Ahdieh-Grant L, Li R, Levine AM, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2004;96:1070-1076.
 266. Omar T, Schwartz S, Hanrahan C, et al. Progression and regression of premalignant cervical lesions in HIV-infected women from Soweto: a prospective cohort. *AIDS*. 2011;25:87-94.
 267. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 2005;6:271-278.
 268. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 2004;364:1757-1765.
 269. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis*. 2010;202:1246-1253.
 270. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*. 2010;55:197-204.
 271. Delmas MC, Larsen C, van Benthem B, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. *AIDS*. 2000;14:1775-1784.
 272. Wright TC Jr, Koulos J, Schnoll F, et al. Cervical intraepithelial neoplasia in women infected with the human immunodeficiency virus: outcome after loop electrosurgical excision. *Gynecol Oncol*. 1994;55:253-258.
 273. Maiman M, Watts DH, Andersen J, et al. Vaginal 5-fluorouracil for high-grade cervical dysplasia in human immunodeficiency virus infection: a randomized trial. *Obstet Gynecol*. 1999;94:954-961.
 274. Robinson WR, Andersen J, Darragh TM, et al. Isotretinoin for low-grade cervical dysplasia in human immunodeficiency virus-infected women. *Obstet Gynecol*. 2002;99:777-784.
 275. Lomalisa P, Smith T, Guidozzi F. Human immunodeficiency virus infection and invasive cervical cancer in South Africa. *Gynecol Oncol*. 2000;77:460-463.
 276. Gichangi P, Bwayo J, Estambale B, et al. HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. *Gynecol Oncol*. 2006;100:405-411.
 277. Mugambe JB, Kavuma A. Effect of HIV serological status on outcome in patients with cancer of cervix treated with radiotherapy. *East Afr Med J*. 2006;83:416-423.
 278. Simonds HM, Wright JD, du Toit N, et al. Completion of and early response to chemoradiation among human immunodeficiency virus (HIV)-positive and HIV-negative patients with locally advanced cervical carcinoma in South Africa. *Cancer*. 2012;118:2971-2979.
 279. Boggess JF, Gehrig PA, Cantrell L, et al. A case-control study of robot-assisted type III radical hysterectomy with pelvic lymph node dissection compared with open radical hysterectomy. *Am J Obstet Gynecol*. 2008;199:357.e1-e7.
 280. Querleu D, Morrow CP. Classification of radical hysterectomy. *Lancet Oncol*. 2008;9:297-303.
 281. Ditto A, Martinelli F, Mattana F, et al. Class III nerve-sparing radical hysterectomy versus standard class III radical hysterectomy: an observational study. *Ann Surg Oncol*. 2011;18:3469-3478.
 282. Charoenkwan K, Srisombon J, Suprasert P, et al. Nerve-sparing class III radical hysterectomy: a modified technique to spare the pelvic autonomic nerves without compromising radicality. *Int J Gynecol Cancer*. 2006;16:1705-1712.
 283. Raspagliesi F, Ditto A, Fontanelli R, et al. Type II versus type III nerve-sparing radical hysterectomy: comparison of lower urinary tract dysfunctions. *Gynecol Oncol*. 2006;102:256-262.
 284. Liang Z, Chen Y, Xu H, et al. Laparoscopic nerve-sparing radical hysterectomy with fascia space dissection technique for cervical cancer: description of technique and outcomes. *Gynecol Oncol*. 2010;119:202-207.
 285. Magrina J, Pawlina W, Kho R, et al. Robotic nerve-sparing radical hysterectomy: feasibility and technique. *Gynecol Oncol*. 2011;121:605-609.
 286. Husain A, Akhurst T, Larson S, et al. A prospective study of the accuracy of 18-Fluorodeoxyglucose positron emission tomography (18FDG PET) in identifying sites of metastasis prior to pelvic exenteration. *Gynecol Oncol*. 2007;106:177-180.
 287. Greer BE, Koh WJ, Figge DC, et al. Gynecologic radiotherapy fields defined by intraoperative measurements. *Gynecol Oncol*. 1990;38:421-424.
 288. Bonin SR, Lanciano RM, Corn BW, et al. Bony landmarks are not an adequate substitute for lymphangiography in defining pelvic lymph node location for the treatment of cervical cancer with radiotherapy. *Int J Radiat Oncol Biol Phys*. 1996;34:167-172.
 289. Dittmer PH, Randall ME. A technique for inguinal node boost using photon fields defined by asymmetric collimator jaws. *Radiother Oncol*. 2001;59:61-64.
 290. Moran MS, Castrucci WA, Ahmad M, et al. Clinical utility of the modified segmental boost technique for treatment of the pelvis and inguinal nodes. *Int J Radiat Oncol Biol Phys*. 2010;76:1026-1036.

291. Jhingran A. Potential advantages of intensity-modulated radiation therapy in gynecologic malignancies. *Semin Radiat Oncol*. 2006;16:144–151.
292. Toita T, Kodaira T, Shinoda A, et al. Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): patterns of care study in Japan. *Int J Radiat Oncol Biol Phys*. 2008;70:788–794.
293. Eifel PJ, Moughan J, Erickson B, et al. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a Patterns of Care Study. *Int J Radiat Oncol Biol Phys*. 2004;60:1144–1153.
294. Fenkell L, Assenholt M, Nielsen SK, et al. Parametrial boost using midline shielding results in an unpredictable dose to tumor and organs at risk in combined external beam radiotherapy and brachytherapy for locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2011;79:1572–1579.
295. Toita T, Kato S, Niiibe Y, et al. Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage I and II uterine cervical cancer (JAROG0401/JROSG04-2). *Int J Radiat Oncol Biol Phys*. 2012;82:e49–e56.
296. Kridelka FJ, Berg DO, Neuman M, et al. Adjuvant small field pelvic radiation for patients with high risk, stage IB lymph node negative cervix carcinoma after radical hysterectomy and pelvic lymph node dissection. *Cancer*. 1999;86:2059–2065.
297. Ohara K, Tsudoda H, Nishida M, et al. Use of small pelvic field instead of whole pelvic field in postoperative radiotherapy for node-negative, high-risk stages I and II cervical squamous cell carcinoma. *Int J Gynecol Cancer*. 2003;13:170–176.
298. Oike T, Ohno T, Wakatsuki M, et al. The benefit of small bowel and pelvic bone sparing in excluding common iliac lymph node region from conventional radiation fields in patients with uterine cervical cancer: a dosimetric study. *J Radiat Res (Tokyo)*. 2010;51:715–721.
299. Yeo RMC, Chia YN, Namuduri RPD, et al. Tailoring adjuvant radiotherapy for stage IB-IIA node negative cervical carcinoma after radical hysterectomy and pelvic lymph node dissection using the GOG score. *Gynecol Oncol*. 2011;123:225–229.
300. Malhotra HK, Avadhani JS, deBoer SF, et al. Duplicating a tandem and ovoids distribution with intensity-modulated radiotherapy: a feasibility study. *J Appl Clin Med Phys*. 2007;8:2450.
301. Shwetha B, Ravikumar M, Palled SR, et al. Dosimetric comparison of high dose rate brachytherapy and intensity-modulated radiation therapy for cervical carcinoma. *J Med Phys*. 2011;36:111–116.
302. Georg D, Kirisits C, Hillbrand M, et al. Image-guided radiotherapy for cervix cancer: high-tech external beam therapy versus high-tech brachytherapy. *Int J Radiat Oncol Biol Phys*. 2008;71:1272–1278.
303. Taylor A, Powell ME. Conformal and intensity-modulated radiotherapy for cervical cancer. *Clin Oncol (R Coll Radiol)*. 2008;20:417–425.
304. Randall ME, Ibbott GS. Intensity-modulated radiation therapy for gynecologic cancers: pitfalls, hazards, and cautions to be considered. *Semin Radiat Oncol*. 2006;16:138–143.
305. Taylor A, Powell ME. An assessment of inter-fractional uterine and cervical motion: implications for radiotherapy target volume definition in gynaecological cancer. *Radiother Oncol*. 2008;88:250–257.
306. Beadle BM, Jhingran A, Salehpour M, et al. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys*. 2009;73:235–241.
307. Stewart J, Lim K, Kelly V, et al. Automated weekly replanning for intensity-modulated radiotherapy of cervix cancer. *Int J Radiat Oncol Biol Phys*. 2010;78:350–358.
308. Bondar L, Hoogeman M, Mens JW, et al. Toward an individualized target motion management for IMRT of cervical cancer based on model-predicted cervix-uterus shape and position. *Radiother Oncol*. 2011;99:240–245.
309. Taylor A, Rockall AG, Powell ME. An atlas of the pelvic lymph node regions to aid radiotherapy target volume definition. *Clin Oncol (R Coll Radiol)*. 2007;19:542–550.
310. Small W Jr, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;71:428–334.
311. Toita T, Ohno T, Kaneyasu Y, et al. A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer. *Jpn J Clin Oncol*. 2010;40:456–463.
312. Lim K, Small W Jr, Portelance L, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys*. 2011;79:348–355.
313. Toita T, Ohno T, Kaneyasu Y, et al. JCOG Radiation Therapy Study Group. A consensus-based guideline defining clinical target volume for primary disease in external beam radiotherapy for intact uterine cervical cancer. *Jpn J Clin Oncol*. 2011;41:1119–1126.
314. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys*. 2006;65:1–7.
315. Zwahlen DR, Ruben JD, Jones P, et al. Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys*. 2009;74:539–545.
316. Keall PJ, Chang M, Benedict S, et al. Investigating the temporal effects of respiratory-gated and intensity-modulated radiotherapy treatment deliveries on *in vitro* survival: an experimental and theoretical study. *Int J Radiat Oncol Biol Phys*. 2008;71:1547–1552.
317. Lee WR. Technology assessment: vigilance required. *Int J Radiat Oncol Biol Phys*. 2008;70:652–653.
318. Macdonald DM, Lin LL, Biehl K, et al. Combined intensity-modulated radiation therapy and brachytherapy in the treatment of cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;71:618–624.
319. Hasselle MD, Rose BS, Kochanski JD, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys*. 2011;80:1436–445.
320. Chen CC, Lin JC, Jan JS, et al. Definitive intensity-modulated radiation therapy with concurrent chemotherapy for patients with locally advanced cervical cancer. *Gynecol Oncol*. 2011;122:9–13.
321. Haie C, Pejovic MH, Gerbaulet A, et al. Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. *Radiother Oncol*. 1988;11:101–112.
322. Rotman M, Pajak TF, Choi K, et al. Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinoma. *JAMA*. 1995;274:387–390.
323. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999;340:1137–1143.
324. Stryker JA, Mortel R. Survival following extended field irradiation in carcinoma of cervix metastatic to para-aortic lymph nodes. *Gynecol Oncol*. 2000;79:99–405.
325. Grigsby PW, Perez CA, Chao KS, et al. Radiation therapy for carcinoma of the cervix with biopsy-proven positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys*. 2001;49:733–738.
326. Small W Jr, Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of arm 1 of RTOG 0116. *Int J Radiat Oncol Biol Phys*. 2007;68:1081–1087.
327. Small W, Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin and amifostine for cervical cancer with positive para-aortic or high common iliac lymph nodes: Results of arm II of Radiation Therapy Oncology Group 0116. *Int J Gynecologic Cancer*. 2011;21:1266–1275.
328. Walker JL, Morrison A, DiSilvestro P, et al. A phase III study of extended field radiation therapy with concomitant paclitaxel and cisplatin chemotherapy in patients with cervical carcinoma metastatic to the para-aortic lymph nodes: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2009;112:78–84.
329. Kagei K, Tokuyue K, Okumura T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 2003;55:1265–1271.
330. Milby AB, Both S, Ingram M, Lin LL. Dosimetric comparison of combined intensity-modulated radiotherapy (IMRT) and proton therapy versus IMRT alone for pelvic and para-aortic radiotherapy in gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2012;82:e477–e484.
331. Kato S, Ohno T, Tsujii H, et al. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 2006;65:388–397.
332. Viswanathan AN, Thomadsen B. American Brachytherapy Society Cervical Cancer Recommendations Committee. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles. *Brachytherapy*. 2012;11:33–46.
333. Viswanathan AN, Beriwal S, De Los Santos JF, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy. *Brachytherapy*. 2012;11:47–52.
334. Eifel PJ, Khalid N, Erickson B, et al. Patterns of radiotherapy practice for patients treated for intact cervical cancer in 2005–2007: a QPRO Study. *Int J Radiat Oncol Biol Phys*. 2010;78:S119–S120.
335. International Commission of Radiation Units and Measurements. *Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology*. ICRU Report 38. Bethesda, MD: ICRU; 1985.
336. Potter R, Limbergen EV, Gerstner N, et al. Survey of the use of the ICRU 38 in recording and reporting cervical cancer brachytherapy. *Radiother Oncol*. 2001;58:11–18.
337. Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: a survey of the American Brachytherapy Society. *Int J Radiat Oncol Biol Phys*. 2010;76:104–109.

338. Lee LJ, Sadow CA, Russell A, et al. Correlation of point B and lymph node dose in 3D-planned high-dose-rate cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys*. 2009;75:803–809.
339. Haie-Meder C, Potter R, Van Limbergen E, et al. Recommendation of Gynecologic (GYN) GEC ESTRO Working Group: concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol*. 2005;74:235–245.
340. Nag S, Cardenes H, Chang S, et al. Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. *Int J Radiat Oncol Biol Phys*. 2004;60:1160–1172.
341. Tan LT. Implementation of image-guided brachytherapy for cervix cancer in the UK: progress update. *Clin Oncol (R Coll Radiol)*. 2011;23:681–684.
342. Pavamani S, D'Souza DP, Portelance L, et al. Image-guided brachytherapy for cervical cancer: a Canadian Brachytherapy Group survey. *Brachytherapy*. 2011;10:345–351.
343. Pötter R, Haie-Meder C, Van Limbergen E, et al. GEC ESTRO Working Group. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol*. 2006;78:67–77.
344. Viswanathan AN, Dimopoulos J, Kirsits C, et al. Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys*. 2007;68:491–498.
345. D'Souza D, Baldassarre F, Morton G, et al. Imaging technologies for high dose rate brachytherapy for cervical cancer: a systematic review. *Clin Oncol (R Coll Radiol)*. 2011;23:460–475.
346. Pötter R, Georg P, Dimopoulos JC, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol*. 2011;100:116–123.
347. Rodrigus P, Winter KD, Venselaar JLM, et al. Evaluation of late morbidity in patients with carcinomas of the uterine cervix following a dose rate change. *Radiother Oncol*. 1997;42:137–141.
348. Newman G. Increased morbidity following the introduction of remote afterloading, with increased dose rate, for cancer of the cervix. *Radiother Oncol*. 1996;39:97–103.
349. Patel FD, Negi PS, Sharma SC, et al. Dose rate correction in medium dose rate brachytherapy for carcinoma of the cervix. *Radiother Oncol*. 1998;49:317–323.
350. Swift PS, Purser P, Roberts LW, et al. Pulsed low dose rate brachytherapy for pelvic malignancies. *Int J Radiat Oncol Biol Phys*. 1997;37:811–817.
351. Bachtary B, Dewitt A, Pintilie M, et al. Comparison of late toxicity between continuous low-dose-rate and pulsed-dose-rate brachytherapy in cervical cancer patients. *Int J Radiat Oncol Biol Phys*. 2005;63:1077–1082.
352. Lee LJ, Das IJ, Higgins SA, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part III: Low-dose-rate and pulsed-dose-rate brachytherapy. *Brachytherapy*. 2012;1:53–57.
353. Hareyama M, Sakata KI, Oouchi A, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. *Cancer*. 2002;94:117–124.
354. Ferrigno R, Nishimoto IN, Novaes PE, et al. Comparison of low and high dose rate brachytherapy in the treatment of uterine cervix cancer: retrospective analysis of two sequential series. *Int J Radiat Oncol Biol Phys*. 2005;62:1108–1116.
355. Falkenberg E, Kim RY, Meleth S, et al. Low-dose-rate vs. high-dose-rate intracavitary brachytherapy for carcinoma of the cervix: the University of Alabama at Birmingham (UAB) experience. *Brachytherapy*. 2006;5:49–55.
356. Stewart AJ, Viswanathan AN. Current controversies in high-dose-rate versus low-dose-rate brachytherapy for cervical cancer. *Cancer*. 2006;107:908–915.
357. Yoshida K, Yamazaki H, Takenaka T, et al. A dose-volume analysis of magnetic resonance imaging-aided high-dose-rate image-based interstitial brachytherapy for uterine cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010;77:765–772.
358. Nomden CN, de Leeuw AA, Moerland MA, et al. Clinical use of the Utrecht applicator for combined intracavitary/interstitial brachytherapy treatment in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2012;82:1424–1430.
359. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: is there an optimal fractionation schedule? *Int J Radiat Oncol Biol Phys*. 1999;43:359–366.
360. Anker CJ, Cachoeira CV, Boucher KM, et al. Does the entire uterus need to be treated in cancer of the cervix? Role of adaptive brachytherapy. *Int J Radiat Oncol Biol Phys*. 2010;76:704–712.
361. Forrest JL, Ackerman I, Barbera L, et al. Patient outcome study of concurrent chemoradiation, external beam radiotherapy, and high-dose rate brachytherapy in locally advanced carcinoma of the cervix. *Int J Gynecol Cancer*. 2010;20:1074–1078.
362. Ohno T, Nakano T, Kato S, et al. Accelerated hyperfractionated radiotherapy for cervical cancer: multi-institutional prospective study of forum for nuclear cooperation in Asia among eight Asian countries. *Int J Radiat Oncol Biol Phys*. 2008;70:1522–1529.
363. Erridge SC, Kerr GR, Downing D, et al. The effect of overall treatment time on the survival and toxicity of radical radiotherapy for cervical carcinoma. *Radiother Oncol*. 2002;63:59–66.
364. Monk BJ, Tian C, Rose PG, et al. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. *Gynecol Oncol*. 2007;105:427–433.
365. Feddock J, Baldwin L, Chen L, et al. In the era of high dose rate (HDR) brachytherapy, prolongation of total treatment time for cervical cancer may not be as detrimental as previously thought. *Gynecol Oncol*. 2012;125:S61 (abstract).
366. Spanos WJ, Clery M, Perez CA, et al. Late effect of multiple daily fraction schedule for advanced pelvic malignancies (RTOG 8502). *Int J Radiat Oncol Biol Phys*. 1994;29:961–967.
367. Movva S, Rodriguez L, Arias-Pulido H, et al. Novel chemotherapy approaches for cervical cancer. *Cancer*. 2009;115:3166–3180.
368. Dueñas-González A, Cetina L, Coronel J, et al. Pharmacotherapy options for locally advanced and advanced cervical cancer. *Drugs*. 2010;70:403–432.
369. Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1999;73:177–183.
370. Pieterse QD, Trimbos JBMZ, Kijman A, et al. Postoperative radiation therapy improves prognosis in patients with adverse risk factors in localized, early-stage cervical cancer: a retrospective comparative study. *Int J Gynecol Cancer*. 2006;16:1112–1118.
371. Ryu SY, Lee WM, Kim K, et al. Randomized clinical trial of weekly vs. triweekly cisplatin-based chemotherapy concurrent with radiotherapy in the treatment of locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:e577–e581.
372. Kim JH, Kim HJ, Hon S, et al. Post-hysterectomy radiotherapy in FIGO stage IB-IIIB uterine cervical carcinoma. *Gynecol Oncol*. 2005;96:407–414.
373. Uno T, Ito H, Isobe K, et al. Postoperative pelvic radiotherapy for cervical cancer patients with positive parametrial invasion. *Gynecol Oncol*. 2005;96:335–340.
374. Estape RE, Angioli R, Madrigal M, et al. Close vaginal margins as a prognostic factor after radical hysterectomy. *Gynecol Oncol*. 1998;68:229–232.
375. Kim RY, Salter MM, Shingleton HM. Adjuvant postoperative radiation therapy following radical hysterectomy in stage IB carcinoma of the cervix: analysis of treatment failure. *Int J Radiat Oncol Biol Phys*. 1988;14:445–449.
376. Small W Jr, Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy*. 2012;11:58–67.
377. Chen M-F, Tseng C-J, Tseng C-C, et al. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys*. 2007;67:1438–1444.
378. Tierney JF, Vale C, Symonds P. Concomitant and neoadjuvant chemotherapy for cervical cancer. *Clin Oncol*. 2008;20:401–416.
379. Al-Mansour Z, Verschraegen C. Locally advanced cervical cancer: what is the standard of care? *Curr Opin Oncol*. 2010;22:503–512.
380. Rodríguez Villalba S, Díaz-Caneja Planell C, Cervera Grau JM. Current opinion in cervix carcinoma. *Clin Transl Oncol*. 2011;13:378–384.
381. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340:1144–1153.
382. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340:1154–1161.
383. National Cancer Institute. NCI issues clinical announcement on cervical cancer: Chemotherapy plus radiation therapy improves survival. [Web page] Available at www.nih.gov/news/pr/fcb99/nci-22.htm accessed April 21, 2012).
384. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage IB cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. *Am J Obstet Gynecol*. 2007;197:503.e1–6.
385. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*. 2001;358:781–786.
386. Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy

- for cervical cancer—a meta-analysis. *Clin Oncol*. 2002;14:203–212.
387. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev*. 2010;(1):CD008285.
 388. Tierney J. Neoadjuvant Chemotherapy for Cervix Cancer Meta-analysis (NACCCMA) Collaboration. Neoadjuvant chemotherapy for locally advanced cervical cancer (Review). *Cochrane Database Syst Rev*. 2004;(1):CD001774.
 389. Rydzewska L, Tierney J, Vale CL, et al. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. *Cochrane Database Syst Rev*. 2010; 20;(1):CD007406.
 390. Information on trial NCT 00039338 (EORTC 55994) available online at: <http://clinicaltrials.gov/ct2/show/NCT00039338> (Accessed on April 23, 2012).
 391. Information on trial NCT 00193739 available online at: <http://clinicaltrials.gov/ct2/show/NCT00193739> (Accessed on April 23, 2012).
 392. Azria E, Morice P, Haie-Meder C, et al. Results of hysterectomy in patients with bulky residual disease at the end of chemoradiotherapy for stage IB2/II cervical carcinoma. *Ann Surg Oncol*. 2005;12(4):332–337.
 393. Distefano M, Fagotti A, Ferrandina G, et al. Preoperative chemoradiotherapy in locally advanced cervical cancer: long term outcome and complications. *Gynecol Oncol*. 2005;99:S166–S170.
 394. Houvenaeghel G, Lelievre L, Gonzague-Casabianca L, et al. Long-term survival after concomitant chemoradiotherapy prior to surgery in advanced cervical carcinoma. *Gynecol Oncol*. 2006;100:338–343.
 395. Classe JM, Rauch P, Rodier JF, et al. Surgery after concurrent chemoradiotherapy and brachytherapy for the treatment of advanced cervical cancer: morbidity and outcome: results of a multicenter study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer). *Gynecol Oncol*. 2006;102:S23–S29.
 396. Morice P, Uzan C, Zafrani Y, et al. The role of surgery after chemoradiation therapy and brachytherapy for stage IB2/II cervical cancer. *Gynecol Oncol*. 2007;107:S122–S124.
 397. Delpech Y, Haie-Meder C, Rey A, et al. Para-aortic involvement and interest of para-aortic lymphadenectomy after chemoradiation in stage IB2/II cervical carcinoma radiologically confined to the pelvic cavity. *Ann Surg Oncol*. 2007;14:3223–3231.
 398. Ferrandina G, Legge F, Fagotti A, et al. Preoperative concomitant chemoradiotherapy in locally advanced cervical cancer: Safety, outcome, and prognostic measures. *Gynecol Oncol*. 2007; 107:S127–S132.
 399. Darus CJ, Callahan MB, Nguyen QN, et al. Chemoradiation with and without adjuvant extrafascial hysterectomy for IB2 cervical carcinoma. *Int J Gynecol Cancer*. 2008;18:730–735.
 400. Huguet F, Cojocariu O-M, Levy P, et al. Preoperative concurrent radiation therapy and chemotherapy for bulky Stage IB2, IIA, and IIB carcinoma of the uterine cervix with proximal parametrial invasion. *Int J Radiation Oncology Biol Phys*. 2008;72:1508–1515.
 401. Fanfani F, Fagotti A, Ferrandina G, et al. Neoadjuvant chemoradiation followed by radical hysterectomy in FIGO Stage IIB cervical cancer. *Int J Gynecol Oncol*. 2009;19:1119–1124.
 402. Colombo PE, Bertrand MM, Gutowski M, et al. Total laparoscopic radical hysterectomy for locally advanced cervical carcinoma (stages IIB, IIA, and bulky stages IB) after concurrent chemoradiation therapy: surgical morbidity and oncological results. *Gynecol Oncol*. 2009; 114:404–409.
 403. Motton S, Houvenaeghel G, Delannes M, et al. Results of surgery after concurrent chemoradiotherapy in advanced cervical cancer, comparison of extended hysterectomy and extrafascial hysterectomy. *Int J Gynecol Cancer*. 2010;20:268–275.
 404. Touboul C, Uzan C, Mauguén A, et al. Prognostic factors and morbidities after completion surgery in patients undergoing initial chemoradiation therapy for locally advanced cervical cancer. *Oncologist*. 2010;15:405–415.
 405. Ferrandina G, Margarit PA, Smaniotto D, et al. Long-term analysis of clinical outcome and complications in the locally advanced cervical cancer patients administered concomitant chemoradiation followed by radical surgery. *Gynecol Oncol*. 2010;119:404–414.
 406. Ferrandina G, Lucida A, Paglia A, et al. Role of comorbidities in locally advanced cervical cancer patients administered preoperative chemoradiation: impact on outcome and treatment-related complications. *Eur J Surg Oncol*. 2012;38:238–244.
 407. Morice P, Rouanet P, Rey A, et al. Results of the GYNECO 02 study, an FNCLCC phase III trial comparing hysterectomy with no hysterectomy in patients with a (clinical and radiological) complete response after chemoradiation therapy for stage IB2 or II cervical cancer. *Oncologist*. 2012;17:64–71.
 408. Gaffney DK, Soisson AP. Simple or complex: optimal therapy for cancer of the cervix. *Gynecol Oncol*. 2010;119:401–403.
 409. Petsuksiri J, Chansilpa Y, Therasakvichya S, et al. Treatment options in bulky stage IB cervical carcinoma. *Int J Gynecol Cancer*. 2008;18:1153–1162.
 410. Klopp AH, Eifel PJ. Chemoradiotherapy for cervical cancer in 2010. *Curr Oncol Rep*. 2011; 13(1):77–85.
 411. Rosa DD, Medeiros LRF, Edelweiss MI, et al. Adjuvant platinum-based chemotherapy for early stage cervical cancer. *Cochrane Database Syst Rev*. 2009;(3):CD005342.
 412. Information on trial NCT 01101451 available online at: <http://clinicaltrials.gov/ct2/show/NCT01101451> (Accessed on April 30, 2012).
 413. Information on trial NCT 00980954 available online at: <http://clinicaltrials.gov/ct2/show/NCT00980954> (Accessed on April 30, 2012).
 414. Information on trial NCT 00806117 available online at: <http://clinicaltrials.gov/ct2/show/NCT00806117> (Accessed on April 30, 2012).
 415. Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. *Int J Radiation Oncology Biol Phys*. 2003;55:1226–1232.
 416. Dueñas-González A, Zarbá JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol*. 2011;29(13):1678–1685.
 417. Information on trial NCT 01414608 available online at: <http://clinicaltrials.gov/ct2/show/NCT01414608> (Accessed on April 30, 2012).
 418. Information on trial NCT 01295502 available online at: <http://clinicaltrials.gov/ct2/show/NCT01295502> (Accessed on April 30, 2012).
 419. Randall ME, Evans L, Greven KM, et al. Interstitial re-irradiation for recurrent gynecologic malignancies: results and analysis of prognostic factors. *Gynecol Oncol*. 1993;48:23–31.
 420. Brabham JG, Cardenas HR. Permanent interstitial reirradiation with ¹⁹²Au as salvage therapy for low volume recurrent gynecologic malignancies. *Am J Clin Oncol*. 2009;32:417–422.
 421. Luo W, Aryal P, Randall ME. Calculation of prescribed dose for permanent implant with Cs-131 using LQ equation including resensitization. *Med Phys*. 2012;39:3811.
 422. Grigsby PW, Vest ML, Perez CA. Recurrent carcinoma of the cervix exclusively in the para-aortic nodes following radiation therapy. *Int J Radiat Oncol Biol Phys*. 1994;28:451–455.
 423. Kim JS, Kim SY, Kim KH, et al. Hyperfractionated radiotherapy with concurrent chemotherapy for para-aortic lymph node recurrence in carcinoma of the cervix. *Int J Radiat Oncol Biol Phys*. 2003;55:1247–1253.
 424. Niibe Y, Kenjo M, Kazumoto T, et al. Japanese isolated para-aortic lymph node recurrence of uterine cervical carcinoma study group. Multi-institutional study of radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma: 84 subjects of a population of more than 5,000. *Int J Radiat Oncol Biol Phys*. 2006;66:1366–1369.
 425. Marnitz S, Kohler C, Muller M, et al. Indications for primary and secondary exenterations in patients with cervical cancer. *Gynecol Oncol*. 2006;103:1023–1030.
 426. Berek JS, Howe C, Lagasse LD, et al. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. *Gynecol Oncol*. 2005;99:153–159.
 427. Benn T, Brooks RA, Powell MA, et al. Pelvic exenteration in gynecologic oncology: a single institution study of over 20 years. *Gynecol Oncol*. 2011;122:14–18.
 428. Maggioni A, Rovigione G, Landoni F, et al. Pelvic exenteration: ten year experience at the European Institute of Oncology in Milan. *Gynecol Oncol*. 2009;114:64–68.
 429. Iglesias DA, Westin SN, Rallapalli V, et al. The effect of body mass index on surgical outcomes and survival following pelvic exenteration. *Gynecol Oncol*. 2012;125:336–342.
 430. Bricker EM. Bladder substitution after pelvic evisceration. *Surg Clin North Am*. 1950;30: 1511–1521.
 431. Penalver MA, Angioli R, Mirhashemi R, et al. Management of early and late complications of ileocolonic continent urinary reservoir (Miami pouch). *Gynecol Oncol*. 1998;69:185–191.
 432. Ramirez PT, Modesitt SC, Morris M, et al. Functional outcomes and complications of continent urinary diversions in patients with gynecologic malignancies. *Gynecol Oncol*. 2002;85: 285–291.
 433. Ungar L, Palfalvi L. Pelvic exenteration without external urinary or fecal diversion in gynecologic cancer patients. *Int J Gynecol Cancer*. 2006; 16:364–368.
 434. McCraw JB, Massey FM, Shanklin KD, et al. Vaginal reconstruction with gracilis myocutaneous flaps. *Plast Reconstr Surg*. 1976;58:176–183.
 435. Ratliff CR, Gershenson DM, Morris M, et al. Sexual adjustment of patients undergoing gracilis myocutaneous flap vaginal reconstruction in conjunction with pelvic exenteration. *Cancer*. 1996;78:2229–2235.
 436. Soper JT, Larson D, Hunter VJ, et al. Short gracilis myocutaneous flaps for vulvovaginal reconstruction after radical pelvic surgery. *Obstet Gynecol*. 1989;74:823–827.

437. O'Connell C, Mirhashemi R, Kassira N, et al. Formation of functional neovagina with vertical rectus abdominis musculocutaneous (VRAM) flap after total pelvic exenteration. *Ann Plast Surg.* 2005;55:470–473.
438. Soper JT, Havrilesky LJ, Secord AA, et al. Rectus abdominis myocutaneous flaps for neovaginal reconstruction after radical pelvic surgery. *Int J Gynecol Cancer.* 2005;15:542–548.
439. Sood AK, Cooper BC, Sorosky JJ, et al. Novel modification of the vertical rectus abdominis myocutaneous flap for neovagina creation. *Obstet Gynecol.* 2005;105:514–518.
440. Soper JT, Secord AA, Havrilesky LJ, et al. Comparison of gracilis and rectus abdominis myocutaneous flap neovaginal reconstruction performed during radical pelvic surgery: flap-specific morbidity. *Int J Gynecol Cancer.* 2007;17:298–303.
441. Mirhashemi R, Averette HE, Estape R, et al. Low colorectal anastomosis after radical pelvic surgery: a risk factor analysis. *Am J Obstet Gynecol.* 2000;183:1375–1379; discussion 1379–1380.
442. Husain A, Curtin J, Brown C, et al. Continent urinary diversion and low-rectal anastomosis in patients undergoing exenterative procedures for recurrent gynecologic malignancies. *Gynecol Oncol.* 2000;78:208–211.
443. Maneo A, Landoni F, Cormio G, et al. Radical hysterectomy for recurrent or persistent cervical cancer following radiation therapy. *Int J Gynecol Cancer.* 1999;9:295–301.
444. Coleman RL, Keeney ED, Freedman RS, et al. Radical hysterectomy for recurrent carcinoma of the uterine cervix after radiotherapy. *Gynecol Oncol.* 1994;55:29–35.
445. Ito H, Shigematsu N, Kawada T, et al. Radiotherapy for centrally recurrent cervical cancer of the vaginal stump following hysterectomy. *Gynecol Oncol.* 1997;67:154–161.
446. Ijaz T, Eifel PJ, Burke T, et al. Radiation therapy of pelvic recurrence after radical hysterectomy for cervical carcinoma. *Gynecol Oncol.* 1998;70:241–246.
447. Grigsby PW. Prospective phase I/II study of irradiation and concurrent chemotherapy for recurrent cervical cancer after radical hysterectomy. *Int J Gynecol Oncology.* 2004;14:860–864.
448. Kotsu T, Yoshida K, Yamazaki H, et al. Preliminary results of magnetic resonance imaging-aided high-dose-rate interstitial brachytherapy for recurrent uterine carcinoma after curative surgery. *J Radiat Res (Tokyo).* 2011;52:329–334.
449. Beitler JJ, Anderson PS, Wadler S, et al. Pelvic exenteration for cervix cancer: would additional intraoperative interstitial brachytherapy improve survival? *Int J Radiat Oncol Biol Phys.* 1997;38:143–148.
450. Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 2007;69:504–511.
451. Long HJ 3rd. Management of metastatic cervical cancer: review of the literature. *J Clin Oncol.* 2007;25:2966–2974.
452. Pectasides D, Kamposioras K, Papaxoinis G, et al. Chemotherapy for recurrent cervical cancer. *Cancer Treat Rev.* 2008;34:603–613.
453. Moore DH. Chemotherapy for advanced, recurrent, and metastatic cervical cancer. *J Natl Compr Canc Netw.* 2008;6:53–57.
454. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2004;22:3113–3119.
455. Long HJ 3rd, Bundy BN, Grendys EC Jr, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2005;23:4626–4633.
456. Hirte HW, Strychowski JE, Oliver T, et al. Chemotherapy for recurrent, metastatic, or persistent cervical cancer: a systematic review. *Int J Gynecol Cancer.* 2007;17:1194–1204.
457. Bloss JD, Blessing JA, Behrens BC, et al. Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2002;20:1832–1837.
458. Information on trial NCT 00803062 available online at: <http://clinicaltrials.gov/ct2/show/NCT00803062> (Accessed on May 2, 2012).
459. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2009;27:4649–4655.
460. Cella D, Huang HQ, Monk BJ, et al. Health-related quality of life outcomes associated with four cisplatin-based doublet chemotherapy regimens for stage IVB recurrent or persistent cervical cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010;119:531–537.
461. Sit AS, Kelley JL, Gallion HH, et al. Paclitaxel and carboplatin for recurrent or persistent cancer of the cervix. *Cancer Invest.* 2004;22:368–373.
462. Tinker AV, Bhagat K, Swenerton KD, et al. Carboplatin and paclitaxel for advanced and recurrent cervical carcinoma: the British Columbia Cancer Agency experience. *Gynecol Oncol.* 2005;98:54–58.
463. Moore KN, Herzog TJ, Lewin S, et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. *Gynecol Oncol.* 2007;105:299–303.
464. Pectasides D, Fountzilas G, Papaxoinis G, et al. Carboplatin and paclitaxel in metastatic or recurrent cervical cancer. *Int J Gynecol Cancer.* 2009;19:777–781.
465. Saito I, Kitagawa R, Fukuda H, et al. A phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent cervical cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group Study (JCOG0505). *Jpn J Clin Oncol.* 2010;40:90–93.
466. Kitagawa R, Katsumata N, Shibata T, et al. A randomized, phase III trial of paclitaxel plus carboplatin (TC) versus paclitaxel plus cisplatin (TP) in stage IVB, persistent or recurrent cervical cancer: Japan Clinical Oncology Group study (JCOG0505). *J Clin Oncol.* 2012;30:15s, Abstract 5006.
467. Tiersten AD, Sellick MJ, Hershman DL, et al. Phase II study of topotecan and paclitaxel for recurrent, persistent, or metastatic cervical carcinoma. *Gynecol Oncol.* 2004;92:635–638.
468. Symonds RP, Davidson SE, Chan S, et al. SCOTCERV: a phase II trial of docetaxel and gemcitabine as second line chemotherapy in cervical cancer. *Gynecol Oncol.* 2011;123:105–109.
469. Tewari KS, Monk BJ. The rationale for the use of non-platinum chemotherapy doublets for metastatic and recurrent cervical carcinoma. *Clin Adv Hematol Oncol.* 2010;8:108–115.
470. Information on trial NCT 01405235 available online at: <http://clinicaltrials.gov/ct2/show/NCT01405235> (Accessed on May 9, 2012).
471. del Campo JM, Prat A, Gil-Moreno A, et al. Update on novel therapeutic agents for cervical cancer. *Gynecol Oncol.* 2008;110:S72–S76.
472. Monk BJ, Willmott LJ, Sumner DA. Anti-angiogenesis agents in metastatic or recurrent cervical cancer. *Gynecol Oncol.* 2010;116:181–186.
473. Soonthornthum T, Arias-Pulido H, Joste N, et al. Epidermal growth factor receptor as a biomarker for cervical cancer. *Ann Oncol.* 2011;22:2166–2178.
474. Goncalves A, Fabbro M, Lhomme C, et al. A phase II trial to evaluate gefitinib as second- or third-line treatment in patients with recurring locoregionally advanced or metastatic cervical cancer. *Gynecol Oncol.* 2008;108:42–46.
475. Schilder RJ, Sill MW, Lee YC, et al. A phase II trial of erlotinib in recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Int J Gynecol Cancer.* 2009;19:929–933.
476. Santin AD, Sill MW, McMeekin DS, et al. Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011;122:495–500.
477. Farley J, Sill MW, Birrer M, et al. Phase II study of cisplatin plus cetuximab in advanced, recurrent, and previously treated cancers of the cervix and evaluation of epidermal growth factor receptor immunohistochemical expression: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011;121:303–308.
478. Kurtz JE, Hardy-Bessard AC, Deslandres M, et al. Cetuximab, topotecan and cisplatin for the treatment of advanced cervical cancer: a phase II GINECO trial. *Gynecol Oncol.* 2009;113:16–20.
479. Information on trial NCT 00997009 available online at: <http://clinicaltrials.gov/ct2/show/NCT00997009> (Accessed on May 9, 2012).
480. Monk BJ, Sill MW, Burger RA, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2009;27:1069–1074.
481. Mackay HJ, Tinker A, Winquist E, et al. A phase II study of sunitinib in patients with locally advanced or metastatic cervical carcinoma: NCIC CTG Trial IND.184. *Gynecol Oncol.* 2010;116:163–167.
482. Monk BJ, Mas Lopez L, Zarba JJ, et al. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. *J Clin Oncol.* 2010;28:3562–3569.
483. Monk BJ, Pandite LN. Survival data from a phase II, open-label study of pazopanib or lapatinib monotherapy in patients with advanced and recurrent cervical cancer. *J Clin Oncol.* 2011;29:4845.
484. Information on trial NCT 01267253 available online at: <http://clinicaltrials.gov/ct2/show/NCT01267253> (Accessed on May 9, 2012).
485. Information on trial NCT 01229930 available online at: <http://clinicaltrials.gov/ct2/show/NCT01229930> (Accessed on May 9, 2012).
486. Information on trial NCT 01266447 available online at: <http://clinicaltrials.gov/ct2/show/NCT01266447> (Accessed on May 9, 2012).
487. Information on trial NCT 01281852 available at <http://clinicaltrials.gov/ct2/show/NCT01281852> (Accessed on May 9, 2012).
488. Information on trial NCT 01237067 available online at: <http://clinicaltrials.gov/ct2/show/study/NCT01237067> (Accessed on May 9, 2012).
489. Averette HE, Nguyen HN, Donato DM, et al. Radical hysterectomy for invasive cervical cancer: a 25-year prospective experience with the Miami technique. *Cancer.* 1993;71:1422–1437.
490. Artman LE, Hoskins WJ, Bibro MC, et al. Radical hysterectomy and pelvic lymphadenectomy

- for stage IB carcinoma of the cervix: 21 years experience. *Gynecol Oncol.* 1987;28:8–13.
491. Lee YN, Wang KL, Lin MH, et al. Radical hysterectomy with pelvic lymph node dissection for treatment of cervical cancer: a clinical review of 954 cases. *Gynecol Oncol.* 1989;32:135–142.
 492. Ralph G, Tamussino K, Lichtenegger W. Urological complications after radical abdominal hysterectomy for cervical cancer. *Baillieres Clin Obstet Gynaecol.* 1988;2:943–952.
 493. Levran SG, Fruchter RG, Maiman M. Radical hysterectomy for cervical cancer: morbidity and survival in relation to weight and age. *Gynecol Oncol.* 1992;45:317–322.
 494. Cohn DE, Swisher EM, Herzog TJ, et al. Radical hysterectomy for cervical cancer in obese women. *Obstet Gynecol.* 2000;96:727–731.
 495. Franchi M, Trimpos JB, Zanaboni F, et al. Randomised trial of drains versus no drains following radical hysterectomy and pelvic lymph node dissection: a European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group (EORTC-GCG) study in 234 patients. *Eur J Cancer.* 2007;43:1265–1268.
 496. Patsner B, Hackett TE. Use of the omental J-flap for prevention of postoperative complications following radical abdominal hysterectomy: report of 140 cases and literature review. *Gynecol Oncol.* 1997;65:405–407.
 497. Jhingran A, Eifel PJ. Perioperative and postoperative complications of intracavitary radiation for FIGO stage I-III carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2000;46:1177–1183.
 498. Perez CA, Grigsby PW, Castro-Vita H, et al. Carcinoma of the uterine cervix. II. Lack of impact of prolongation of overall treatment time on morbidity of radiation therapy. *Int J Radiat Oncol Biol Phys.* 1996;34:3–11.
 499. Perez CA, Grigsby PW, Lockett MA, et al. Radiation therapy morbidity in carcinoma of the uterine cervix: dosimetric and clinical correlation. *Int J Radiation Oncol Biol Phys.* 1999;44:855–866.
 500. Eifel PJ, Levenback C, Wharton JT, et al. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1995;32:1289–1300.
 501. Andreyev HJ, Vlavianos P, Blake P, et al. Gastrointestinal symptoms after pelvic radiotherapy: role for the gastroenterologist. *Int J Radiat Oncol Biol Phys.* 2005;62:1461–1471.
 502. Parkin DE, Davis JA, Symonds RP. Urodynamic findings following radiotherapy for cervical carcinoma. *Br J Urol.* 1988;61:213–217.
 503. Lajer H, Thranov KR, Skovgaard LT, et al. Late urologic morbidity in 177 consecutive patients after radiotherapy for cervical carcinoma: a longitudinal study. *Int J Radiat Oncol Biol Phys.* 2002;54:1356–1361.
 504. Bergmark K, Avall-Lundqvist E, Dickman PW, et al. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med.* 1999;340:1383–1389.
 505. Huh SJ, Kim B, Kang MK, et al. Pelvic insufficiency fracture after pelvic irradiation in uterine cervix cancer. *Gynecol Oncol.* 2002;86:264–268.
 506. Narayanan P, Nobbenhuis M, Reynolds KM, et al. Fistulas in malignant gynecologic disease: etiology, imaging, and management. *RadioGraphics.* 2009;4:1073–1083.
 507. Feddock J, DeSimone C, Kudrimoti M, et al. Risk factors for fistula formation in patients with cervical cancer treated with radiation therapy include postradiation biopsy. *Gynecol Oncol.* 2011;120:S114 (abstract).
 508. Ikushima H, Osaki K, Furutani S, et al. Pelvic bone complications following radiation therapy of gynecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures. *Gynecol Oncol.* 2006;103:1100–1104.
 509. Oh D, Huh SJ, Nam H, et al. Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. *Int J Radiat Oncol Biol Phys.* 2008;70:1183–1188.
 510. Fink D, Chetty N, Lehm JP, et al. Hyperbaric oxygen therapy for delayed radiation injuries in gynecologic cancers. *Int J Gynecol Cancer.* 2006;16:638–642.
 511. Craighead P, Shea-Budgell MA, Nation J, et al. Hyperbaric oxygen therapy for late radiation tissue injury in gynecologic malignancies. *Curr Oncol.* 2011;18:220–227.
 512. Green JA, Kirwan JJ, Tierney J, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database Syst Rev.* 2005;(1):CD002225.
 513. Vale CL, Tierney JF, Davidson SE, et al. Substantial improvement in UK cervical cancer survival with chemoradiotherapy: results of a Royal College of Radiologists' audit. *Clin Oncol.* 2010;22:590–601.
 514. Vale C, Nightingale A, Spera N, et al. Late complications from chemoradiotherapy for cervical cancer: reflections from cervical cancer survivors 10 years after the National Cancer Institute alert. *Clin Oncol.* 2010;22:588–589.
 515. Bloss JD, DiSaia PJ, Mannel RS, et al. Radiation myelitis: a complication of concurrent cisplatin and 5-fluorouracil chemotherapy with extended field radiotherapy for carcinoma of the uterine cervix. *Gynecol Oncol.* 1991;43:305–308.
 516. Coulombe G, Thiessen B, Balkwil S, et al. Polyradiculopathy post-concomitant chemoradiation for carcinoma of the uterine cervix treated with pelvic and para-aortic fields. *Gynecol Oncol.* 2005;99:774–777.
 517. Matthews KS, Rocconi RP, Straughn JM Jr. Complete uterine necrosis following chemoradiation for advanced cervical cancer: a case report. *Gynecol Oncol.* 2007;106:265–267.
 518. Bifulco G, Dario Mandato V, Piccoli R, et al. Multiple bowel stenosis and perforation as long-term complications of chemoradiotherapy for advanced cervical cancer in a young woman: case report. *Tumori.* 2008;94:592–595.
 519. Samanta DR, Senapati SN, Sharma PK, et al. Acute myelogenous leukemia following treatment of invasive cervix carcinoma: a case report and a review of the literature. *J Cancer Res Ther.* 2009;5:302–304.
 520. Barbera L, Thomas G. Venous thromboembolism in cervical cancer. *Lancet Oncol.* 2008;9:54–60.
 521. Jacobson D, Lammi J, Zamba G, et al. Thromboembolic events in patients with cervical carcinoma: incidence and effect on survival. *Gynecol Oncol.* 2009;113:240–244.
 522. Wang F, Fu S, Freedman RS, et al. Venous thromboembolism syndrome in gynecologic cancer. *Int J Gynecol Cancer.* 2006;16(suppl. 1):458–471.
 523. Dusenbery KE, McGuire WA, Holt PJ, et al. Erythropoietin increases hemoglobin during radiation therapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 1994;29:1079–1084.
 524. Wun T, Law L, Harvey D, et al. Increased incidence of symptomatic venous thrombosis in patients with cervical carcinoma treated with concurrent chemotherapy, radiation, and erythropoietin. *Cancer.* 2003;98:1514–1520.
 525. Jacobson GM, Kamath RS, Smith BJ, et al. Thromboembolic events in patients treated with definitive chemotherapy and radiation therapy for invasive cervical cancer. *Gynecol Oncol.* 2005;96:470–474.
 526. Anders JC, Grigsby PW, Singh AK. Cisplatin chemotherapy (without erythropoietin) and risk of life-threatening thromboembolic events in carcinoma of the uterine cervix: the tip of the iceberg? A review of the literature. *Radiat Oncol.* 2006;1:14–17.
 527. Ferroni P, Formica V, Roselli M, et al. Thromboembolic events in patients treated with antiangiogenic drugs. *Curr Vasc Pharmacol.* 2010;8:102–113.

Corpus: Epithelial Tumors

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Endometrial cancer (EC) accounts for nearly 50% of all new gynecologic cancers diagnosed in the United States. It is the fourth most common malignancy in women, and the eighth most common cause of cancer death. The American Cancer Society (ACS) estimated that there were 47,130 new cases of endometrial carcinoma and 8,010 deaths from advanced or recurrent disease in 2012 (1). The death rate per 100,000 women from all malignancies in the United States was 160.49, with uterine cancers contributing at a rate of 4.13 (1). Worldwide, EC is only second to cervical cancer in frequency. The ACS reported that the incidence of EC rose 13% from 1987 to 2012; however, the numbers of deaths rose ~250% in the same time period. Endometrial carcinoma occurs most often in the sixth and seventh decades of life, with an average age at onset of 60 years. It is estimated that 75% to 85% of the cases occur in patients 50 years old and older, and 95% occur in patients over 40 years of age (2, 3). The disease, although reported in patients as young as age 16 years, is rare in patients younger than 30 years of age.

EC is commonly confined to the uterus at diagnosis. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program demonstrated that Stage I disease was found in 73% of patients, and 10% had Stage II disease (4). The 26th Annual Report of the International Federation of Gynecology and Obstetrics (FIGO) on 9,386 EC patients demonstrated that 83% of patients were Stage I or II (5). With the favorable disease distribution at presentation, it is not surprising that most patients have a favorable prognosis. Results from FIGO show that 85% to 91% of Stage I patients are alive at 5 years, and patients in the SEER database with localized disease have 96% 5-year survival (4, 5). As a result, EC has been considered a "good cancer"; that is, most patients present with early-stage, highly curable disease. Despite the favorable characteristics for most patients, those with high-risk factors, including increased age, higher tumor grade, aggressive histology, and advanced stage, face real challenges.

The management of EC has undergone continued evolution. In the past, most patients received some form of pre- or postoperative radiation in combination with a simple hysterectomy. With a better understanding of the relationship between uterine factor and risk of nodal disease and recurrence, selective use of surgical staging was integrated. This was followed by an era where, increasingly, surgical therapy expanded to include routine use of pelvic and paraaortic lymphadenectomy. Minimally invasive techniques were studied and have been routinely adopted into the management of women with EC. Today, greater emphasis is being placed on the selection of particular patients for whom lymphadenectomy may best offer better outcomes, and whose avoidance may result in less morbidity. Understanding tumor biology as it relates to predicting recurrence and survival, and how genetic changes can be exploited to direct postoperative therapies, represent our current challenge. Over 10 years ago,

the National Cancer Institute convened an expert panel to develop a national 5-year plan for research priorities in gynecologic cancers. The resulting report, Priorities of the Gynecologic Cancer Progress Review Group (PRG), specified that understanding tumor biology was the central key toward controlling gynecologic cancers. For EC, one of the top research priorities defined by the PRG was to identify prognostic and predictive markers for treatment efficacy and toxicity. In a 2006 State of the Science Meeting, in Manchester United Kingdom, a series of research questions on prevention, adjuvant treatment, and treatment of advanced or recurrent disease were proposed setting the stage for a clinical trials agenda over the next 5 years (6). In 2011, the Society of Gynecologic Oncologists conveyed a panel of experts that produced a report "Pathway to Progress in Women's Cancers". That report detailed areas of research, by disease site, on which the women's cancer community should focus for the next decade. For EC, the suggested road map for the future of women's cancer care research would include research related to obesity, predicting risk of metastatic disease, targeting therapy based on risk factors and molecular characteristics of disease, and cost-effective care to suggest prioritization of research strategies (7).

Current clinical controversies center on identifying which patient populations might benefit most from lymphadenectomy, developing alternatives to performing lymphadenectomy, and creating risk models to assist with selection of patients who may benefit most from adjuvant therapies. While we suspect that an increased use of surgical staging has translated to a better understanding of risk, data also suggest that despite negative nodes, uterine factors play a significant contribution to risk of recurrence. Current trends also suggest a less frequent use of pelvic radiation therapy or no use of any radiation (8). There have been important developments in chemotherapy in EC. Combination chemotherapy is increasingly used in the primary management of advanced and recurrent disease, and may hold promise in an adjuvant setting. How to best integrate radiation therapy and which specific techniques to consider are being studied in going clinical trials. Hormonal therapy remains an important option and our understanding of steroid receptors at a molecular level may help to determine which patients may benefit most (9). Enhanced understanding of biologically relevant targets has fostered the development of new classes of agents that attempt to exploit susceptible pathways in tumor cells, and targeted agents are being integrated into large clinical trials (10, 11).

ANATOMY

The uterus is a fibromuscular pelvic organ situated between the bladder and the rectum, and enveloped by peritoneal reflections.

It is divided into the fundus, isthmus, and cervix. The uterine wall is composed of the outer smooth muscle myometrium and inner cavity lined by glandular endometrial epithelium with supporting stroma (endometrium). Five paired ligaments cover or support the uterus: broad, round, utero-sacral, cardinal, and vesico uterine. The utero-sacral and cardinal ligaments provide the greatest support within the pelvis and, contrary to cervical cancer, are infrequently involved with tumor spread. Blood is supplied to the uterus by the uterine artery, a branch of the hypogastric artery, which enters the wall of the uterus at the isthmus after it crosses over the ureter. It anastomoses with the ovarian artery in the ovarian ligament.

Malignant transformation of the endometrium is manifest in many fashions based on the anatomical relationships. Tumor growth may be confined to the endometrium, invade the underlying myometrium, penetrate to the uterine serosal surface or adjacent bladder or rectum, or extend into the cervical canal and invade cervical glands or stroma. Peritoneal disease spread may occur via transmigration from the fallopian tubes or through serosal penetration. Hematogenous spread is not uncommon in EC.

The lymphatics of the myometrium drain into the subserosal network of lymphatics, which coalesce into larger channels before leaving the uterus. Lymph flows from the fundus toward the adnexa and infundibulopelvic ligaments. The lymph flow from the lower and middle thirds of the uterus tends to spread in the base of the broad ligaments toward the lateral pelvic sidewall. There are four drainage channels from the uterus: from the fundus; in the folds of the broad ligament, along the mesosalpinx and fallopian tubes; and along the round ligaments. The drainage sites are principally reflected in metastatic potential to pelvic and paraaortic lymph nodes (LN), and occasionally involve inguinal nodes.

EPIDEMIOLOGY AND RISK FACTORS

The most important risk factor for the development of EC is age. EC is primarily a disease of postmenopausal woman, with median age at cancer diagnosis of 60 years (5). Approximately 85% of cases occur after the age of 50, the peak age-specific incidence is from 75 to 79 years (109 per 100,000), and only 5% of cases are from patients younger than 40 years of age (2, 3, 12). The ACS showed the probability of developing a uterine cancer to be one in 142 from age 40 to 59, one in 124 from age 60 to 69, and one in 78 from age 70 and older (1). Not unexpectedly, with an aging U.S. population, the total number of cases of EC has shown yearly increases, whereas the annual age-adjusted incidence rate peaked in the mid-1970s (33.8 per 100,000) and has remained stable at 23 to 25 cases per 100,000 women over the last 10 years (1).

Race also appears to play a role in the development of EC. The rates of EC are highest in North America and northern Europe, lower in eastern Europe and Latin America, and lowest in Asia and Africa (13). Factors accounting for these findings include differences in rates of obesity, use of hormone replacement therapy (HRT), and reproductive factors. In the United States, non-Hispanic White women have the highest age-adjusted incidence of EC at 25.4 (per 100,000 women), compared to women of African American (19.5), Asian (15.8), or Hispanic (17) heritage (14). African American women, however, have a much higher mortality rate (7.1 vs. 3.9 per 100,000) and lower 5-year survival (61% vs. 84%) compared to non-Hispanic White women. Relative survival in White women exceeds that for African Americans by at least 7% at every stage of diagnosis (1). In the 2012 ACS report, incidence rates of uterine cancers in White women were noted to have stabilized, but have increased by nearly 2% per year for African American women since 2004 (1).

Multiple explanations have been suggested to explain the differences in outcomes between racial groups, including differences in frequency of high-risk tumor types, differences in access to care (reduced use of surgery and radiation), and differences in medical comorbidities among races. Data from SEER demonstrated that African American women were more frequently diagnosed with higher stage, grade, and high-risk histologies than non-Hispanic White women, but there was no difference in the frequency of recommended therapy types between races (4). In two analyses of nearly 1,200 patients with advanced or recurrent EC participating in phase 3 chemotherapy trials conducted by the Gynecologic Oncology Group (GOG), African American race was independently associated with a lower likelihood of response to chemotherapy (relative odds of response 0.62) and decreased overall survival (OS) (hazard ratio [HR], 1.26) compared to White women (15, 16). These results suggest that racial disparity in outcomes exist even though patients were treated in similar fashion. Interestingly, one small study comparing microarray-based expression profiling between stage-, grade-, and histology-matched African American and Caucasian patients found no clear differences in global gene expression profiles, suggesting that environmental or social issues played a greater role in explaining disparity (17).

Most cases of endometrial carcinoma are thought to be sporadic; however, some cases clearly have a hereditary basis. The Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) is an autosomal-dominant cancer susceptibility syndrome associated with early-onset colon, rectal, ovary, small bowel, ureter/renal pelvis cancers, and EC. Lynch syndrome-related ECs account for 2% to 5% of all ECs, and occur in nearly 10% of women diagnosed with EC less than 50 years of age (18). The lifetime risk of EC in Lynch syndrome women is 40% to 60%, a risk similar to that of developing colon cancer. The risk of ovarian cancer is 10% to 12%. In about 50% of cases where patients have both colonic and gynecologic cancers (endometrial or ovarian), the gynecologic cancer precedes the diagnosis of colon cancer (19). The syndrome is most commonly due to germ-line mutations of one of the DNA mismatch repair genes *MSH2*, *MLH1*, or *MSH6*. In one study, 23% of EC patients diagnosed at less than 50 years of age with one relative having a Lynch type cancer had a mismatch repair gene mutation (20). Prophylactic hysterectomy and bilateral salpingo-oophorectomy has been shown to be an effective strategy for preventing ovarian and ECs in these high-risk patients (21).

Controversy exists regarding the relationship between *BRCA1* and *BRCA2* mutations and the risk of EC. Germ-line mutations of *BRCA1* and *BRCA2* account for a large proportion of hereditary breast and ovarian/primary peritoneal cancers. In 1999, Hornreich et al. presented a case report of sisters with the same *BRCA1* mutation who were diagnosed with serous carcinomas of the uterus and suggested a possible association (22). Several larger studies have attempted to address this hypothesis. In one study of 199 Ashkenazi Jewish patients with EC from a single institution, Levine et al. genotyped all patients for founder *BRCA1* and *BRCA2* mutations that existed in that patient population. The frequency of germ-line mutations (3 per 199, 1.5%) in EC patients was comparable to the baseline rate of 2% in the Ashkenazi population, suggesting no increased risk (23). In a large prospective study by Beiner et al., 857 known *BRCA1* and *BRCA2* carriers aged 45 to 70 were followed over time for the development of EC (24). With an average length of follow-up of 3.3 years, six women developed EC. Four of the six patients had used tamoxifen. Compared to the expected rate of EC in a general population, *BRCA* carriers who did not receive tamoxifen did not have a significant increase in risk of developing EC, whereas those patients who had received tamoxifen had a 11.6 incidence ratio ($p = 0.0004$). Barak evaluated 289 Jewish women with EC (80% type I, 20% type II tumors) for predominant mutations in Jewish populations (*BRCA1*, *BRCA2*, *MSH2*,

MSH6 selected mutations). Five women were found with *BRCA1/2* mutations, reflecting a rate similar to that seen in the general Ashkenazi Jewish population, and the authors indicated the data did not support screening in based on an EC diagnosis (25).

The clinical picture in endometrial carcinoma is as varied as are the associated risk factors for its development. One of the paradigms for bridging the gaps between epidemiologic, clinical-pathologic, and molecular factors seen in EC types is the relatively simple, yet attractive, classification system of ECs suggested by Bokhman in 1983 (26). ECs are thought to broadly arise from one of two different pathways: estrogen dependent or estrogen independent (Table 22.1). Based on the clinical and histologic features, ECs have been divided into type I and type II tumors. Type I tumors are more common (85%), tend to be found in younger women, and develop via a precursor lesion of atypical hyperplasia. These tumors are associated with a predisposing history of hyperestrogenism. They tend to be well differentiated and have minimal myometrial invasion, and as a result typically have a favorable outcome. Type II tumors account for a small percentage of endometrial carcinomas, occur in an older population, and frequently develop in the face of an atrophic endometrium. About half of all relapses occur in this group. Serous, clear-cell, and perhaps grade 3 tumors fit into the type II category. Despite the broad generalizations of the two categories, translational science data lend support for a separation into these groups at a molecular level. For example, mutations of *TP53* are common in uterine papillary serous carcinoma (UPSC), and rare in type I tumors (27). In type I tumors, *PTEN* mutations are common, but are rare with UPSC tumors. Global gene expression profiles have also been shown to be different between type I and II tumors (28).

Endogenous or exogenous exposure to estrogen is believed to be an important risk factor for the development of endometrial hyperplasia and type I cancers (29). Estrogens not opposed by progestins lead to increased mitotic activity of endometrial cells, resulting in more frequent errors in DNA replication and somatic mutations (30). These genetic changes are manifest clinically in endometrial hyperplasia and cancer. Estrogen excess as

an etiology for cancers is supported by epidemiologic features of the disease. Patients with chronic anovulation, nulliparity, early age of menarche, and late menopause have classically been identified with EC. Occasionally, endometrial hyperplasia or cancer develops in the setting of an estrogen-producing ovarian tumor (granulosa cell tumor) (31). The use of unopposed estrogens as part of hormone replacement strategies was first defined as an important risk factor in 1975 when the age-adjusted rate for EC peaked at nearly 33.8 per 100,000 (32, 33). A meta-analysis of 30 studies showed that the relative risk of ever users of estrogen therapy was 2.3 compared to nonusers, and it increased to 9.5 in users of 10 or more years (34).

Obesity is an increasingly common problem in the United States, and is estimated to account for 17% to 46% of EC incidence in postmenopausal women (35). Studies have shown that plasma concentrations of androstenedione and estrogens are correlated with body weight in postmenopausal women (36). Aromatization of androstenedione to estrone in adipose cells is believed to be the principal mechanism of excess estrogen production. While much of the data suggest that the relationship is strongest between estrogen exposure and type I cancers, Weiss et al. demonstrated in a case-control study that the risk of more aggressive tumors (higher grade or higher stage) was also seen with unopposed estrogen therapy, obesity, low parity, and history of diabetes. The authors suggested that the risk of EC was influenced by similar risk factors, regardless of tumor aggressiveness (37). Diabetes has also been associated classically with type I ECs (38, 39). Only non-insulin-dependent diabetes (type 2 diabetes mellitus [DM]), characterized by insulin resistance and elevated insulin levels, appears to be associated with EC (40). Hyperinsulinemia and higher levels of insulin-like growth factor 1 are thought to have neoplastic potential and, coupled with increased estrogen, are responsible for cancer development (41, 42).

Tamoxifen and Endometrial Cancer

Tamoxifen is a selective estrogen receptor modulator (SERM) with antiestrogenic properties in the breast, and estrogenic effects in tissues such as bone, the cardiovascular system, and the uterus. It has been used in prevention and treatment for all stages of breast cancer. An association with tamoxifen and EC was first reported by Killackey et al. in 1985 (43). The strongest data initially implicating tamoxifen use and the subsequent development of EC were published in 1989 by Fornander et al. (44). The investigators reviewed the frequency of new primary cancers as recorded in the Swedish Cancer Registry for a group of 1,846 postmenopausal women with early breast cancer who were included in a randomized trial of adjuvant tamoxifen. They noted a 6.4-fold increase in the relative risk of EC in 931 tamoxifen-treated patients compared to 915 patients in the control group. The dose of tamoxifen in this study was 40 mg/day, and the greatest cumulative risk of developing EC was after 5 years of tamoxifen use.

Fisher et al. published data regarding the association between tamoxifen use and the development of EC when they reported the findings of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial (45). Data regarding the rates of endometrial and other cancers were analyzed on 2,843 patients with node-negative, estrogen receptor (ER)-positive, invasive breast cancer randomly assigned to placebo or tamoxifen (20 mg/day) and on 1,220 tamoxifen-treated patients registered in NSABP B-14 subsequent to randomization. The average annual hazard rate for EC in the placebo group was 0.2 out of 1,000 and 1.6 out of 1,000 for the randomized tamoxifen-treated group. The relative risk of an EC occurring in the randomized, tamoxifen-treated group was 7.5. Similar results were seen in the 1,220 registered patients who received tamoxifen. The mean duration of tamoxifen

Table 22.1 Comparison Between Type I and Type II Endometrial Cancers

	Type I	Type II
<i>Clinical Features</i>		
Risk factors	Unopposed estrogen	Age
Race	White > Black	White = Black
Differentiation	Well differentiated	Poorly differentiated
Histology	Endometrioid	Nonendometrioid
Stage	I/II	III/IV
Prognosis	Favorable	Not favorable
<i>Molecular Features</i>		
Ploidy	Diploid	Aneuploid
K-ras overexpression	Yes	Yes
HER2/neu overexpression	No	Yes
P53 overexpression	No	Yes
<i>PTEN</i> mutations	Yes	No
Microsatellite instability	Yes	No

therapy was 35 months, with 36% of the ECs developing within 2 years of therapy. Of the 23 cases of endometrial cancer developing while on tamoxifen, six cases occurred following less than 12 months of exposure, suggesting that some of the cancers may have been present prior to starting tamoxifen therapy.

Any conclusions drawn regarding the risks of tamoxifen treatment in inducing EC must weigh the benefits of tamoxifen in reducing breast cancer recurrence and new contralateral breast cancers. In the B-14 trial, the cumulative rate per 1,000 women with breast cancer relapse was reduced from 227.8 in the placebo group to 123.5 in the randomized tamoxifen-treated group. In addition, the cumulative rate of contralateral breast cancer was reduced from 40.5 to 23.5, respectively, in the two groups. Taking into account the increased cumulative rate of EC, there was a 38% reduction in the 5-year cumulative hazard rate in the tamoxifen-treated group. Thus, the benefit of tamoxifen therapy for breast cancer outweighs the potential increase in EC being reported.

The suspected mechanism for EC development following tamoxifen exposure is thought to be related to its estrogenic effects on the endometrium. As such, type I, low-grade/early-stage cancers would be expected. A report from the Yale Tumor Registry by Magriples et al. suggested that uterine cancers occurring in breast cancer patients on tamoxifen may behave more aggressively and carry a worse prognosis (46). Other studies, however, have not been able to confirm these findings (Table 22.2) (45, 47–49). It would appear from the available literature that there is no difference in the stage, grade, or prognosis of ECs associated with tamoxifen use.

More commonly, breast cancer patients are being managed with different strategies, which may reduce the impact of tamoxifen on EC risk. Next generation SERM agents, such as raloxifene, are effective in preventing breast cancer and reducing osteoporosis. In a large case-control study of women with (547 cases) and without (1,410 controls) EC, raloxifene users had a 50% reduction in risk of EC compared to nonusers, and tamoxifen users had three times the odds of developing EC compared to those who had used raloxifene (50). Compared to SERMs,

aromatase inhibitors prevent estrogen synthesis by inhibiting the conversion of androgens to estrogens. Third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) are replacing tamoxifen for many breast cancer patients with ~50% of postmenopausal ER-positive patients receiving aromatase inhibitors (49). In clinical trials, compared to tamoxifen, aromatase inhibitors have lower incidences of vaginal bleeding or EC (50–53). In premenopausal patients, aromatase inhibitors have little activity, and tamoxifen will continue to have a role.

Protective Factors

Factors that reduce circulating estrogen levels (weight loss/exercise, cigarette smoking) appear to be protective against EC. Similarly, progestins antagonize the effects of estrogen on the endometrium and prevent the development of hyperplasia and cancer when added to estrogens (endogenous or exogenous). Combined estrogen–progestin HRT has been associated with reductions in the risk of EC in most, but not all, studies. Prior use of oral contraceptives also appears to be protective against the development of EC (54).

NATURAL HISTORY OF DISEASE

A better understanding of the natural history of EC has developed through evaluation of the patterns of spread. In a landmark study, the GOG performed a surgical pathologic study (GOG 33) in 621 patients with clinical Stage I–occult Stage II EC who underwent a standardized surgical procedure including exploration of the abdomen with biopsy of suspicious findings, collection of peritoneal fluid for cytologic evaluation, abdominal hysterectomy and bilateral salpingo-oophorectomy, and pelvic and paraaortic nodal dissection (55). The results of this study demonstrated important relationships regarding uterine tumor characteristics and spread of disease, and should be ingrained into the memory of those caring for patients with ECs.

Table 22.2 Clinicopathologic Data from Series Reporting on Tamoxifen-Associated Uterine Cancer

	Magriples	Barakat	Fisher	van Leeuwen	van Leeuwen	Total (%)
No. patients	15	23	25	17	23	103
FIGO stage						
I	7	15	21	14	17	74 (71.8)
II	0	2	1	2	3	8 (7.8)
III	2	5	1	0	0	8 (7.8)
IV	0	1	1	1	0	3 (2.9)
Unstaged	6	0	1	0	3	10 (9.7)
Histology						
Endometrioid	9	17	18	16	17	77 (74.8)
High-risk ^a	6	6	7	1	6	26 (25.2)
Grade (adenocarcinoma)						
Low (grade 1,2)	5	13	18	15	Not given	51 (72.9) ^b
High (grade 3)	10	4	5	0	Not given	19 (27.1) ^b
Deaths from uterine cancer	5 (33%)	5 (22%)	4 (16%)	3 (10%)	0 (0%)	17 (16.5)

^aIncludes papillary serous, clear-cell sarcoma.

^bGrade only known for 70 patients.

Overall, 22% of patients with seemingly uterine confined disease were found to have extrauterine spread. Pelvic and/or paraaortic metastases were found in 11% of patients, 12% had positive peritoneal cytology, 5% had adnexal involvement, and 6% had gross intraperitoneal spread. Nodal metastases were related to tumor grade and depth of myometrial invasion, and patients with positive cytology, or adnexal or intraperitoneal spread also had increased frequency of nodal disease.

Patterns of failure in patients with recurrent EC demonstrate, alone or in combination, hematogenous, lymphatic, intraperitoneal, or local/contiguous spread. As attention has increasingly focused on therapies (surgical, radiation, chemotherapy) to reduce particular sites of recurrences, several have argued for defining relationships between initial disease spread and subsequent risk of recurrence (56). In GOG 33, treatment was not specified by protocol, but results showed that outcomes could be predicted by extent of disease found at surgery, thus demonstrating the important relationship between what is learned at surgical staging and recurrence risk (57).

DIAGNOSTIC EVALUATION

Screening

Many ECs develop by way of a precursor lesion. Estrogen-related cancers frequently develop secondary to atypical endometrial hyperplasia (AEH) or demonstrate AEH in the uterus at the time of hysterectomy. Serous tumors also may develop endometrial intraepithelial carcinoma (EIC) through a precursor lesion (58). Prompt recognition of precursor lesions with institution of proper treatment will prevent cancers and their sequelae. The relatively low prevalence of EC in the population (5 per 1,000 women >45 years) makes standardized screening inefficient. There are a few uncontrolled studies lending some support to the efficacy of screening programs (59, 60). No randomized trials have been published. No health economic data have been presented in relation to the published reports. The American College of Obstetrics and Gynecology (ACOG) and the Society of Gynecologic Oncology do not recommend routine screening of patients for uterine cancer (61, 62). The ACS does recommend annual endometrial biopsies starting at age 35 for women known to have or be at risk for HNPCC.

In lieu of routine screening, prompt assessment of symptomatic patients and those at high risk should be considered. Because 95% of endometrial carcinomas occur in women of 40 years old and older, and because endometrial hyperplasia tends to occur in premenopausal and perimenopausal women, it is appropriate to evaluate individuals past their fourth decade of life if there is abnormal bleeding. Similarly, a higher degree of suspicion should be held for younger patients with high-risk characteristics including significant obesity, polycystic ovarian syndrome/chronic anovulation, or tamoxifen exposure.

Prevention

Due to the increased risk of EC associated with unopposed estrogens, women with an intact uterus should rarely, if ever, be prescribed estrogen-only replacement therapy. The addition of progestins to the regimens of patients treated with exogenous estrogen may prevent endometrial hyperplasia and protect against the development of carcinoma (54). Continuous or sequential progestin regimens may be used, but the most important factor is administration of a progestin for at least 10 to 14 days each month. In patients with chronic endogenous estrogen exposure such as obese women with polycystic ovarian syndrome or chronic anovulation, and perimenopausal women

with menometrorrhagia, periodic treatment with a progestin to create scheduled withdrawal bleeding and prevent hyperplasia may be considered (63).

In most cases, patients with hyperplasia with atypia should be treated by vaginal or abdominal hysterectomy to prevent the development of EC (64). Surgery is the definitive therapy as it stops bleeding, prevents cancer, and alleviates the potential of medical failure. Patients with AEH remain at high risk for recurrence of AEH or cancer during their lifetime, even after successful medical therapy (65). Most importantly, despite a preoperative diagnosis of AEH, many patients will be found to have a cancer at the time of hysterectomy (65, 66). Older data suggested that if the endometrial sample is obtained by a biopsy or curettage, 15% to 25% of patients with the diagnosis of atypical hyperplasia may have a uterine carcinoma (67). Prospective data from a large surgical-pathologic trial conducted by the GOG demonstrated that, of 289 patients with a community diagnosis of AEH, 40% had an EC (66). Neither the type of preoperative endometrial biopsy (office endometrial biopsy [EMB], or dilatation and curettage [D&C]) nor the use of an expert pathology panel was associated with a better prediction of who had cancer or not. Patients with significant medical comorbidities, advanced age, or those desiring future fertility may be managed with progestational therapy (68). It has been suggested that a D&C should be performed in those patients who will be medically managed with progestins for therapeutic effect (surgical curettage of tissue) and to better define the risk of an unrecognized cancer, while the data to support these practices are limited. When progestins are used to manage AEH, the specific agents, doses, and schedules may mirror those used to manage dysfunctional uterine bleeding, or advanced or recurrent cancer. To assess the success of medical therapy, endometrial biopsies should be performed at 3- to 4-month intervals provided cancer is not identified (69).

Screening and prevention strategies for women on tamoxifen are more challenging. Women with intact uteri who are taking tamoxifen for either treatment or prevention of breast cancer should be informed of the increased relative risk of developing EC with the use of tamoxifen. This risk is balanced by the reductions in recurrence or development of a contralateral breast cancer. Women on tamoxifen should be encouraged to report abnormal bleeding or vaginal discharge. Screening of asymptomatic women on tamoxifen therapy with ultrasound or endometrial biopsies is not recommended (70, 71).

CLINICAL PRESENTATION

The classic symptom of endometrial carcinoma is abnormal uterine bleeding. A variety of conditions give rise to abnormal bleeding, but particular suspicion should be held for postmenopausal women, and women aged 40 and above with high-risk factors. Approximately 10% of symptomatic postmenopausal patients will be found to have a cancer on biopsy (72). In one series, using age >70 years, diabetes, or nulliparity as risk factors, patients with all three factors had an 87% chance of having an AEH/carcinoma diagnosis, whereas only 3% had significant pathology in the absence of all risk factors (73). Additionally, patients with EC may present with vaginal discharge or have a thickened endometrium incidentally noted on ultrasound performed for another reason. Pap smear screening is not designed to identify EC, but occasionally, patients will have abnormal cervical cytology (atypical glandular cells of undetermined significance [AGUS], adenocarcinoma *in situ* [AIS]). Patients with intraperitoneal disease may present with similar complaints as patients with ovarian cancer such as abdominal distension, pelvic pressure, and pain.

Historically, when EC was a clinically staged disease (FIGO, 1971) fractional D&C was the procedure of choice to evaluate

abnormal bleeding. Fractional D&C permitted assessment of the uterine size and allowed for endocervical curettage, important steps in the staging process. The standard procedure starts with curettage of the endocervix prior to cervical dilatation. Careful sounding of the uterus is performed followed by dilatation of the cervix, followed by systematic curetting of the entire endometrial cavity. Cervical and endometrial specimens should be kept separate and forwarded for pathologic interpretation.

Pathologic evaluation of the endometrium provides histologic diagnosis and can identify other etiologies of bleeding such as chronic endometritis, atrophy, polyps, cervical cancer, or unusual histologic variants (carcinosarcoma, serous carcinoma, placental nodule), which may alter management. Tissue evaluation by office EMB or D&C offer similar information when adequately performed. Today EMB has largely replaced D&C as the diagnostic procedure of choice. In the GOG hyperplasia study, 63% of the specimens were from EMB (Vabra, Novak, Pipelle) and 37% were from D&C (66). Results of endometrial biopsies correlate well with endometrial curettings, and the accuracy to detect cancer is 91% to 99% (74, 75). The accuracy of identifying cancers with EMB is higher in postmenopausal patients than in premenopausal, and a positive study has shown cancer is more accurate for identifying disease than it is in excluding it. Cases where office biopsy cannot be obtained (cervical stenosis, patient intolerance of procedure) or results are nondiagnostic should be followed by D&C. In cases of abnormal bleeding that persists despite negative biopsy, additional investigation is warranted.

Hysteroscopy has been advocated as an adjuvant to D&C to improve detection of pathology in the evaluation of postmenopausal bleeding. Whether it improves the sensitivity to detect hyperplasia and cancers is controversial (76). Hysteroscopy is more accurate in postmenopausal patients, and is more accurate in detecting cancer versus other pathology than it is in identifying cancer or hyperplasia versus other pathology. One concern is that hysteroscopy may promote transtubal migration of tumor cells, which can be detected as malignant pelvic washings on cytology. In one retrospective study, an odds ratio of 3.88 for positive cytology was seen in hysteroscopic D&Cs compared to D&C alone, and the authors cautioned against hysteroscopy to evaluate EC (77). Similarly, a review of literature suggested that water-based hysteroscopy was associated with increased frequency of positive cytology at time of hysterectomy (78). Positive peritoneal cytology as the sole extrauterine factor is no longer recognized as a stage-defining characteristic under the FIGO 2009 system, however (79). No prospective studies have been performed to date, and it remains uncertain what effect positive washing produced by hysteroscopy has, if any, on prognosis.

Ultrasound is commonly used as a less invasive tool to evaluate abnormal bleeding. The measurement of endometrial thickness (ET) has been shown to best predict the absence of carcinoma, with a false-negative rate of 4%, using a threshold value of less than 5 mm (80, 81). The specific ET used for a cutoff value depends on the menopausal status of the patient population evaluated and on the use of HRT. For example, postmenopausal patients on HRT have a median ET 2 to 3 mm more than those not on HRT (82). In a meta-analysis of 85 studies, Smith-Bindman et al. reported that a cutoff level of greater than 5 mm would detect 96% of cancers, and would have a 39% false-positive rate (81). Transvaginal ultrasound measuring the lining thickness of the endometrium has excellent negative predictive value for ruling out ECs or hyperplasia when the thickness is less than 5 mm, but provides less information when greater than 5 mm. Given a pretest probability of having EC in a postmenopausal patient with vaginal bleeding of 10%, a normal endometrial stripe is associated with a 1% chance of a cancer. A consensus panel, composed of radiologists, pathologists, and gynecologic oncologists, suggested that when ET is less than 5

mm, the test can be considered negative for EC (83). For patients with ET greater than 5 mm, EMB, D&C with hysteroscopy, or saline infusion sonohysteroscopy should be performed. Saline infusion sonohysteroscopy has been suggested to better define findings in the endometrial cavity noted on ultrasound and provide clearer distinction of polyps, fibroids, and cancers (84). It is more likely to be successful in premenopausal patients than in postmenopausal patients. The role of vaginal ultrasound in the evaluation of bleeding remains somewhat controversial due to the belief of the importance of histology in defining treatment (for benign and malignant conditions) and of the concern for missed cancers. Good clinical judgment would suggest that patients with ET less than 5 mm who have persistent bleeding undergo tissue biopsy.

DIAGNOSTIC WORKUP

Preoperative Assessment

Following the diagnosis of EC, the surgeon must assess the surgical risks of the patient, evaluate the patient for possible metastatic spread, and determine the most appropriate surgical procedure. EC patients are frequently elderly and suffer from obesity, hypertension, diabetes, or cardiac disease. In a series of 595 consecutive patients, Marziale et al. found an operability rate of 87% (85). Preoperative assessment must be performed, occasionally requiring consultation with additional specialists. At a minimum, patients require a thorough examination to evaluate for evidence of cardiac or pulmonary disease, and to determine the surgical approach. A chest x-ray and electrocardiogram (EKG), complete blood count, and assessment of electrolytes and renal function are standard in this population. Preoperative counseling includes obtaining permission to remove the uterus, tubes, and ovaries, and permission for thorough intra-abdominal exploration with biopsy and tumor removal as necessary, including removal of the pelvic and paraaortic LN.

Evaluation of Metastatic Spread

A thorough physical examination may discover suspicious supraclavicular, inguinal, and/or occasional pelvic LN as well as suggest the presence of pleural effusions, ascites, or omental caking. The pelvic examination can suggest cervical, vaginal, or adnexal spread. An assessment of uterine size and mobility is important, particularly in patients being considered for vaginal approaches (laparoscopic-assisted vaginal hysterectomy [LAVH], total vaginal hysterectomy [TVH]). A chest radiograph is done to search for metastatic tumor as well as to evaluate the cardiopulmonary status of the patient. For patients without obvious extrauterine disease, surgery is the next step. In cases where intra-abdominal, gross cervical, or distant disease spread is suspected, additional studies such as CT scans, magnetic resonance imaging (MRI), or cystoscopy and proctoscopy may be needed to assist with surgical planning.

In general, there is very limited need for imaging studies prior to surgery since findings typically do not result in management changes as most patients present with Stage I–II disease, and the surgery is essentially the same for Stage I–III patients. Imaging studies have significant limitations in detecting nodal disease, which tends to be microscopic in 90% of cases (86, 87). In a small series of higher risk patients who underwent preoperative FDG PET/CT, Signorelli and colleagues showed a 78% patient sensitivity and 93% negative predictive value (88). The GOG is conducting an ongoing prospective assessment of PET/CT in patients with endometrial and cervical cancer (GOG 233). In a prospective blinded comparison of the accuracy of preoperative transvaginal ultrasound to frozen section assessment of

myometrial invasion, intraoperative frozen section outperformed ultrasound. The sensitivity and specificity of predicting invasion (none, <50%, >50%) of the ultrasound was 75% and 89%, respectively (89). Patient review of systems and clinical examination frequently lead to suspicion of gross extrauterine disease. Imaging studies may be of better use in certain situations. Serous and clear-cell tumors have a greater frequency of extrauterine disease spread, and imaging studies may offer additional information in some cases. In some settings, imaging studies may help some to determine whether to refer to a gynecologic oncologist or perform surgical staging when it would not otherwise be considered. In addition, imaging studies may have their greatest utility in helping to counsel young patients who are considering fertility preservation options. MRI has been suggested to have more value than computed tomography (CT) scans in assessing myometrial invasion, cervical invasion, and nodal disease, with several reports indicating a 75% to 90% accuracy rate for determining muscle involvement (90, 91). However, limitations do exist, making routine use more difficult to recommend (92, 93). At the present time, the only way to accurately diagnose the extent and depth of intrauterine invasion is by histologic examination of the hysterectomy specimen.

Biomarkers which predict the presence of extrauterine disease spread might be useful to triage patients to referral centers, for consideration of surgical staging, or to define risk. A variety of biomarkers have been suggested as possible candidates with CA-125 being the most studied (94, 95). Attempts have been made to correlate CA-125 levels with extent of extrauterine disease as serum levels are frequently elevated in patients with advanced or metastatic EC. This observation was first reported by Niloff et al. in 1984 (96). Values exceeding 35 U/mL were found in 14 (78%) of 18 patients with Stage IV or recurrent disease, although none of 11 patients with Stage I disease had elevations. Hsieh et al. reviewed preoperative serum CA-125 levels, operative records, and pathologic reports in 141 patients diagnosed with endometrial carcinoma to find out if the preoperative level of CA-125 can provide additional information to determine the extent of lymphadenectomy required in the surgical staging and which cutoff is optimal in this respect (97). Of 141 patients, 124 were staged surgically and 24 (19%) were found to have lymph node metastasis. In the node-positive group, median preoperative serum levels were 94 U/mL (range 17–363 U/mL). Multivariate analysis showed lymph node metastasis had the most significant effect on the elevation of CA-125 levels (>40 U/mL). The sensitivity and specificity for screening lymph node metastasis were 78% and 84%, respectively. The data of Hsieh et al. give evidence that preoperative CA-125 levels greater than 40 U/mL can be considered an indication for full pelvic and paraaortic lymphadenectomy in the surgical staging of endometrial carcinoma. Rose et al. (98) found serial CA-125 measurements to be most useful in patients with high-risk disease whose initial stage was II, III, or IV, or whose tumor was grade 3 or of clear-cell, or serous histology. Fifteen (94%) of 16 patients with recurrent disease had an elevated CA-125 level. Serial measurements of CA-125 are also used to monitor for recurrence and to assess response to tumor therapy in patients whose levels were initially elevated at diagnosis. In the LACE trial, which compared laparotomy to laparoscopy in the management of early-stage EC, 657 patients had preoperative CA-125 levels, which were correlated with extrauterine disease spread. Using a cutoff of 30 U/mL, 15% were noted to have elevated CA-125 levels, and of these, 37% had intrauterine disease (99). Ideally, serum biomarkers or tests that can be performed on diagnostic samples (EMB, D&C specimens) would be most useful.

Determining the Surgical Procedure

Of all the female pelvic malignancies, EC seems to have more advocates for different treatment plans than any other. The standard

Table 22.3 Corpus Cancer Surgical Staging, FIGO 1988

Stages/Grades	Characteristics
IA G123	Tumor limited to endometrium
IB G123	Invasion to less than half of the myometrium
IC G123	Invasion to less than half of the myometrium
IIA G123	Endocervical glandular involvement only
IIB G123	Cervical stromal invasion
IIIA G123	Tumor invades serosa or adnexae or positive peritoneal cytology
IIIB G123	Vaginal metastases
IIIC G123	Metastases to pelvic or paraaortic lymph nodes
IVA G123	Tumor invades bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph node

treatment for this disease has been and remains a hysterectomy. However, through the years, preoperative and postoperative irradiation has had an important role in the management of this disease. The first significant report of employing irradiation in the management of patients with EC was the publication of the “Stockholm technique” by Heyman in 1935 (100). The use of intracavitary implants using Heyman’s method became increasingly popular in the ensuing years. Subsequently, reports comparing results in patients treated with a single intrauterine tandem with those treated with multiple intrauterine capsules revealed a lower incidence of residual disease and an improved 5-year survival rate, favoring the patients treated with capsules (101, 102). Lewis et al. in cooperative studies in the late 1960s showed that 25% of patients had deep myometrial invasion if treated initially by surgery, and only 8% had deep invasion if treated by preoperative irradiation (103). Patients frequently were managed with preoperative radiation (whole pelvic radiation [WPR], low-dose-rate [LDR] implant with or without WPR) followed within 4 to 6 weeks by a complete hysterectomy. While surgical evaluation of LN in EC was reported in the 1960s, it was not widely embraced (104–106). The GOG undertook the large surgical-pathologic study, GOG 33, of clinical Stage I EC to better define patterns of spread with the hope that defining pathologic relationships would lead to a tailored (rather than a universal) approach to radiation (55, 57). The results of this study subsequently led to the incorporation of a surgical staging system, FIGO 1988 (Table 22.3). In 2009, FIGO updated staging for EC (Table 22.4) (79).

Contemporary management for most patients with EC remains surgical and includes, at the minimum, an initial surgical exploration with collection of peritoneal fluid for cytologic evaluation (intraperitoneal cell washings), through inspection of the abdominal and pelvic cavities with biopsy or excision of any extrauterine lesions suspicious for tumor, and total extrafascial hysterectomy with bilateral salpingo-oophorectomy. In 2009, FIGO removed the status of cytology as a stage-defining criteria (IIIA, by FIGO 1988); however, there was not an intent to discontinue the practice of cytologic evaluation. When the tradition has been to perform this surgery abdominally (typically through a vertical midline incision), minimally invasive techniques have increasingly been integrated into the forefront. The uterus should be particularly observed for tumor breakthrough of the serosal surface. The distal ends of the fallopian tubes are clipped or ligated to prevent possible tumor spill during

Table 22.4 Corpus Cancer Surgical Staging, FIGO 2009

Stages/Grades	Characteristics
IA G123	No or less than half myometrial invasion
IB G123	Invasion equal to or more than half of the myometrium
II G123	Tumor invades the cervical stroma but does not extend beyond the uterus
IIIA G123	Tumor invades serosa of the corpus uteri and/or adnexae
IIIB G123	Vaginal and/or parametrial involvement
IIIC1 G123	Metastases to pelvic lymph nodes
IIIC2 G123	Metastases to paraaortic lymph nodes, with or without positive pelvic nodes
IVA G123	Tumor invades bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph node

Histopathology, Degree of Differentiation

Cases should be grouped by the degree of differentiation of the adenocarcinoma:

G1	5% or less of a nonsquamous or nonmucinous solid growth pattern
G2	6% to 50% of a nonsquamous or nonmucinous solid growth pattern
G3	More than 50% of a nonsquamous or nonmucinous solid growth pattern

Notes on Pathologic Grading

Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1.

In serous adenocarcinomas, clear-cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rules Related to Staging

Because corpus cancer is now surgically staged, procedures previously used for determination of stages are no longer applicable, such as the finding of fractional D&C to differentiate between stages I and II.

It is appreciated that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted.

Ideally, width of the myometrium should be measured, along with the width of tumor invasion.

D&C, dilatation and curettage; FIGO, International Federation of Gynecology and Obstetrics.

uterine manipulation. To complete the surgical staging of EC, the removal of bilateral pelvic and paraaortic LN is also required.

When surgical staging is performed, a bilateral pelvic and paraaortic nodal lymphadenectomy is frequently performed. The margins of the pelvic nodal dissection are comparable to what is used for a pelvic nodal dissection with cervical cancer and are outlined by the margins of the circumflex iliac vein distally and the bifurcation of the iliac vessels proximally, with the lateral margin being the genitofemoral nerve and the medial

margin being the superior vesical artery. The floor of the dissection is the obturator nerve. Nodal/fatty tissue is skeletonized from these structures. In cases of bulky nodal disease, complete resection/debulking rather than biopsy to solely demonstrate metastatic disease is favored where possible. The common iliac nodes can be removed as a separate specimen, or divided at a midpoint along the vessels, submitting the inferior half with the pelvic nodes, and the superior half with the paraaortic nodes. Particularly on the left side, the common iliac nodes will be quite lateral in location and will require sufficient mobilization to visualize the nodes. Removal of paraaortic nodes can be performed through a midline peritoneal incision over the common iliac arteries and aorta, or by mobilizing the right and left colon medially (107). In each case, LN are resected along the upper common iliac vessels on either side and from the lower portion of the aorta and vena cava. At the present time, the inferior mesenteric artery is used to demarc the superior extent of the paraaortic nodal dissection, although some prefer to routinely extend the dissection to the level of the renal vessels (108). If suspicious nodes extending to the renal vessels are identified, they should be removed if possible.

In cases with gross omental or intraperitoneal disease spread, cytoreductive surgery with total omentectomy, radical peritoneal stripping, and, occasionally, bowel resection are required. The goal of reducing the residual disease to no or small volumes akin to what is performed for ovarian cancer is increasingly considered. In cases complicated by medical comorbidity, advanced age, or obesity, or when nodal dissection cannot or will not be performed, TVH with or without laparoscopic/robotic assistance may also be utilized. Following surgical assessment, patients may be classified based on pathologic features as to their risk of recurrence, and those deemed to be at sufficient risk may be offered adjuvant therapies.

Nonsurgical Management

The principal management of most patients with EC is surgical. The decision to use surgery is a function of patient and disease status. Patients with significant medical comorbidities who are not acceptable candidates for surgery (markedly advanced age, diminished performance status, severe cardiac/pulmonary disease, massive obesity) may be managed by alternative means. Primary radiation therapy without surgery has been used, and is discussed later in this chapter. Progestational therapy may be used for those who are inoperable or in younger patients who elect for fertility preservation (68, 109). Patients not undergoing surgery should be clinically staged according to the clinical staging system proposed by FIGO in 1971 (Table 22.5) (110). Those who do undergo initial hysterectomy are staged by the 2009 FIGO (revised 1988) system (Table 22.4) (79). Patients who are obese but otherwise surgical candidates may undergo an abdominal panniculectomy to enhance surgical exposure to facilitate hysterectomy and nodal dissection (111, 112). For patients presenting with disseminated or nonresectable disease, nonsurgical options including radiation, chemotherapy, or hormonal therapy have also been used. Surgery may be required to control vaginal bleeding in some of these cases.

Approximately 5% of women with EC are diagnosed under the age of 40 (4). For some younger women, the standard treatment of hysterectomy is unacceptable due to desires to maintain fertility. EC in younger women is usually associated with early-stage, low-grade disease and carries a favorable prognosis, making medical management an attractive option to some (69, 109, 113). Patients without myometrial invasion are thought to be the best candidates, and may undergo pelvic MRI to assess for myometrial involvement. Progestational therapy, most commonly with medroxyprogesterone acetate or megestrol acetate, has been successful in reversing malignant changes in up to 76%

Table 22.5 Corpus Cancer Clinical Staging, FIGO 1971

Stage	Characteristics
I	Carcinoma is confined to the corpus
IA	Length of the uterine cavity is 8 cm or less
IB	Length of the uterine cavity is more than 8 cm
<i>Histologic subtypes of adenocarcinoma</i>	
G1	Highly differentiated adenomatous carcinoma
G2	Differentiated adenomatous carcinoma with partly solid areas
G3	Predominantly solid or entirely undifferentiated carcinoma
II	Carcinoma involves the corpus and cervix
III	Carcinoma extends outside the uterus but not outside the true pelvis
IV	Carcinoma extends outside the true pelvis or involves the bladder or rectum

of cases (109, 113). Increasingly, there has been a consideration for progestin-based intrauterine devices, although the data are limited. In a 2012 systematic review of the literature, 74% of AEH and 72% of grade 1 EC patients achieved a pathological complete response (CR) for 6 months or longer with oral progestins (114). The range of complete responses was 50% to 95% for AEH, and 50% to 100% for grade 1 cancer. The mean time required to achieve the CR was 6 months. Of the 22 patients reported with grade 1 cancer treated with IUD, 68% achieved a CR. Because response may be temporary or incomplete, periodic sampling of the endometrium is advised. Penner and colleagues suggested that lack of response to progestin therapy is more common when the first response assessment shows lack of response, despite adjacent stromal decidualization (115).

Vaginal Hysterectomy

Vaginal hysterectomy with or without postoperative radiation may be another option for managing complicated patients. Vaginal hysterectomy has often been cited as the simplest and least morbid approach to hysterectomy, and has produced similar treatment outcomes in patients with clinical Stage I EC (116). It is often used as an alternative to an abdominal approach in obese and poor-surgical-risk patients (117). Limitations include the lack of exploration of the intraperitoneal cavity, inability to procure cytologic washings, greater difficulty in performing an oophorectomy, and inability to perform lymph node sampling. As lymph node metastasis is related to such high-risk features as

poor differentiation, unfavorable histologic subtypes, and deep myometrial invasion, the risk of extrauterine disease following TVH must be estimated based on uterine pathology (55).

Nodal Dissection

The value of staging any malignancy relates to the ability to describe the extent of disease at diagnosis, and to define comparable patient populations for whom prognosis and therapy are similar. Given the inability to accurately detect disease spread for many gynecologic malignancies, solely based on clinical examination and imaging studies, surgical staging systems that require pathologic evaluation of sampled sites have been largely incorporated into practice. The value of surgical staging as it relates to ECs has been the subject of increased scrutiny and debate over the last several years. For ECs, the ability of surgical staging to accurately identify spread to draining lymph node basins and how this information (or lack of it) changes prognosis and alters the use of postoperative therapies are a source of controversy. Proponents of routine surgical staging suggest that the ability to identify otherwise unrecognized disease spread to the nodes changes the postoperative therapies that are given, and is the most accurate way to assess risk. Most controversial is the assertion that surgical staging has a therapeutic benefit independent of the node status (positive or negative for metastatic disease).

Fundamentally, surgeons must determine for themselves whether or not they believe that surgical staging has sufficient value to offer it for all patients or only selectively, based on risk factors identified pre- and intraoperatively. If a patient will not be offered surgical staging/nodal dissection, then minimizing surgical morbidity with a vaginal or minimally invasive (laparoscopic-assisted, robotic) approach seems warranted. In this case, lower risk/quicker recovery comes at the cost of less information. In cases where nodal dissection will or potentially will be performed, patients must be adequately counseled regarding the risks and benefits. The principal risks attributable to nodal dissections include increased operative time, potential for blood loss associated with vascular injury, ileus, genitofemoral nerve injury with resulting numbness and paresthesias over medial thighs, lymphocyst formation, and lymphedema (Table 22.6) (57, 118, 119, 174). In general, the risks associated with nodal dissections are low and acceptable. Patients who have nodal dissections and receive pelvic radiation therapy may be at a greater risk of bowel morbidity than those without dissections (121). Nodal dissections also require the involvement of someone trained and skilled to perform the procedure. The principal advantage of comprehensive staging is that the physician and patient are provided with the greatest amount of information. In the contemporary management of EC, this information results in less use of radiation, and substitution of vaginal cuff brachytherapy (VCB) for pelvic radiation (106, 122, 123).

The importance, extent, and technique of nodal dissection are hotly debated. Questions relate to which patients should be

Table 22.6 Risks Associated with Nodal Dissection: Surgical Complication Rates Associated with Abdominal Hysterectomy + Pelvic and Paraaortic Lymph Node Dissection

Study	N	Hemorrhage (%)	GU injury (%)	DVT/PE (%)	Lymphocyst (%)	Other
Morrow, 1991	895	2.2	0.4	2	1.2	—
Homesley, 1992	196	6% transfused	—	4	—	“Serious” 6%
Orr, 1997	396	4.2% transfused	0.6	1.5	1.2	—
Mariani, 2006	96 node-positive patients	—	1	1	3.1	—

Note: DVT/PE, deep vein thrombosis/pulmonary embolism; GU, genitourinary.

offered and could benefit from surgical staging (all, some, none), and what is the optimal surgical procedure to be performed (biopsy of enlarged/visible nodes, lymphadenectomy). Controversy also exists between those surgeons who perform only pelvic dissections and those who advocate pelvic and paraaortic nodal dissection. If paraaortic nodes are removed, are bilateral nodes required, and to what superior extent (inferior mesenteric artery, renal vessels) should the dissection proceed?

Nodal Dissection—None

In the United States, comprehensive surgical staging of EC is infrequently performed. Only 30% to 40% of patients undergo nodal assessment, indicating that the majority of U.S. patients are not staged (123). Many gynecologists are neither trained in the techniques of lymphadenectomy nor familiar with the concept of full surgical staging. Full staging is more commonly performed by specialized surgeons, such as gynecologic oncologists (124, 125). Philosophically, those opposed to nodal dissections suggest that most patients are at low risk for nodal disease, treatment decisions can be based on final pathologic information, and, despite node dissection, the majority of patients who are node negative do not get benefit (126). Most patients with EC do present with low-risk features. In the entire GOG 33 study population of 621 patients, 75% had grade 1–2 tumors, 59% had inner one-third or less myometrial invasion, and only 9% of patients had positive LN (55). The Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) trial evaluated patients with Stage IC, grade 1; Stage IB–C, grade 2; or Stage IB, grade 3 who underwent hysterectomy without lymph node dissection and compared observation to postoperative pelvic radiation (127). Of note, based on grade and depth of invasion, approximately 60% of patients enrolled in GOG 33 would have had disease characteristics required for eligibility in the PORTEC trial. This patient population managed without nodal dissection had favorable outcomes with or without radiation therapy (5-year survival rates of 85% observation, 81% with pelvic radiation) in the PORTEC study (127). In a follow-up study including 427 patients with higher risk disease (age > 60 years plus either grade 1–2 and outer 50% invasion, or grade 3 with inner 50% invasion, or Stage IIA (1988 FIGO) disease), the PORTEC 2 study compared pelvic radiation therapy to VCB. None of the patients underwent nodal assessment, and 5-year PFS (78% to 83%) and survival (80% to 85%) suggested that even intermediate risk patients may be managed without lymphadenectomy, albeit at the cost of requiring adjuvant therapy, with resulting favorable outcomes (128). Trimble et al. reported on data from Stage I EC patients collected by SEER from 1988 to 1993 and showed that 5-year relative survival for patients without nodal dissection was 98% compared to 96% in those undergoing nodal dissection and suggested that nodal dissection did not convey a benefit for the overall population (129). Unfortunately, data on adjuvant therapy use were not available. It is suspected that increased use of radiation in unstaged patients may produce similar outcomes to patients who are staged and who avoid radiation therapy.

In a nonrandomized trial comparing hysterectomy with or without pelvic lymphadenectomy, followed by radiation therapy, 14% of patients (n = 207) with negative nodes treated with VCB recurred compared to 16% who did not have a lymphadenectomy (n = 660) (130). While the authors noted similar cancer-free survival between the groups, all patients who did not have nodal dissections received both pelvic radiation and VCB to attain these results.

Two randomized trials comparing hysterectomy with or without lymphadenectomy have been reported. A Study in the Treatment of Endometrial Cancer (ASTEC) randomized patients with 1,369 EC to hysterectomy with (LND group) or without (no LND group) pelvic lymphadenectomy (131). Following

surgery, patients with Stage I–IIA disease were then randomized again to observation or pelvic radiation therapy if they had grade 3, serous, or clear-cell histology; greater than 50% myometrial invasion; or endocervical glandular invasion (Stage IIA). Nodal status did not alter the use of radiation therapy such that node positive patients could be assigned to observation. Treatment centers were also permitted to use VCB regardless of pelvic radiation assignment based on institutional preference. As a result, a patient with unknown nodal status could receive VCB and not be considered to have received radiation therapy. Of the LND group, 54 patients were found to be positive nodes (9%) compared with 9 (1.3%) patients in the no-LND group. The quality of the nodal dissection has been criticized in this study as 8% of patients within the LND group did not get a nodal dissection, 12% had less than five nodes removed (median = 12 nodes), and paraaortic nodal dissection was not performed. There was no difference in progression-free survival (PFS) (HR, 1.0) or survival (HR, 1.25; $p = 0.14$) between the LND groups. Pelvic lymphadenectomy was associated with a longer operative time, and increased frequency of ileus (3% vs. 1%), deep venous thrombosis (1% vs. 0.1%), lymphocysts (1% vs. 0.3%), and wound complications (1% vs. 0.3%) compared to the no LND group. The frequency of transfusions and length of hospitalization were comparable between groups. The authors concluded that the results suggest no evidence of benefit for PFS/OS for pelvic lymphadenectomy and that it “could not be recommended as a routine procedure for therapeutic purposes” (131).

A similar study was performed by Italian investigators (CONSORT trial). In this trial, 514 patients were assigned to hysterectomy with or without pelvic lymphadenectomy (132). Patients were required to have myometrial invasion, and patients with grade 1 tumors and less than 50% invasion were excluded. In the no-LND group, 22% of patients had nodal dissections due to clinical suspicion with 14% of these cases, or 3% of the entire no-LND arm, having node positive disease. In the LND group, the median number of nodes removed was 26. Paraaortic dissection could be performed at the surgeon’s discretion and was done in 26% of cases. In the LND group, 13% were found to have positive nodes. Lymphocysts and lymphedema were more common in the LND group, but other early and late complications were similar. Postoperative therapy was not protocol prescribed, but the use of radiation therapy was more common in the no LND group (25% vs. 17%). The 5-year disease-free survival (DFS) was 81% in both groups, and 5-year survival was 90% in the no-LND group versus 86% in the LND group (HR 1.2, $p = 0.5$). The authors concluded that pelvic lymphadenectomy could not be recommended as a routine procedure for therapeutic purposes (132).

Both the ASTEC (A) and Italian (I) studies have been heavily criticized (133–134). Weaknesses of the studies relate to the absence of treatment in patients identified with positive nodes (A), lack of prescribed adjuvant therapy (I), limited power to show improvements in outcome if one truly existed (A,I), poor quality of the LND (A), absence of paraaortic nodal dissection (A,I), lack of quality-of-life assessment evaluating effect of both surgery and downstream use of adjuvant therapy (A,I), and the over representation of low-risk patients (A,I). Despite these limitations, these datasets provide the only level 1 evidence on the role of lymphadenectomy. The studies also suggest that the marginal benefit that lymphadenectomy may provide is likely to be modest for most patients. In addition, the data provide a strong argument that removing negative nodes is unlikely to significantly improve outcomes.

Without nodal information, physicians must rely on uterine factors to estimate the probability for nodal disease and pelvic failure to determine the need for postoperative radiation. Risk assessments may be based on nodal positivity estimates from GOG 33 or based on uterine factor derived risk groups treated with or without radiation therapy (PORTEC, GOG 99)

(55, 121, 127, 135). Nodal positivity is not infrequent in patients with higher risk uterine factors based on GOG 99 or PORTEC models. Nugent and colleagues classified a series of 352 clinical Stage I, endometrioid adenocarcinoma patients into risk groups based on PORTEC and GOG 99 models. Nodal positivity rates were 20% with PORTEC and 35% with GOG 99 H-IR criteria (127). Without specific nodal information, treatments must be based on estimates of risk/probability; this estimation can result in an increase in the use of radiation, particularly if the primary benefit of postoperative radiation is in node-positive patients. Complicating the issue of nodal dissection is that nodal status is only one of several important prognostic factors (136, 137). Kwon and colleagues performed a population-based cohort study of 316 EC patients who underwent lymphadenectomy and reported that pelvic node status was not an independent determinant of survival whereas prognosis was determined more by uterine factors (137).

The absence of nodal dissection may also lead to poorer outcomes. For example, a subset of 99 patients with Stage IC, grade 3 EC, who did not have lymph node dissection, were not eligible, but were treated with pelvic radiation and followed prospectively within the PORTEC trial (138). Five-year survival for this group of patients was 58%, and 12% had vaginal or pelvic failures despite WPR. It is interesting to note that the outcome of this group is poorer than what has been reported in patients with Stage IIIC EC managed by lymphadenectomy followed by radiation (139–141). If patients are not to have nodal dissection, then it would seem reasonable to consider minimally invasive or vaginal approaches to reduce morbidity.

Nodal Dissection—Selective

Surgical staging is the most accurate way to determine the extent of disease spread. Palpation of pelvic LN is not sufficiently accurate, with a sensitivity of 72% in a recent prospective study (142, 143). The baseline rate of nodal disease in an “all comers” population of EC patients is roughly 9% (Table 22.7). Increasingly, the challenge has been how to identify the smaller portion of patients at high risk from the larger low-risk population. Clearly, subgroups of patients at very high risk (nonendometrioid histology, carcinosarcoma, gross cervical involvement, gross intrauterine disease spread) exist, but these represent a minority of the 400,000 cases of uterine cancer per year in the United States. Many gynecologic oncologists consider nodal assessment to be a fundamental step in the evaluation and management of most women with EC, and nodal assessment has been incorporated into the surgical staging of EC since 1988.

Increasingly, there has been a discussion in the literature to attempt to describe which populations should be offered

Table 22.8 Histologic Grade and Depth of Invasion

Depth	Grade, No. of Patients			Total (%)
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	
Endometrium only	44 (24)	31 (11)	11 (7)	86 (14)
Superficial	96 (53)	131 (45)	54 (35)	281 (45)
Middle	22 (12)	69 (24)	24 (16)	115 (19)
Deep	18 (10)	57 (20)	64 (42)	139 (22)
Total	180 (100)	288 (100)	153 (100)	621 (100)

Source: Reprinted from Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. *Cancer*.1987;60:2035–2041, with permission.

lymphadenectomy, and the optimal strategy for defining those at risk (tumor biomarkers, frozen section criteria, sentinel nodal evaluation). Many believe that nodal dissections should be reserved for those with sufficient risk of nodal disease (55, 57, 144, 145). What risk of nodal disease (3%, 5%, 10%, etc.) warrants the procedure is debated—that is, at what level would one be comfortable missing unrecognized nodal spread. Equally important in the discussion is the understanding of whether uterine risk factors, independent of nodal status, should drive risk assessment and use of adjuvant therapy, and whether adjuvant therapies given to those with node positive or node status unknown perform similarly.

Historically, data from GOG 33 demonstrated important relationships between tumor grade and depth of invasion and frequency of nodal disease that can be used to decide whether to perform nodal assessments (Tables 22.8 and 22.9) (55). For example, the risk of pelvic nodal disease was 3% for all patients with grade 1 tumors, but was 11% with deeply invasive (outer one-third myometrial invasion) tumors. Patients with grade 3 tumors had a risk of pelvic nodal metastases of 18%, and 34% with deep invasion. With cervical invasion, the rate of pelvic nodal disease was 16%. Patients with serous or clear-cell histology also warrant nodal dissection as ~30% to 50% will have nodal disease, and even in the absence of myometrial invasion, nodal metastases have been reported in up to 36% of patients (146). Some advocate that LN need not be sampled for tumor limited to the endometrium, regardless of grade, because less than 1% of these patients have disease spread to pelvic or paraaortic LN (55, 147). A gray zone in deciding about lymph node sampling is represented by patients whose only risk factor is inner one-half myometrial invasion, particularly if the grade is 2 or 3. This group has 5% or less chance of node positivity (55). In the most recent survey of SGO members, 35% of respondents reported doing lymphadenectomy for grade 1 tumors; however, the use increased to 60% for grade 2, and 90% for grade 3 (108).

Increasingly, the debate has focused on appropriate selection of patients at such low risk for nodal metastasis that lymphadenectomy may be safely avoided. While flawed, the ASTEC and Italian studies have suggested that routine nodal dissection may have limited value. If the primary value of lymphadenectomy is to identify patients with positive nodes as a “diagnostic test” that defines patients who need additional/different postoperative therapy, there is value in defining populations at sufficiently low risk for whom no lymphadenectomy is required. In 2000, the Mayo group described a model that could classify a group with a low risk of nodal disease spread and high DFS based on frozen section evaluation of the uterus, which showed grade 1 to 2 endometrioid tumor, inner 50% invasion, and tumor size

Table 22.7 Frequency of Nodal Disease

Study	Reference	N	Frequency of Nodal Disease
GOG 33	(62)	621	9%
ASTEC			
(+) LND		686	9%
(-) LND	(157)	685	1%
CONSORT			
(+) LND		264	13%
(-) LND	(158)	250	3%
LAP II	(224)	2510	9%
PORTEC H-IR Criteria	(163)	66	20%
GOG 99 H-IR Criteria	(163)	188	35%

Table 22.9 Frequency of Nodal Metastasis Among Risk Factors

Risk Factor	No. of Patients	Pelvic No. (%)	Aortic No. (%)
Histology			
Endometrioid adenocarcinoma	599	56 (9)	30 (5)
Others	22	2 (9)	4 (18)
Grade			
1 Well	180	5 (3)	3 (2)
2 Moderate	288	25 (9)	14 (5)
3 Poor	153	28 (18)	17 (11)
Myometrial invasion			
Endometrial	87	1 (1)	1 (1)
Superficial	279	15 (5)	8 (3)
Middle	116	7 (6)	1 (1)
Deep	139	35 (25)	24 (17)
Site of tumor location			
Fundus	524	42 (8)	20 (4)
Isthmus-cervix	97	16 (16)	14 (14)
Capillary-like space involvement			
Negative	528	37 (7)	19 (9)
Positive	93	21 (27)	15 (19)
Other extrauterine metastasis			
Negative	586	40 (7)	26 (4)
Positive	35	18 (51)	8 (23)
Peritoneal cytology^a			
Negative	537	38 (7)	20 (4)
Positive	75	19 (25)	14 (19)

^aNine patients did not have cytology reported.

Source: Modified with permission from Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. *Cancer*.1987;60:2035.

less than 2 cm (148). Mariani subsequently reported on a prospective experience of 422 patients and reported that 33% of patients with endometrioid type tumors would qualify as low risk in this model. The authors also showed that 22% of patients with risk factors outside of their low-risk model had positive nodal spread at time of lymphadenectomy (149). Several other investigators have attempted to validate these findings. Convery and colleagues tried to replicate the conditions of Mayo criteria (which are assessed intra-operatively by frozen section) by retrospectively evaluating 602 patients with grade 1–2 endometrioid EC and who had intra-operative assessment of tumor (for depth of invasion ± tumor size) (150). The authors showed that 2/110 (1.8%) patients meeting the Mayo criteria who underwent a lymphadenectomy removing at least eight nodes were found to have metastatic spread to LN. Milam attempted to validate the Mayo criteria using a 971-patient surgical dataset from patients participating in the GOG Lap 2 trial (randomized trial of laparoscopy vs. open hysterectomy with pelvic and para-aortic lymphadenectomy (151). Of 971 patients with endometrioid adenocarcinoma and complete data, 65 (7%) were identified

with positive LN. Patients were classified into a “low risk” category based on 3 Mayo criteria; grade 1–2 tumor, less than 50% myometrial invasion, and tumor size less than 2 cm. These risk characteristics were assigned based on final pathology report and not frozen section, however as was used in the Mayo studies. Approximately 40% of patients met the low-risk criteria, and of these, 3/389 (0.8%) had positive LN.

Kang, reporting for the Korean GOG, retrospectively evaluated 540 patients with endometrioid-type cancers who had undergone preoperative EMB, CA-125 level, and MRI followed by hysterectomy and pelvic lymphadenectomy to create a risk model for predicting nodal disease (152). The model was developed on a 360-patient training set and validated against a 180-patient cohort. Interestingly, the logistic regression model included only data from the MRI and CA-125 level; grade was not an independently significant variable. The authors suggested that based on preoperative information, they could classify 53% of patients as low risk (<50% myometrial invasion and absence of enlarged nodes or extrauterine disease by MRI and CA-125 < 35 IU/ml). Of the low-risk group, only one patient had positive nodal disease (1.7% false-negative rate) suggesting that these patients may avoid an unnecessary lymphadenectomy.

Low-grade tumors appear to be the best population for developing criteria to limit lymphadenectomy. Bernardini performed a retrospective comparison between two academic institutions’ preferences for management of preoperative grade 1 endometrioid EC (153). Of 483 cases with a preoperative grade 1 cancer, final pathology was grade 1 in 357/483 (74%) cases, and 20% were upgraded (grade 2, 18%; grade 3, 2%). In one institution, surgical staging was performed in 50% of cases, and four (3%) patients were identified with nodal disease. At the second institution, lymph node dissection was performed in only 12% of patients, and three (1.4%) were found to have positive nodal disease. At the second institution, postoperative use of radiation therapy was more common (21% vs. 7%), although older patient age, capillary space invasion, and cervical involvement were more common at the second site. Despite the differences in surgical practice, the 3-year survival was 96% at both centers. These data indicate that there is little margin to improve outcomes through strategies directed at all patients in this patient population.

Selective use of nodal dissection highlights the balance between the likelihood of identifying otherwise unrecognized disease against cost, morbidity, and use of adjuvant therapy (with downstream cost, morbidity). The overall surgical complication of lymphadenectomy is approximately 20%. The serious complication rate is ≤6%, and is likely to be lower with surgeons who more frequently perform the procedure (57, 118–120). Downstream utilization of adjuvant therapy, which may occur more frequently in the absence of lymphadenectomy, must also be considered into this balance. While the proposed models predicting low-risk disease status appear to be accurate, it is important to understand that the pre-test probability of having positive nodes in a large patient population with grade 1 to 2 endometrioid tumors is ~3% to 7%, illustrating the narrow margin in improved outcome (e.g., identify 100% of patients with positive nodes and then use adjuvant therapy which cures 100% of these) that lymphadenectomy may be able to offer in this population of patients. Lymphadenectomy perhaps allows for fine tuning the management of low-risk patients, but does not appear to be the driver of outcomes.

Intraoperative assessment of the uterus has been used to guide the surgeon as to when to perform a nodal dissection. Gross inspection of the uterus immediately following its removal can be used to estimate the degree of myometrial invasion. If the uterus is opened by the operating surgeon, care should be employed to avoid distortion of the anatomy. Optimally, the unfixed uterus should be opened by the surgical pathologist, who can grossly estimate the depth of invasion, assess involvement of the cervix, and later sample the tumor for histologic assessment. There is

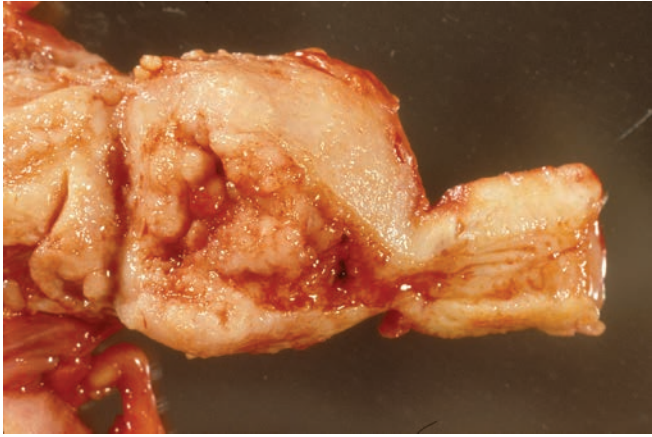


FIGURE 22.1. Endometrioid adenocarcinoma. A polypoid adenocarcinoma of the endometrium that fills much of the lumen and superficially invades the myometrium.

no typical gross appearance of an endometrial carcinoma. Most are polypoid or ulcerative. Carcinoma usually differs in texture and color from the surrounding normal endometrium. The normal endometrium is irregular and tan, but a carcinoma is usually shaggy, white to gray-white, and focally hemorrhagic. Areas of myometrial invasion may be visible as gray-white to white, with yellow areas disclosing necrosis (Figs. 22.1 and 22.2). The texture may be soft, friable, or firm depending on the degree of necrosis.

Doering et al. reported a 91% accuracy rate for 148 patients for determining the depth of myometrial invasion by gross visual examination of the cut uterine surface (154). A prospective study indicated that visual inspection of less than or greater than 50% correlated with microscopic assessment in 85% of cases (143). However, the sensitivity of determining greater than 50% was lower at 72%. Invasion of the myometrium may be more extensive microscopically than is evident visibly because of the characteristic infiltrative growth pattern of the tumor. In a retrospective study by Goff and Riche, the gross estimation by pathologists of myometrial invasion in grades 2 and 3 tumors was poor (155). With invasion, the uterine cavity usually enlarges and the myometrium thickens, but a small uterus may have myometrial penetration to the serosa.

Nodal Dissection—Routine

Data from 1990 to 2000s provided support for performing uniform comprehensive surgical staging for nearly all patients

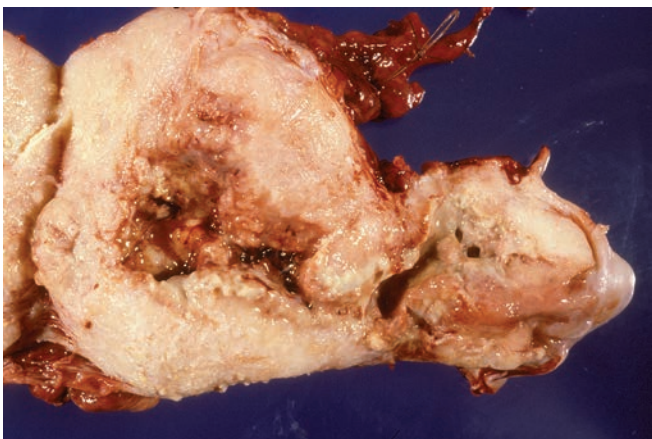


FIGURE 22.2. Endometrial adenocarcinoma. An ulcerating and deeply invasive adenocarcinoma that extends into the uterine cervix.

with EC. The rationale for uniform staging includes the lack of a patient population for whom nodal disease is so low that nodes should be omitted, the inaccuracy of preoperative or intraoperative assessments predicting the risk for nodal disease, the potential for therapeutic benefit in node-positive and -negative patients, and the lack of significant morbidity associated with the procedure. Postoperative adjuvant decisions are best made with the most complete information. If nodal assessment is the predominant factor by which to categorize patients into risk groups, routine nodal dissection is the best method by which to determine which few patients will require adjuvant therapy.

What constitutes an acceptable rate of nodal disease in EC to warrant the procedure is surgeon dependent. In cervical cancer, routine pelvic lymphadenectomy is advocated for all Stage IA2 tumors where nodal positivity rates are 3% to 5%. For clinical Stage I ovarian cancer, paraaortic dissection is recommended for all given the 6% risk of paraaortic disease. In EC, major complication rates associated with nodal dissection are 2% to 6%, suggesting that this might be an appropriate level of risk to balance against the risk of nodal metastases. Data from GOG 33 show that only patients with tumor limited to the endometrium had a risk of pelvic nodal disease $\leq 3\%$, and this group accounted for only 14% of the entire study population.

Frozen section assessment has been the traditional tool to facilitate decisions on selective nodal dissections. Several studies have demonstrated inaccuracies with frozen sections in the interpretation of grade and depth of myometrial invasion compared to final pathology (156, 157). In one prospective evaluation, frozen section determination of depth of invasion correlated with final pathology in 67% of cases but resulted in upstaging in 28% of cases (156). Patients with grade 1 EC or AEH were upstaged in 61% of cases. The clinical significance of these errors has been debated (126), but many believe that such unexpected up-staging justifies routine staging even in seemingly low-risk patients (156, 157). Data also suggest that the strategy of routine nodal dissection is more cost effective than either no staging or selective staging based on frozen section results (158).

The technique of nodal dissection has undergone evolution. In an era where everyone was to receive radiation therapy, there was little value for a complete evaluation of LN. Removal of palpably enlarged nodes, “plucking” of visibly noted nodes, and “sampling” have given way to a more thorough assessment. Only 10% of patients with metastases to LN will have grossly enlarged nodes and frequently, even in these cases, direct palpation through the overlying peritoneum will fail to identify them (55). Today, adjuvant therapies are based on the extent of disease, and are often only reserved for node-positive patients. Nodal assessments should sufficiently examine sites at risk, including external iliac, hypogastric, and obturator nodes in the pelvis, common iliac nodes, and paraaortic nodes. Moving from a sampling technique to a more thorough lymphadenectomy is not associated with increased complication rates (159). Nodal dissection should be bilateral given the frequency of both left and right paraaortic involvement (160, 161). It is interesting to note that GOG 33 only specified right-sided paraaortic removal in the surgical protocol. Likewise, the nodal dissection is more apt to be representative when a larger number of nodes are removed.

An assessment of pelvic and paraaortic LN is required to assign stage according to FIGO 2009. The 2009 staging system now separates stage subcategories based on extent of nodal disease (IIIC1, pelvic positive, IIIC2, any paraaortic positive) (79). Two principal nodal basins drain the uterus: the lower and middle portion of the uterus drains laterally to the pelvic LN; the upper corpus and fundus drain to the paraaortic nodes. When LN are positive, paraaortic nodes are involved in ~50% of the time. Isolated paraaortic nodes with negative pelvic nodes are uncommon, particularly with grade 1–2 tumors, and are involved in only ~2% of cases (55, 162). Paraaortic nodal

Table 22.10 Relationship between Pelvic and Paraaortic Nodal Involvement in Patients with Node-Positive Endometrial Cancer

Study	N	Surgical Technique	Pelvic (+) Only (%)	Pelvic and Para-aortic (+) (%)	Para-aortic Only (%)	Any Involvement of Para-aortic Nodes (%)
Creasman (1987) (162a)	70	Routine: sampling	51	31	17	48
Schorge (1996)	35	Selective: lymphadenectomy	74	17	9	26
Hirahatake (1997)	42	Routine: systematic lymphadenectomy	57	38	5	42
Onda (1997)	30	Routine: systematic lymphadenectomy	33	60	6.6	66
McMeekin (2001)	47	Routine: lymphadenectomy	38	41	21	62
Otsuka (2002) (162b)	23	Selective: systematic lymphadenectomy	66	33	10	43
Havrilesky (2005)	96	Selective: lymphadenectomy	52	30	18	48

dissection is more difficult to perform than pelvic dissection, by laparotomy or by laparoscopy, and is associated with greater risk. As such, some advocate for pelvic nodal dissections with only selective performance of paraaortic nodal dissections. In GOG 33, 46% of the positive paraaortic LN were enlarged, and 98% of the cases with aortic node metastases came from patients with positive pelvic nodes, adnexal or intra-abdominal metastases, or outer one-third myometrial invasion (55). These risk factors affected only 25% of the patients, yet they yielded most of the positive paraaortic node patients.

The importance of paraaortic nodal spread in node-positive EC cannot be ignored (Table 22.10). Data from GOG 33 showing that of all patients, isolated paraaortic nodal metastases occurred in 2%, are often taken out of context (55). If the goal of nodal dissection is to identify the node-positive patient population and to remove involved nodes, paraaortic disease is seen in 40% to 66% of patients with node-positive/Stage IIIC1/2 EC, including isolated positive paraaortic nodes in up to 7% to 21% of cases in certain groups. If only pelvic nodes are removed, when they are positive, paraaortic nodes will be positive in addition in nearly 30% to 40% of cases. It makes less sense to remove only pelvic or only paraaortic nodes given this data. Data would also suggest that when positive, outcomes are improved in patients who have complete surgical resection of paraaortic nodes. Chuang et al. reported on their experience with selective pelvic and or paraaortic dissections and found that failure to systematically remove pelvic and paraaortic nodes resulted in an increased frequency of recurrence in undissected retroperitoneal sites (163). Similarly, Mariani et al. showed that patients at high risk for paraaortic nodal disease (based on invasion >50%, palpable positive pelvic nodes, positive adnexa) who did not have paraaortic dissection or who had biopsy only and who were managed as though paraaortic nodes were positive had 5-year survival of 71% compared to 85% for those patients with positive paraaortic nodes who did undergo complete resection (159). Lymph node recurrences were detected in 37% of those not having paraaortic dissection compared to none in patients with positive but resected paraaortic nodes, suggesting a possible therapeutic effect of removing involved paraaortic nodes.

A provocative study from Japan (SEPAL study) was published in early 2010 which retrospectively compared the practices of two centers with regards to use of pelvic with or without paraaortic lymphadenectomy (164). At one center, systematic pelvic lymphadenectomy was performed in 325 patients. With a median of 34 pelvic nodes removed, the incidence of Stage IIIC disease was 12%. At the second institution, 346 patients underwent pelvic and paraaortic lymphadenectomy. With a median of 59 pelvic and 23 paraaortic nodes resected, Stage IIIC disease was identified in 16%. The centers were well matched

for stage and tumor grade, but the center where paraaortic lymphadenectomy was performed used adjuvant chemotherapy more commonly (47% vs. 27%). Patients were classified into low-versus-intermediate to high-risk groups, and outcomes were compared based on lymphadenectomy type. In the intermediate-high-risk group (but not low risk), recurrence-free, disease specific, and OS were significantly better in those women receiving paraaortic dissections. In a multivariate analysis, age, tumor type, nodal spread, and type of lymphadenectomy were independently associated with improved survival. The authors suggested that if future lymphadenectomy trials were to be conducted, both pelvic and paraaortic lymphadenectomy should be performed (164).

At the present time, the superior extent of paraaortic dissection should be at least to the level of the inferior mesenteric artery. Some suggest that dissections should proceed to the level of the renal vessels given the venous and lymphatic drainage following the infundibulopelvic ligament. In one series, 7 out of 11 patients had positive paraaortic nodes identified above the inferior mesenteric artery (165). The Mayo group noted that when paraaortic nodes were positive, 77% of cases had involvement above the IMA (149). This extended paraaortic dissection is feasible laparoscopically as well (166, 167). Prospective data describing the frequency of high paraaortic/pararenal nodes are awaited.

The retrospective data suggesting a therapeutic benefit supports but does not prove the hypothesis that lymphadenectomy is therapeutic. These studies are largely from single institutions, have short follow-up, suffer from selection biases, and do not clearly account for stage migration. Despite these limitations, the therapeutic value of lymphadenectomy is supported by several reports. Kilgore et al. were among the first to report a therapeutic effect of nodal dissections in a series of 649 clinical Stage I-occult II patients who were classified based on the extent of nodal dissection (168). Patients who underwent multiple site pelvic nodal dissection (defined by nodal dissection of at least four pelvic nodal sites) and had a mean of 11 nodes removed had improved survival over those patients who did not have nodes sampled. The survival advantage for multiple site dissection persisted even when patients were stratified into low-risk (uterine-confined disease) and high-risk (extrauterine disease) groups who received radiation. An explanation for this may be the removal of unrecognized micrometastasis, which goes undetected by standard pathologic processing techniques. Girardi et al. performed pelvic lymphadenectomy in 76 patients with EC (169). Nodal tissue was processed as step serial sections, and 37% of positive nodes were less than 2 mm in diameter, suggesting that nodal metastases may be missed in a proportion of node-positive patients processed in a less-extensive manner. Others have shown improvement in outcomes following a

more complete nodal dissection in node-negative populations. Cragan et al. evaluated 509 Stage I–IIA patients who underwent selective pelvic +/- paraaortic lymphadenectomy and found a survival advantage for patients with grade 3 tumors who had greater than 11 pelvic nodes removed, compared to those with ≤ 11 nodes removed (HR, 0.25) (170). For patients with high-risk features (grade 3, $>50\%$ myometrial invasion, serous/clear-cell tumors) 5-year survival was 82% when greater than 11 nodes were removed versus 64% when ≤ 11 nodes were removed. Chan et al. reported on the effect of a more complete nodal dissection in over 12,000 women with EC tracked in the SEER data system. In patients with high-risk disease (IB/grade 3, IC, II–IV), 5-year survival was proportional to the number of nodes removed, increasing from 75% to 87% when 1 versus >20 nodes were removed (171). In a multivariate analysis, a more extensive nodal assessment was an independent predictor of survival. Prospective data from the ASTEC and Italian studies suggest that there is no therapeutic benefit to resecting negative LN (131, 132). The use of postoperative adjuvant therapy in patients without nodal dissection may obscure potential benefit of lymphadenectomy, making benefit difficult to measure. Likewise, patients with low-risk uterine factors may be identified with nodal disease.

In patients with positive pelvic and/or paraaortic nodes, complete resection followed by adjuvant therapy results in superior outcomes. Havrilesky reported on 91 patients with Stage IIIC disease, including 39 with microscopic involvement of the LN and 52 with grossly enlarged nodes. Five-year survival was 58% for patients with microscopic LN, 48% for those with grossly positive LN completely resected, and only 22% in cases where the nodes were not resected. The authors felt that this data suggested a therapeutic benefit for lymphadenectomy (172). Bristow et al. evaluated 41 patients with bulky adenopathy who underwent complete resection of involved nodes. Compared with patients who had gross residual disease in LN remaining after surgery, those with resected disease had longer PFS (38 vs. 9 months) (173). Mariani et al. showed that pelvic sidewall failure at 5 years was 57% for patients who had inadequate nodal dissection and/or no adjuvant radiation compared to 10% when patients had adequate (removal >10 nodes) lymphadenectomy and received radiation (174). The best outcomes reported for node-positive patients follow complete nodal dissection. For example, in one series, of 30 Stage IIIC patients managed with systematic pelvic and paraaortic lymphadenectomy (average number nodes removed, 66) followed by radiation therapy and chemotherapy, 5-year survival was 100% for patients with positive pelvic nodes and 75% for positive paraaortic nodes (139).

The most cogent argument for routine staging is that following thorough nodal assessment, most patients with node-negative disease can accurately be classified as low risk, and may avoid pelvic radiation or receive VCB in lieu of pelvic radiation therapy. Three randomized trials comparing radiation to observation have failed to demonstrate a survival advantage for adjuvant pelvic radiation therapy in patients with Stage I–II disease, suggesting that in the absence of nodal disease, no therapy is a reasonable option (121, 127, 175). Indeed, patients with negative nodes and low-risk uterine factors (which account for 2/3 of Stage I–II EC patients) have incredibly low risk of recurrence and death (2% cancer specific death at 48 months, with or without pelvic radiation) (121). Retrospective studies have shown how the incorporation of a strategy using lymphadenectomy changes the use of postoperative radiation (106, 118, 122, 176). In a SEER review of 26,043 women with EC, patients with intermediate-risk disease who underwent nodal assessment were less likely to receive external beam pelvic radiation therapy and more likely to receive vaginal brachytherapy compared to women who did not undergo nodal assessment (123). In the absence of nodal disease, recurrence risk is low and OS is high, with no radiation or with the substitution of VCB.

Alternatives to Lymphadenectomy

Given the debate as to the value of lymphadenectomy, a variety of alternative strategies have been evaluated. The concept of lymphatic mapping by sentinel lymph node dissection has been accepted into practice in patients with breast cancer and melanoma, and is increasingly being used in vulvar cancers. The technique uses a preoperative local injection of radioactive colloid 6–12 hours preoperatively followed by a lymphoscintigram, with or without an immediately preoperative injection of a colorimetric dye (isosulfan blue). The theory suggests that regional nodal spread first moves to a “sentinel” node(s) for which markers (lymphoscintigram, gamma counter, gross blue appearance of node) make apparent. By selectively resecting the sentinel node, the “at risk node” is evaluated, but other nodes are retained *in situ*, thus reducing morbidity, length of surgery, and blood loss. For sentinel mapping to be effective, reproducible techniques must be developed and validated, standard nodal processing (serial sectioning, immunohistochemical evaluations) must be developed, and the false-negative rate must be low. Given the pretest probability for nodal disease is low ($\sim 9\%$) in an all-comer population, large studies will be required to adequately evaluate sentinel node mapping.

The appropriate site of injection for colloid/blue dye is evident in vulvar cancers and cutaneous melanomas; however, there is debate on where to inject the uterus to be representative of nodal drainage of the tumor. Possible sites of injection include the uterine fundus, cervix, or hysteroscopic injection of the tumor (177). As lymphatic drainage of the uterus is complex, it is unclear whether injections of the cervix mirror drainage of the uterus in general, or specifically of the tumor. For example, there is discussion in the literature as to whether cervical injections may identify paraaortic sentinel nodal disease. In addition to the surgical technique, controversy exists as to the best way to process sentinel node specimens. Immunohistochemical processing searching for cytokeratin is important in that it increases the detection of micro-metastatic implants, although the clinical significance of this type of disease is uncertain (178, 179).

Investigators at Memorial Sloan-Kettering Cancer Center have performed a series of sentinel node mapping surgeries on 266 patients, followed by pelvic $\pm$ paraaortic lymphadenectomy. Using a cervical injection technique, they reported sentinel detection was possible in 84% of cases, 12% of cases had positive nodal disease, and metastatic cells were three times more likely in sentinel nodes than in nonsentinel nodes (180). In a meta-analysis of 26 series on sentinel node dissection, Kang estimated the detection rate for sentinel nodes was 78%, and the sensitivity was 93%. In a disease where baseline rates of nodal involvement are roughly 10%, this translates to a $\sim 1\%$ false-negative rate (181). As most of the series in the meta-analysis included small numbers of patients, the authors cautioned against routine substitution of sentinel nodal mapping for lymphadenectomy based on the current data.

Minimally Invasive Surgery for Endometrial Cancer

After several years of debate and discussion, minimally invasive techniques have been integrated into the management of EC as a standard of care. Techniques utilized in the initial treatment of EC include laparoscopic assisted vaginal hysterectomy (LAVH), total laparoscopic hysterectomy (TLH), and robotic hysterectomy with pelvic and paraaortic nodal dissection to stage patients. Minimally invasive staging techniques include transperitoneal and extraperitoneal assessment of nodes, and may be done at the time of hysterectomy or at a later time to re-stage patients following incomplete surgical staging. The decade of the 1990s advanced the use of minimally invasive surgery and introduced the laparoscopic techniques and tools required for comprehensive

surgical staging of EC. As the initial debate on LAVH focused on whether laparoscopic techniques could be substituted for abdominal ones, in EC, debate has focused on whether laparoscopic surgical staging could be substituted for open procedures. Initial case reports and small single-institutional series describing technique and demonstrating feasibility were replaced by large series, small randomized trials, and subsequently, multi-institutional randomized controlled trials (182–187).

Improvements in laparoscopic equipment facilitated the development of LAVH. Building on that experience, and coupled with the introduction of better optics for visualization, laparoscopic resection of LN became possible. Querleu et al. were the first to report pelvic lymphadenectomy for cervical cancer in 1991 (188), followed by Nezhat et al. who reported in 1992 on the use of laparoscopic pelvic and paraaortic lymphadenectomy with radical hysterectomy in cervical cancer (189). When first utilized in EC, laparoscopic paraaortic node dissection only evaluated right-sided nodes (182). Techniques have subsequently been developed allowing for dissection to include the left paraaortic nodes and for extraperitoneal approaches (166, 167, 190).

Childers et al. (182, 183) described the initial experience of LAVH in 59 patients with clinical Stage I endometrial carcinoma. Laparoscopic pelvic and right-sided aortic lymph node samplings were performed in patients with grade 2 or 3 lesions, or with grade 1 lesions and greater than 50% myometrial invasion on frozen section. For the group, the mean weight was 153 pounds, and in two patients, laparoscopic lymphadenectomy was precluded by obesity. Six patients had the procedure converted to open due to intraperitoneal disease, and two patients required laparotomy to manage complications, including a transected ureter and a cystotomy. The mean hospital stay was 2.9 days. Since that time, many retrospective series have appeared in the literature describing techniques and presumed advantages. In general, mean operating times are longer for laparoscopy, but the overall complication rates, length of stay, and hospital charges were lower. With short follow-up, there was no significant difference in disease recurrence between the two groups.

Prospective data have also emerged. A small prospective, randomized trial comparing laparoscopic-assisted vaginal versus abdominal surgery in patients with EC was reported by Malur et al. (184). They randomized 70 patients with EC FIGO Stage I–III to laparoscopy-assisted simple or radical vaginal hysterectomy, or simple or radical abdominal hysterectomy with or without lymph node resection. Blood loss and transfusion rates were significantly lower in the laparoscopic group. The number of pelvic and paraaortic LN, duration of surgery, and incidence of postoperative complications were similar for both groups. No significant differences in disease recurrence rate and long-term survival were found between the laparoscopic and laparotomy groups (97.3% vs. 93.3% and 83.9% vs. 90.9%, respectively). Malzoni and colleagues reported on a 159-patient trial comparing TLH to TAH with lymphadenectomy (191). The authors reported less blood loss, shorter hospitalization, and less common ileus with TLH. Operative time was longer (136 vs. 123 minutes) with TLH, but there was no difference in number of nodes removed, frequency of Stage IIIC disease, ability to do paraaortic dissection, or in recurrence. The LACE trial compared TLH (n = 190) to TAH (n = 142) in 332 patients with Stage I EC (with or without lymphadenectomy) (187). The preliminary report designed to specifically assess quality of life endpoints showed that 2.4% of laparoscopic cases required conversion to an open approach, operating time for TLH on average was 30 minutes longer, grade 3–4 adverse events were more frequent (23% vs. 12%) in the TAH groups, and quality of life assessments favored TLH for up to 6 months post surgery. Concurrent lymph node assessment was more common with TAH versus TLH (68% vs. 41%), and ~20% of patients participating in the

study received some form of adjuvant therapy (chemotherapy, radiation, or both).

The largest and most comprehensive data set to date comes from the large prospective, randomized trial conducted by the GOG (Lap II trial) (186). The study was designed to compare laparoscopic hysterectomy with comprehensive surgical staging to the traditional laparotomy technique (using a 2:1 randomization favoring the laparoscopic arm) to determine the complete staging rates, safety, short-term surgical outcomes, and long-term cancer recurrence and survival. The study enrolled 920 patients to the open arm, and 1,696 to laparoscopy. The rate of conversion from laparoscopy to open procedure was 26%, and was most frequently related to poor visibility (15%), extrauterine cancer spread (4%), and bleeding (3%). The conversion rate increased with increasing patient obesity, with the laparoscopic success rate being 90% with a body mass index (BMI) less than 20, 65% with BMI = 35, and 34% with BMI = 50. The median number of removed nodes was similar between each technique, as were the frequencies of patients found to have positive LN. Complication rates (combined rates of vascular, urinary, bowel, nerve, or other complications) for those who had an open procedure were 7.6%, compared to 9.5% of patients randomized to laparoscopy. Of the 1,242 patients randomized to laparoscopy who had the procedure successfully completed laparoscopically, the complication rate was 4.9%. Comparing patients who underwent open surgery versus successful completion of laparoscopy, operative time was longer (median 70 minutes), but hospital time was shorter (2 vs. 4 days) with laparoscopy. Postoperative arrhythmia, pneumonia, ileus, antibiotic use, and any complication greater than grade 2 were lower in the laparoscopic group. The authors concluded that laparoscopic surgical staging is an acceptable and possibly a better option, particularly when the surgery can be successfully completed laparoscopically.

Results of long-term survival in laparoscopically treated compared to laparotomy-treated EC patients suggest comparable outcomes. Tozzi, reporting on the first prospective trial (n = 122 patients), reported DFS of 91% with LAVH and 94% with laparotomy, with survival of 86% versus 90%, respectively (192). In a subsequent evaluation of recurrence and survival data from the GOG LAP 2 trial published in 2012, 3-year recurrence rates were 11.4% with laparoscopy versus 10.2% with open surgery, and 5-year survival was 90% in each arm (193).

Age and obesity have been suggested as relative contraindications to laparoscopic surgery. In the GOG Lap II trial, the median age was 63 years. Scribner et al. evaluated the surgical experience of uterine cancer patients age ≥65 years who underwent LAVH with pelvic and paraaortic lymphadenectomy (n = 67) or abdominal hysterectomy with pelvic and paraaortic lymphadenectomy (n = 45) (194). Laparoscopic staging could be completed in 78% of patients. In the laparoscopic group, the BMI was 29.5 kg/m² (range, 15.9–54.7), and 33% had a history of prior laparotomy. For the 22% of patients who required a conversion to laparotomy, obesity (10%), bleeding (6%), and intraperitoneal disease (5%) were the most frequent reasons. Similar nodal counts (29 laparoscopy, 29 open) were noted, the operative time was longer (236 vs. 148 minutes), and hospital stay was shorter (median 3 vs. 5.6 days) with laparoscopy. The authors concluded that with the anticipated growth of an aging patient population, laparoscopic management is a viable option.

Obese patients have been suggested to be poor laparoscopic candidates due to difficulties in establishing pneumoperitoneum, poorer visualization, inability to tolerate steep Trendelenburg positioning needed to facilitate the surgery, and difficulties with ventilation. In the report by Childers et al. mean patient weight was only 153 pounds (182, 183). It is important to recognize that regardless of surgical approach, complete surgical staging is more difficult in an obese patient. Scriber et al. compared 55 obese patients (median weight 96.6 kg, median BMI 40) who underwent LAVH with pelvic and paraaortic lymphadenectomy

to 45 patients (median weight 101 kg, median BMI 39) who had abdominal hysterectomy with pelvic and paraaortic lymphadenectomy (195). Successful completion of laparoscopy was possible in 64%, with patients with a BMI <35 kg/m² having an 82% success rate compared to 44% when the BMI was greater than 35 kg/m². Eltabbakh et al. evaluated 40 women with BMI between 28 and 60 who were treated with LAVH and compared them to 40 similar women treated by abdominal approach (196). Laparoscopic conversion was only required in 8% of patients. Laparoscopic surgery was associated with a longer operative time (195 vs. 138 minutes), but more pelvic nodes (mean 11 vs. 5), less pain medicine requirement, and shorter hospital stay (2.5 vs. 5.6 days) were recorded. Total laparoscopic hysterectomy has also been shown to be feasible in heavier patients (197). In the prospective GOG series, there was ≥80% success rate with patients with a BMI of 27 or less, but even at a BMI of 35, 65% could have successful laparoscopic surgery (186).

Robotic surgery may represent the next step forward in minimally invasive surgery. Since FDA approval for hysterectomy and myomectomy procedures in 2005, there has been an increasing utilization of robotic surgery within Gyn-oncology. To date, greater than 15 series ranging in size from 4 to 405 patients have described robotic experience or compared outcomes to laparoscopy and/or open procedures (Table 22.11) (198–207, 212). Proposed robotic surgery advantages include improved visualization with 3-D optics, “wrist-like” motion of instruments allowing greater dexterity, reduction in tremor, an easier learning curve for adoption compared to straight-stick laparoscopy, and more comfortable ergonomics. Published data suggest comparable outcomes with respect to blood loss, nodal counts, and operative time compared to laparoscopy. Mean nodal counts and operative complications are comparable to laparoscopy, with several series suggesting lower postoperative complications compared to open surgery. As with new surgical techniques, there is a learning curve through which additional experience leads to quicker operative times and higher nodal retrieval rates. The Ohio State group has suggested that 20 procedures are required for proficiency (205).

Robotic surgery may offer unique opportunities for obese patients (206). Several series suggest that robotics may overcome some of the challenges with laparoscopy and may reduce morbidity seen with open cases. Seamon and colleagues reported that in a series of 109 obese patients (mean BMI 40) treated by robotic hysterectomy and staging, the conversion rate was 16%. The 92 patients successfully treated by robotic platform were compared to a matched cohort of 162 laparotomy patients. Total nodal counts (~24 nodes each group) and frequency of adequate lymphadenectomy (defined as at least 10 nodes removed) were similar in both groups, but blood transfusion rate, hospital stay

complications, and wound problems were reduced with robotic surgery.

Arguments have been advanced for and against each of the surgical approaches to EC. Vaginal hysterectomy was once a favored operation, but it did not allow for routine removal of the ovaries in some patients, permit inspection of the peritoneal cavity or the retroperitoneum for metastatic disease, or allow collection of peritoneal fluid for cytology (207). Laparoscopic-assisted or total laparoscopic approaches overcome these limitations, however. Compared to open procedures, LAVH/TLH are thought to lead to reduced incisional complications, wound infections, ileus, hospital stay, cost, and improved rate of recovery and quality of life (186, 188, 208). Data from prospective studies also showed that short-term (6 weeks–6 months) patient-assessed quality of life assessments also favor minimally invasive surgery (208). In patients requiring postoperative radiation, laparoscopic surgical staging followed by radiation therapy is suggested to result in fewer bowel adhesions and radiation-induced bowel injuries. Criticisms of LAVH/TLH with laparoscopic nodal dissection relate to the learning curve required to learn new or unfamiliar procedures, the increased length of operative times, and concerns about the adequacy of the nodal dissection. Studies do suggest that with increased experience, operative times decrease and nodal counts increase. Laparoscopy also introduced different procedural-related complications. Rarely, the technique has been associated with port-site recurrences or intraperitoneal dissemination of disease by laparoscopic gas and/or uterine manipulation.

Whether a minimally invasive procedure is comparable to an open approach must be judged by the ability to accurately dissect appropriate nodal basins, to remove an adequate/representative number of LN, to identify metastatic disease, and by the rates of recurrence. The technique used to remove the uterus/ovaries is not the source of controversy, although TLH and robotic hysterectomy may facilitate removal of larger uteri or assist with cases with poor descensus compared to LAVH. Comprehensive surgical staging allows for appropriate risk stratification to make appropriate treatment recommendations. Multiple reports demonstrated similar node counts for open, laparoscopic, and robotic techniques in the surgical staging of EC (186, 198). In the GOG Lap II trial, median numbers of nodes from pelvic and paraaortic basins, and frequencies of positive nodes were comparable in the surgical arms (186). Despite the potential benefits of laparoscopic surgery, if laparoscopic nodal dissection cannot be performed, conversion to laparotomy is advised when incomplete staging results would yield inadequate information for treatment planning.

Minimally invasive surgery must be performed with an acceptable complication rate to be considered a viable option.

Table 22.11 Selected Robotic Surgery Series in Endometrial Cancer

Study	N (Robot Cases)	Type of Study	Procedure	OR Time (min) (mean/median)	# Nodes (mean/median)
Boggess et al. (2008)	103	Compare to LSC + Open	Hyst + PPALND	191	33
DeNardis et al. (2008)	87	Compare to LSC	Hyst + PPALND	177	19
Veljovich et al. (2008)	25	Compare to LSC + Open	Hyst ± LND	283	18
Holloway et al. (2009)	100	Case series	Hyst + PPALND	171	19
Seamon (2009)	105	Compare to LSC	Hyst + PPALND	242	31
Lowe et al. (2009)	405	Case series	Hyst ± LND	172	14
Lim (2010)	122	Compare to LSC	Hyst + PPALND	147	25

LSC, laparoscopic; Open, laparotomy; Hyst, hysterectomy; PPALND, pelvic paraaortic lymph node dissection; LND, lymph node dissection unspecified.

In one series reporting on complication rates with an institution's first 100 pelvic and paraaortic nodal dissections, conversion to manage complications was required in five to control bleeding, and one to repair a ureteral injury (209). In another group's experience with 150 patients, seven major vascular injuries were reported, but only four patients required laparotomy (210). Querleu et al. reported on intraoperative and postoperative complications of laparoscopic node dissection from 1,192 pelvic and paraaortic nodal dissections (211). Only 13 open procedures were required to complete the nodal dissections, and a laparotomy was required in seven cases to manage complications. Eleven intraoperative vascular injuries were noted, but none required laparotomy to manage. In the GOG Lap 2 study, intraoperative complications were comparable (7.6% open, 9.5% randomized to laparoscopy, 4.9% successful completion of laparoscopy) (186). Postoperative complications and short-term quality of life improvements favored laparoscopy. A meta-analysis of robotic studies for gynecologic conditions noted that for endometrial series, robotic surgery was associated with less blood loss and less frequent conversions to open procedure compared to laparoscopy.

Restaging

One of the more useful roles of minimally invasive surgery is in restaging patients who underwent hysterectomy only. Patients who undergo hysterectomy without nodal dissection and who have pathologic risk factors for potential nodal spread face a difficult dilemma. Patients may elect to receive radiation or chemotherapy (presume nodes are positive), elect observation (presume nodes are negative), or undergo a second operation. A second laparotomy can be difficult to accept. Laparoscopic staging offers the patient a less invasive option to collect information. Childers et al. reported the initial experience with restaging in 13 patients, finding disease in three patients (213).

Recommendations for Minimally Invasive Surgery

Standard of care today includes minimally invasive surgery in the management of EC. Additional training and experience are required for successful completion of these procedures, just as they are with open procedures. The demonstration of comparable surgical endpoints (similar numbers of nodes removed, similar frequency of positive nodes, recurrence rates, and survival) along with shortened hospital stay, quicker recovery, and better quality of life indicators compared to open procedures suggest that appropriate patients should be counseled regarding this option. Challenges remain on how to increase the minimally invasive training of gynecologic oncologists in practice and fellows in training programs. As with open procedures, defining which populations should be considered for nodal assessment and for postoperative therapies continues to be an important research focus.

Surgical Management of Intraperitoneal Disease

The management of patients with Stage IV disease depends on the ability to resect disease. In patients with distant metastasis, there may be a limited role for surgery such as to provide control of vaginal bleeding. In patients with intraperitoneal disease, options include resecting easily removable disease (uterus, adnexa, omentum) versus a more extensive cytoreductive effort. The value of extensive cytoreductive surgery in EC has not been as well studied as it has been in ovarian cancer. Historically, limitations in postoperative therapies (lack of enthusiasm for whole abdominal radiation, marginally effective chemotherapy

regimens, reliance on hormonal therapy) perhaps reduced interest. Several retrospective reports suggest that survival correlates with volume of residual disease (214). Shih et al. reported on 58 patients with Stage IV endometrioid disease treated from 1977 to 2003 of whom 9 had no gross residual, 11 had less than 1 cm residual, and 32 had residual greater than 1 cm (215). The median survival for the entire population group was 19 months; however, median survival was 42 months for patients with no gross residual disease. In a multivariate analysis of the data, residual disease and the use of postoperative adjuvant chemotherapy were independently associated with survival. Bristow et al. demonstrated that optimal cytoreduction (<1 cm) could be obtained in 55% of Stage IV patients, and required omentectomy (93%), peritoneal stripping (65%), and bowel resection (29%) to do it (214). In patients with serous histology, similar survival improvements were seen with optimal debulking of intraperitoneal disease (216).

Surgical Recommendations

The contemporary management of EC has significantly changed. We believe that patients must be appropriately counseled with regards to the presumed benefits of lymphadenectomy as well as the potential risks. Data for the ASTEC and Italian lymphadenectomy trials provide doubt as to the benefit of resecting negative nodes, but both studies clearly demonstrate that nodal disease cannot be found unless one searches for it. The clinician is challenged with finding the "needle in the haystack" in a disease where the baseline rate of nodal metastasis is ~9%. How many patients should undergo a procedure that is not likely to benefit them is balanced by how many patients with unrecognized nodal disease we are uncomfortable with. The marginal benefit achieved by lymphadenectomy and the downstream costs associated with or without its use in terms of adjuvant therapy, outcomes, and quality of life need to be better defined so that patients and physicians can make choices based on good information. Clinical pathologic models that define low-risk populations for whom lymphadenectomy may be safely avoided appear to be promising, but need to be validated prospectively in large series. In the future, biomarker-based testing or sentinel nodal assessment may serve as an alternative to lymphadenectomy, but data is immature at this point to recommend routinely. Increasing the proportion of patients who undergo minimally invasive surgery to manage EC is an important goal and driven by the data. Patients who *a priori* are deemed not to be candidates for staging should be considered for vaginal or minimally invasive hysterectomies. Surgical therapy for EC removes the disease and defines populations at risk for recurrence and death. Surgical staging, or the lack of it, defines patient groups into surgically staged node positive or negative, or unstaged. Comprehensive staging most accurately assigns stage and associated prognosis, although the magnitude of the risk assignment is tempered by the frequency of positive nodes, uterine risk factors, and use of adjuvant therapy. Staging also allows for a more tailored approach to the use of adjuvant therapies. For patients with resectable intraperitoneal disease, cytoreductive surgery can result in optimal volumes of residual disease, and perhaps improved outcomes.

PATHOLOGY

Hyperplasia

The current classification of endometrial hyperplasia accepted by both the International Society of Gynecologic Pathologists (ISGP) and the World Health Organization (WHO) is based

Table 22.12 Classification of Endometrial Hyperplasia

Types of Hyperplasia	Progressing to Cancer (%)
Simple (cystic without atypia)	1
Complex (adenomatous without atypia)	3
Atypical	
Simple (cystic with atypia)	8
Complex (adenomatous with atypia)	29

on the schema of Kurman and Norris (217), which divides hyperplasia on the basis of architectural features into simple or complex and on the basis of cytologic features into typical or atypical (Table 22.12). The resulting classification has four categories as follows: *simple hyperplasia* (SH); *complex hyperplasia* (CH), *simple atypical hyperplasia* (SAH); and *complex atypical hyperplasia* (CAH). SH is defined as an increase in the number of endometrial glands, which may be dilated with little crowding or have an irregular outline and exhibit crowding. CH is characterized by glands with irregular outlines, marked structural complexity, and back-to-back crowding. The designation atypical hyperplasia is used to denote a proliferation of glands exhibiting cytologic atypia, recognized as nuclear enlargement, the presence of nucleoli, or a change from an elongated to a more ovoid or round nucleus. The chromatin may be either evenly or irregularly dispersed. The justification for this classification system rests on three retrospective studies that demonstrate a higher rate of progression of CAH to adenocarcinoma (217–219). It is sometimes difficult to apply this system, which requires one to make a distinction between cytologically atypical nuclei and those without atypical nuclei since a spectrum of nuclear variability actually exists. As noted by Kendall et al., the definitions of architectural complexity and nuclear atypia potentially rest on a multitude of criteria, and some but not all criteria may be fully developed in any given case.

Several reports have addressed the reproducibility of diagnoses of hyperplasia (220). Intraobserver reproducibility was generally found to be moderate to good, whereas interobserver reproducibility was poor to moderate for various diagnostic categories. These studies probably overestimate the interobserver reproducibility since they used expert gynecologic pathologists and specified the classification to be used. In a prospective study by the GOG, neither community-based nor expert panel diagnosis of atypical hyperplasia was highly accurate (66). The current classification of hyperplasia relies on a combination of multiple architectural and cytologic criteria. It is hardly surprising that interobserver reproducibility is relatively low when multiple criteria are used to classify a lesion since each pathologist must assign a relative value or weight to each potentially conflicting criterion. Other factors contributing to low reproducibility include: (a) the fragmentary nature of curettings; (b) the presence of borderline lesions; (c) uncertainty about the significance of focal hyperplasia; (d) the inadequacy of published descriptions and understanding of terms used to define architectural or cytologic atypia; and (e) the difficulty associated with the translation of verbal descriptions into light microscopic interobserver reproducibility for images.

The gross manifestations of endometrial hyperplasia are highly varied. The endometrium is often of diffusely increased thickness (5–10 mm or greater), vaguely nodular, tan, and soft without hemorrhage or necrosis. However, hyperplasia may be focal or multifocal in a background of polyps or cycling endometrium, or even occasionally may be associated with a diffusely

thin endometrial lining. Part of the variability may reflect a reduction in the ET due to prior endometrial sampling. Coexistent adenocarcinoma is present in 1% to 40% of hysterectomies performed to treat hyperplasia, with the latter number reflecting the frequent co-occurrence of carcinoma with atypical CH.

Endometrial Intraepithelial Neoplasia

Based on a combination of morphologic, molecular, and morphometric information, Mutter et al. have proposed an alternative classification scheme to replace the current WHO hyperplasia terminology (221, 222). They have presented data that endometrial intraepithelial neoplasia (EIN) is the histopathologic presentation of a monoclonal endometrial preinvasive glandular proliferation that is the immediate pathologic precursor of endometrioid endometrial adenocarcinoma. Monoclonality and forward carryover of EIN mutations into subsequent carcinoma were the original molecular standards used for EIN diagnosis. Computer-assisted morphometric analysis of more than 20 features was carried out initially, and the three features seen in molecularly defined precancers enabled an objective delineation of histologic diagnostic criteria (the D-score). The principal components assessed included a reduction in the volume of stroma and an increased variability in nuclear shape gland contour. Several of these features have been translated to characteristics that can be assessed subjectively by the surgical pathologist (Fig. 22.3). These features include the following: (a) the area of the glands exceeds that of stroma; (b) nuclear and cytoplasmic features of the affected glandular cells differ from those of the background glands, and may include loss of nuclear polarity or increased nuclear pleomorphism; in the absence of any background glands, a highly abnormal cytology is sufficient; (c) the maximum diameter exceeds 1 mm; (d) benign conditions including disordered proliferation, polyps, and repair are excluded; and (e) the cribriform or maze-like pattern of carcinoma is excluded. There is a high degree of concordance between EIN diagnoses rendered by computer and those made subjectively by pathologists, and either has superior cancer predictive value when compared to the 14-fold increased cancer risk conferred by the presence of atypia compared to lack thereof in the WHO hyperplasia schema. Clinical outcome studies have shown that almost 40% of women with an EIN diagnosis will be diagnosed with endometrial

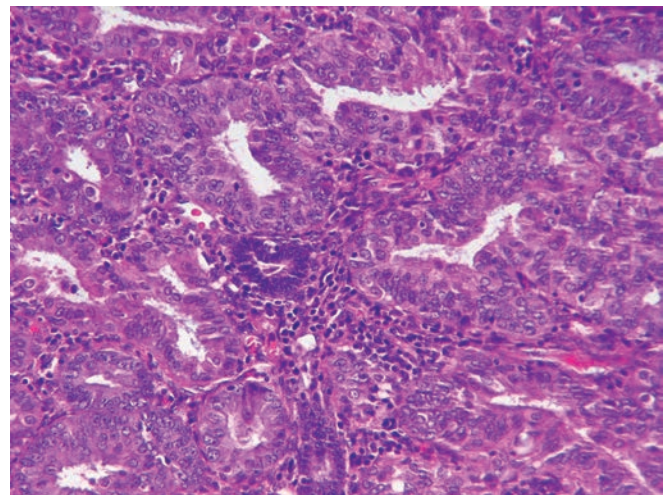


FIGURE 22.3. A lesion that could be classified in two different systems as either endometrial intraepithelial carcinoma or complex atypical hyperplasia based on gland crowding and cytologic atypia. Note the presence of a residual inactive endometrial gland that may be used as a reference for estimating cytologic atypia.

carcinoma within 1 year and, for those who do not develop cancer within 12 months, a 45-fold increased risk of future EC exists. Correspondingly, absence of an EIN lesion in an initial representative biopsy, including those with only benign hyperplasia, confers very high (99%) negative predictive value for concomitant or future adenocarcinoma.

While EIN shares many features with atypical CH, the two entities are not entirely overlapping. The concept of EIN is appealing since there appears to be a strong biologic basis, with EIN representing a clonal process, while disordered proliferation and hyperplasia remain as diffuse endometrial physiologic responses to an abnormal stimulus (unopposed estrogen stimulation).

Simple Hyperplasia

In SH, the endometrium is thicker than usual, with dilated glands that have outpouchings and invaginations, producing an irregular outline to the enlarged glands. The glands are crowded, the stroma is more densely cellular than usual, and some foam cells may exist within the stroma. Follow-up of patients with this condition reveals little or no progression to carcinoma.

Complex Hyperplasia

The endometrium is increased in thickness by back-to-back glands in cases of CH. Most glands have irregular outlines. The two main features differentiating this from SH are the high ratio of glands to stroma, with some back-to-back glands that have very little intervening stroma. Epithelial stratification is a frequent finding, producing an appearance of two to four cell layers. Mitotic activity is highly variable, but may range to up to ten mitotic figures per ten high-power fields.

Atypical Hyperplasia

Atypical hyperplasia is characterized by cytologic atypia of the glands, which may vary unpredictably according to vagaries of histologic preparation. The architecture may reflect simple or CH, although it is usually complex. The cells lining the glands display nuclear hyperchromatism and nuclear enlargement, and have an increased nucleus-cytoplasm ratio. Nuclei are irregular in size and shape, and have a thickened nuclear membrane, inconspicuous to prominent nucleoli, and a coarse chromatin texture. At times, the nuclei may appear clear with scattered, coarse chromatin clumps.

Progression from Hyperplasia to Cancer

The natural history of endometrial hyperplasia is difficult to define for a variety of reasons, four of which follow: (a) pathologic criteria—criteria and terminology for the various forms of hyperplasia have changed repeatedly; (b) initial sampling—the method of initial diagnosis is often curettage, which removes part or all of the lesion to be studied; (c) coexisting lesions—other lesions such as adenocarcinoma may coexist at the time of diagnosis without our knowledge, since the curettage or biopsy samples only a minority of the endometrium; and (d) subsequent intervention—hormonal or surgical intervention usually interrupts observations of the natural history of the hyperplasia. Nevertheless, there are reasonably good data to support the following assertions: (a) endometrial hyperplasia is commonly a consequence of unopposed prolonged estrogen stimulation; (b) some hyperplasias may regress if the estrogenic stimulus is removed or in response to progestational or antiestrogenic treatment; (c) some hyperplasias coexist with, or progress to, invasive adenocarcinoma; and (d) the probability of progression to adenocarcinoma is related to the degree of architectural

or cytologic atypia. Progression from hyperplasia to carcinoma occurs in only 1% of patients with SH and in 3% of patients with CH (65). Progression from atypical hyperplasia is much higher; 8% of patients with SAH and 29% of those with CAH develop carcinoma (Table 22.12) (65, 217). Glandular complexity superimposed on atypia probably places the patient at greater risk than does cytologic atypia alone, but the point is unsettled.

Pathologic Diagnosis

The ISGP and the WHO last revised the classification of uterine tumors in 2003 (223), and the portion pertaining to carcinomas of the endometrium is presented in Table 22.13. This relatively simple classification scheme accommodates the vast majority of endometrial carcinomas and distinguishes among neoplasms of significantly different prognosis. Mixed carcinomas with two distinctive cell types are relatively common, and are defined as those carcinomas in which the secondary component constitutes at least 10% of the neoplasm.

In most endometrial samples, the distinction of adenocarcinoma from hyperplasia is straightforward. However, a small fraction of problematic cases with complex proliferations truly tax the abilities of experts as well as novices to classify them correctly. The diagnosis of a well-differentiated adenocarcinoma is made in the presence of any of the following criteria: (a) irregular infiltration of glands in an altered fibroblastic stroma; (b) a confluent glandular pattern that results in either a cribriform arrangement or confluent interconnected glands; or (c) extensive papillary growth of epithelium and stroma into glandular lumina (217).

Histologic Grade

The differentiation of a carcinoma is expressed as its grade. Grade 1 lesions are well differentiated and are generally associated with a good prognosis. Grade 2 tumors (Fig. 22.4) are moderately well differentiated and have an intermediate prognosis, and grade 3 reflects poorly differentiated lesions, which frequently have a poor prognosis. Both architectural criteria and nuclear grade are used in the FIGO and ISGP-WHO committee (274) classification of tumors and are applied to endometrioid cell types including

Table 22.13 Classification of Endometrial Carcinoma

Endometrioid adenocarcinoma
Villoglandular
Secretory
Ciliated cell
Adenocarcinoma with squamous differentiation
Mucinous adenocarcinoma
Serous adenocarcinoma
Clear-cell adenocarcinoma
Squamous cell carcinoma
Small cell carcinoma
Transitional cell
Undifferentiated (and de-differentiated) carcinoma
Mixed types
Miscellaneous carcinomas
Metastatic carcinoma

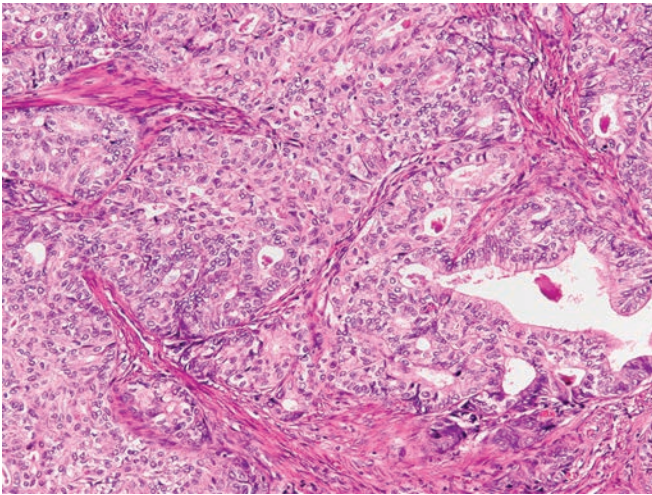


FIGURE 22.4. Endometrioid adenocarcinoma, grade 2. The glandular component is a caricature of proliferative phase glands, with stratification and a shared luminal border to the neoplastic cells. In grade 2 carcinomas, regions of solid neoplastic growth occupy between 5 and 50% of the surface area of the carcinoma.

variants and mucinous carcinomas (Table 22.13). In contrast, serous, clear-cell, and undifferentiated carcinomas are considered high grade by definition, and are not graded numerically. The architectural grade is determined as follows: grade 1—an adenocarcinoma in which less than 5% of the tumor growth is in solid sheets; grade 2—an adenocarcinoma in which 6% to 50% of the neoplasm is arranged in solid sheets of neoplastic cells; grade 3—an adenocarcinoma in which greater than 50% of the neoplastic cells are in solid masses. Regions of squamous differentiation are excluded from this assessment. The FIGO rules for grading state that notable nuclear atypia, inappropriate for architectural grade, raises the grade of a grade 1 or grade 2 tumor by one. However, FIGO did not define notable nuclear atypia. Justification and clarification for this modification based on extreme nuclear pleomorphism were provided in a recent GOG study. For 715 women with nonserous endometrial carcinomas, three nuclear grades were defined as follows: grade 1—round to oval nuclei with even distribution of chromatin and inconspicuous nucleoli; grade 2—irregular, oval nuclei with chromatin clumping and moderate-size nucleoli; and grade 3—large, pleomorphic nuclei with coarse chromatin and large, irregular nucleoli. Patients with tumors of architectural grade 1 or 2, but with a majority of cells having nuclei of grade 3, had a significantly worse behavior, justifying an up-grading by one grade (225).

Taylor et al. (226) proposed a two-tiered system for grading endometrial carcinoma based on a study of 85 patients with Stage I and II EC. They divided tumors at 10% intervals based on the percentage of solid tumor growth and found that tumor recurrences were confined to the subset with greater than 20% solid tumor. They also found that this binary division yielded a higher degree of interobserver agreement than three architectural grades. Lax et al. (227) have presented preliminary data on a binary architectural grading system based on the presence of greater than 50% solid growth, a diffusely infiltrative growth pattern, and tumor cell necrosis. These methods will need to be replicated in a larger patient population before an assessment of their prognostic utility can be made.

Cell Types

Endometrioid Adenocarcinoma. Endometrioid adenocarcinoma is the most common form of carcinoma of the endometrium, comprising 75% to 80% of the cases (55). It varies from well

differentiated to undifferentiated. Characteristically, the glands of endometrioid adenocarcinoma are formed of tall columnar cells that share a common apical border, resulting in a smoothly delineated, round or oval luminal contour. With decreasing differentiation, there is a preponderance of solid growth rather than gland formation, and the cells lining glandular lumina become more numerous but not necessarily clearly stratified. Stromal invasion manifested by a desmoplastic host response or vascular invasion is often not evident in the biopsy or curettage specimen.

Villoglandular Carcinoma. There has been considerable confusion about the definition and significance of papillary carcinoma of the endometrium. A variety of cell types of endometrial adenocarcinoma with differing biologic behavior, including serous, clear-cell, mucinous, and villoglandular carcinoma, may grow in a papillary fashion. Thus, the adjective *papillary* does not represent a cell type but rather an architectural pattern.

Villoglandular carcinoma is a relatively common subtype of endometrioid adenocarcinoma characterized by neoplastic columnar cells covering delicate fibrovascular cores. The apical cytoplasmic borders are straight, the nuclei are usually low grade, and the tumor cells architecturally resemble those of other endometrioid adenocarcinomas, with which they are often admixed. In the largest study to date, villoglandular carcinomas were better differentiated than endometrioid carcinomas, but the age at diagnosis, depth of myometrial invasion, nodal spread, and survival were similar to those of endometrioid carcinomas, justifying their classification as a subtype of endometrioid adenocarcinoma (228).

Secretory Carcinoma. Secretory carcinoma is a variant of endometrial carcinoma, but it is unusual and represents no more than 2% of the cases (229). It is identified by its well-differentiated glandular pattern, consisting of columnar epithelial cells containing intracytoplasmic vacuoles similar to secretory endometrium. It is usually grade 1 architecturally and by nuclear features. There is minimal cellular atypia, stratification, and pleomorphism. The intracellular secretions are not mucin but glycogen. The cellular features of secretory carcinoma differentiate it from clear-cell carcinoma, which is more papillary with more pleomorphic nuclei. By its lack of mucin, secretory carcinoma may be differentiated from mucinous carcinoma. Recognition of secretory carcinoma is important because it has a less virulent clinical course (230), although the clinical profile of patients is similar to that of patients with adenocarcinoma.

Ciliated Carcinoma. Ciliated carcinoma is rare. Ciliated cells are more commonly identified in endometrial hyperplasia and in benign metaplasia (tubal metaplasia), but they may occur in endometrioid carcinomas. Associated with prior exogenous estrogen use, this cell type is reported to have a good prognosis (231).

Adenocarcinoma with Squamous Differentiation. Foci of squamous differentiation are found in about 10%–25% of endometrial adenocarcinomas (Fig. 22.5). Historically, the tumors were sometimes separated into adenoacanthoma or adenosquamous carcinoma based on whether the squamous component appeared histologically benign or malignant (232, 233). However, in about 30% of cases, the squamous component is not clearly benign or malignant. In a GOG study of early-stage disease, it was noted that these tumors with squamous regions behave in a fashion similar to endometrioid carcinomas without squamous differentiation (234). The squamous areas usually mirror the degree of differentiation, which, coupled with assessment of histologic grade and other conventional prognostic factors, is thus more useful for prognostication and determination of adjuvant therapy than the historic terms *adenoacanthoma* and *adenosquamous carcinoma*, which are confusing and should be abandoned.

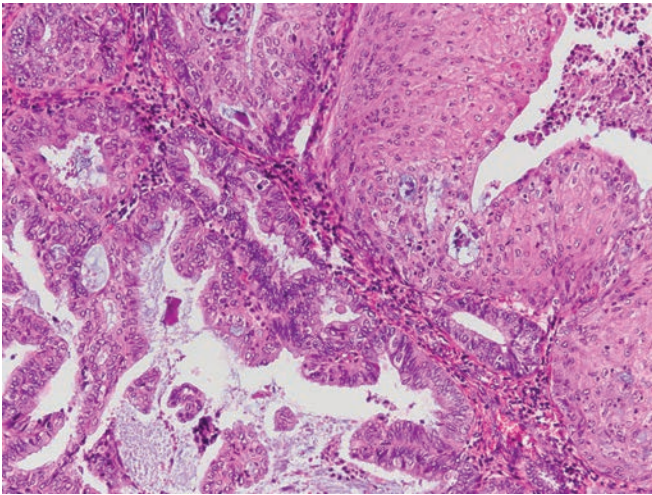


FIGURE 22.5. Endometrioid adenocarcinoma with squamous differentiation. The squamous component may form keratin pearls, but more often simply is characterized by acquisition of more abundant, deeply eosinophilic cytoplasm and distinct cell borders (upper right of figure). The squamous component may appear histologically benign or malignant.

Mucinous Adenocarcinoma. Mucinous adenocarcinoma is rare in the endometrium in contrast to its high frequency in the endocervix. It has been reported to represent between 1% and 9% of endometrial adenocarcinomas (235), but the former figure is probably more accurate. If present as the major cellular component of an endometrial carcinoma, this tumor resembles mucinous carcinoma seen in the ovary and endocervix. Two patterns occur: In one, the cells are columnar with basally oriented nuclei; in the other, the cells are more pseudostratified, as in an adenocarcinoma of the colon or mucinous carcinoma of the ovary (Fig. 22.6). The characteristic cellular pattern should represent over 50% of the entire tumor. Typically, there are either papillary processes or cystically dilated glands lined by columnar or pseudostratified columnar epithelium. The cytoplasm is positive for carcinoembryonic antigen (CEA), mucicarmine, and periodic acid-Schiff stain (PAS), but it is diastase resistant. This tumor differs from clear-cell carcinoma and secretory endometrium by having more mucin and less glycogen. The glandular architecture is usually well maintained, and most are well

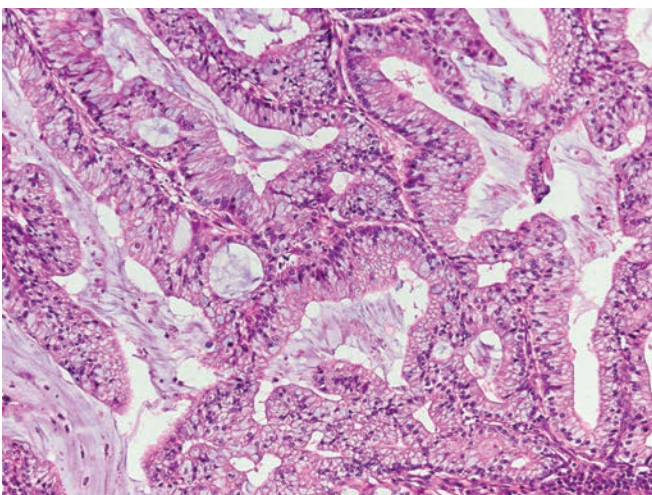


FIGURE 22.6. Mucinous adenocarcinoma. The apical cytoplasm cells as well as the lumens of glands are filled with a pale basophilic mucoid product.

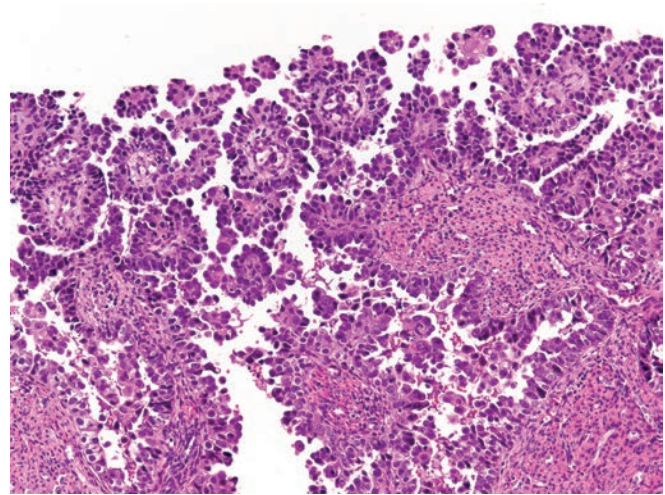


FIGURE 22.7. Serous carcinoma often arises in an otherwise endometrium of older women, and superficially, portions usually have a highly papillary architecture.

differentiated (235). To establish the origin in the endometrium, exclusion of a primary endocervical tumor may be required. If the endocervical sample demonstrates the same neoplasm, the site of origin must be carefully established because this cell type is common in the endocervix (236). Neither the pattern, the type of mucin staining, nor the presence of CEA can reliably distinguish mucinous adenocarcinoma of the endometrium from its more common counterpart in the endocervix (237). Mucinous carcinoma of the endometrium has the same prognosis as common endometrial carcinoma.

Serous Carcinoma. Serous carcinoma of the endometrium closely resembles serous carcinoma of the ovary and fallopian tube because its papillary growth and cellular features are similar (Figs. 22.7 and 22.8). It is usually found in an advanced stage in older women. Fibrous papillary fronds are lined by epithelial cells, which are almost devoid of cytoplasm, but which manifest stratification, atypism, pleomorphism, mitotic figures, and bizarre forms. These fronds often detach or demonstrate a terminal growth of tiny papillary excrescences and individual cells, which detach easily (Fig. 22.7). A second pattern of irregular

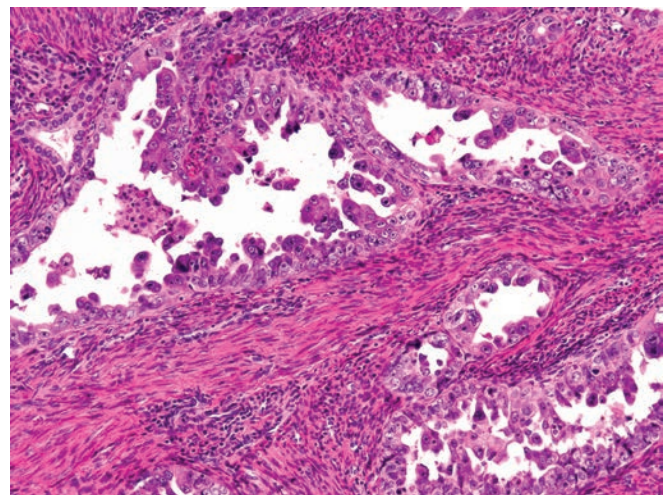


FIGURE 22.8. Serous carcinoma is characterized by high-grade cytologic atypia in cells that do not share a common apical border. The papillary architecture may be replaced by gaping glands at the interface with the myometrium.

gaping glands lined by cuboidal cells with scalloped, apical borders may be present, particularly in the deeper aspect of the tumor (Fig. 22.8). Lymphatic invasion is commonplace in the myometrium. Distinction from clear-cell carcinoma may be difficult but can usually be accomplished on the basis of a greater degree of papillary processes, greater nuclear atypia, and less cytoplasm in papillary serous carcinoma. Psammoma bodies are frequently observed in serous carcinoma, but solid growth is more common in clear-cell carcinoma.

Serous carcinoma represents approximately 10% of endometrial carcinomas, which is fortunate because it is an aggressive tumor. The tumors often deeply invade the myometrium, and unlike typical endometrioid adenocarcinoma, there is a propensity for peritoneal spread. Unfortunately, advanced-stage disease or recurrence is common even when serous carcinomas are apparently only minimally invasive or even confined to the endometrium in polyps (146, 238, 239). Since the metastatic disease is often identified only microscopically, about 60% of patients are up-staged following complete surgical staging (146). A report by Wheeler et al. (240) stressed the prognostic importance of meticulous surgicopathologic staging. They and others found that serous carcinoma truly confined to the uterus had an overall excellent prognosis, whereas patients with extrauterine disease, even if only microscopic in size, almost always suffered recurrence and death from tumor (241, 242).

EIC is a histologically distinctive lesion that is specifically associated with serous carcinoma of the endometrium (243–247). Serous carcinomas most often arise from a background of atrophy or polyps rather than hyperplasia (243, 244, 245), and they are not epidemiologically related to unopposed estrogen stimulation. EIC has been proposed to represent a form of intraepithelial tumor characteristic of serous carcinoma, and it is the precursor to invasive serous carcinoma. Mutations in p53 that can be detected immunohistochemically as overexpression of the antigen are found in most cases, and the mutation is shared with that found in the invasive serous carcinoma (Fig. 22.9). EIC is usually found in the endometrium harboring a serous carcinoma (244), but occasionally occurs in the absence of any invasive carcinoma. In such cases, it may be associated with synchronous serous carcinoma in the peritoneum (245).

Clear-Cell Carcinoma. Clear-cell adenocarcinoma of the endometrium is generally recognized and defined on the basis of the

distinctive clearing of the cytoplasm of neoplastic cells growing in any combination of solid, glandular, tubulocystic, or papillary configurations. About 4% of endometrial adenocarcinomas are of clear-cell type (248–250). In contrast with the diethylstilbestrol (DES)-related clear-cell carcinomas of the vagina and cervix, clear-cell carcinoma of the endometrium is almost exclusively a disease of menopausal women. The mean age at diagnosis is about 68 years, which is similar to that of serous adenocarcinoma and about 6 years older than that of typical endometrial adenocarcinoma (250). It is a biologically aggressive neoplasm, with a 5-year survival rate varying from only about 20% to 65% (5, 248, 250).

The hallmark of clear-cell carcinoma is the presence of neoplastic cells with optically clear cytoplasm, reflecting an abundance of glycogen. Four basic architectural patterns of clear-cell adenocarcinoma exist, including solid, glandular, tubulocystic, and papillary, but most cases display an admixture of patterns. The solid pattern consists of masses of large neoplastic cells of polygonal shape with clear to faintly eosinophilic cytoplasm and distinct cell membranes. The glandular pattern is reminiscent of the tubular glands of endometrioid adenocarcinoma, whereas the tubulocystic pattern is formed of dilated spherical-appearing glands. The papillary pattern is architecturally identical to that of serous carcinoma, with generally short, branching fibrovascular cores, often hyalinized, covered by neoplastic cells. The latter three patterns often have lining cells with a hobnail appearance, resulting from the scalloped apex of individual neoplastic cells that project along the surface (Fig. 22.10).

Squamous Carcinoma. Although focal squamous differentiation is common in endometrial adenocarcinoma, pure squamous carcinoma of the endometrium is extremely rare, representing less than 1% of endometrial carcinoma, and with only about 60 reported cases (251, 252). Most patients are postmenopausal, and the average age at diagnosis is about 65 years. Squamous carcinoma of the endometrium is established as primary in the endometrium after a cervical origin is ruled out. There must be no connection with or spread from benign or malignant cervical squamous epithelium. It is often associated with cervical stenosis, pyometra, and chronic inflammation. About 60% of the cases have been confined to the uterus, and the prognosis for these patients has been relatively good. In contrast, less than 15% of women with advanced-stage disease have survived

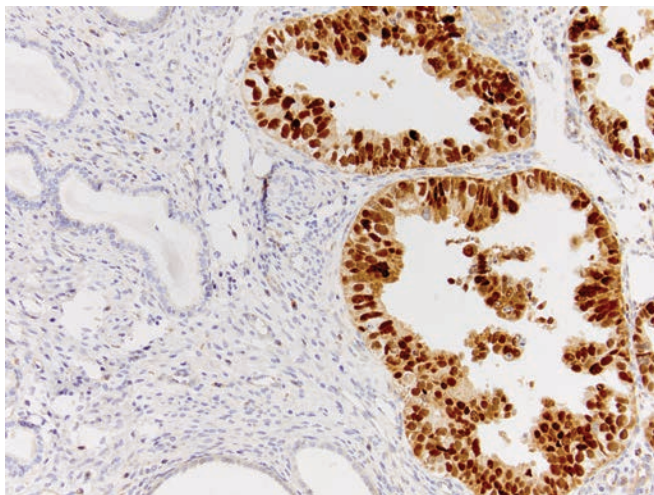


FIGURE 22.9. Endometrial intraepithelial carcinoma is the precursor lesion of invasive serous carcinoma. It shares histologic and immunohistochemical features with serous carcinoma, including frequent overexpression of p53. In this case, there is nuclear localization of stain in EIC (on right), but no staining of the benign glands or stroma of the polyp in which it has arisen (on left).

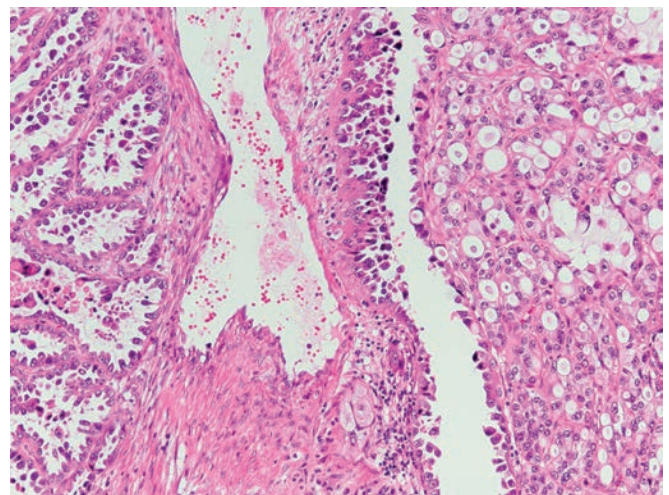


FIGURE 22.10. Clear-cell carcinoma. In this tumor, a tubulocystic pattern with a lining of hobnail cells is present on the left, while a solid pattern is present on the right. Any mixture of solid, tubulocystic, papillary, or glandular architecture may occur.

2 years after diagnosis. Histologic grade does not appear to correlate with the probability of survival.

Undifferentiated Carcinoma. Undifferentiated carcinoma of the endometrium has been described as a distinct tumor type. These neoplasms are composed of a monotonous proliferation of medium sized, round or polygonal cells growing in sheets with no specific pattern. Mitotic figures are numerous. No glandular, squamous, or sarcomatous differentiation is detected in routinely stained sections. Keratins and epithelial membrane antigen are detected by immunohistochemistry in fewer than 20% of the cells in most cases, in contrast to diffuse staining in most high-grade endometrioid carcinomas. Selected cases may contain neurosecretory granules in a minority of the cells as demonstrated by immunohistochemical stains. Neurosecretory products are apparently not released into the patient's circulation or are not in an active form because no affected women have manifested symptoms. Most patients present with tumors of advanced stage, and the behavior is usually aggressive. A *glassy cell carcinoma* has also been described, which comprises less than 1% of endometrial carcinomas. It is characterized by cytoplasm that has a ground-glass appearance, as in the cervix. Although few cases have been reported, like serous and clear-cell carcinomas, glassy cell carcinoma appears to be aggressive (253).

Mixed Cell Type. If an endometrial carcinoma manifests two or more different cell types, each representing at least 10% or more of the tumor, the term *mixed cell type* is appropriate.

Metastatic Carcinoma to the Endometrium. Malignancies in other organs may metastasize to the endometrium. The most common extragenital sites are breast, stomach, colon, pancreas, and kidney, although any disseminated tumor could involve the endometrium. The ovaries are the most likely genital sources of metastasis. Metastatic carcinoma presents as abnormal vaginal bleeding, and the initial specimen for evaluation is usually a biopsy or curetting. Although the metastatic disease may appear as a large focus, individual and small groups of malignant cells may subtly intermingle with normal endometrium or myometrium. Lymphatics are usually involved. Special stains for mucin, CEA, or melanin may suggest that the cells are not of endometrial origin. In some instances, unusual cell types, such as signet-ring cells, may be present, suggesting a metastasis from the gastrointestinal (GI) tract. It is uncommon but not exceptional for the endometrial sample to be the first indication of an occult primary lesion (254).

Simultaneous Tumors. Cancers of an identical cell type may be discovered in the ovary and endometrium simultaneously (255). Usually, the primary site is assigned to the area having the largest tumor mass and most advanced stage. In certain situations, primary malignancies in the endometrium and ovary may coexist. This "field effect" of the "extended müllerian system" may occur in 15% to 20% of endometrioid carcinomas of the ovary (256). In a review of a GOG study of 74 patients with simultaneously detected endometrial and ovarian carcinoma with disease grossly limited to the pelvis, only 16% of women suffered a recurrence of disease, with a median follow-up of 80 months. This group of patients was atypical, with 86% having endometrioid histology in both sites. Recurrence was statistically related to the presence of microscopic metastases or high histologic grade (257).

Carcinomas of more advanced histologic grade and cell type are more difficult to assign to the field effect because of a higher probability of invasion and metastasis at the time of surgery (230). If the endometrial tumor is less than 5 cm in diameter, the ovarian lesion is unilateral, invasion is less than the middle third, vessels are not involved, and the endometrial carcinoma is well differentiated; metastasis to the ovary is unlikely (258).

PATHOLOGIC FACTORS OF PROGNOSTIC SIGNIFICANCE

Pathologic information has been used to estimate risk of nodal metastasis and to define prognosis (recurrence, survival) in EC. Prognostic factors have been identified within each stage of EC, and the discussion of prognostic factors is probably best served by discussing factors within comparably staged groups, more so than as isolated factors. For example, in GOG 99, which compared observation to pelvic radiation therapy in patients with Stage I–II EC and pathologically negative LN, a model based on combinations of patient age and tumor grade, depth of invasion, and lymphovascular space invasion (LVSI) could predict patients at highest risk for recurrence (121). Similarly, PORTEC identified a combination of 2 of 3 factors; age greater than 60, grade 3 tumor, and depth of invasion greater than 50% which defined patients at high risk for local-regional failure when managed by surgery alone (135). Increasingly, risk models are used to counsel patients as to the marginal benefit of postoperative therapies.

Predicting Nodal Disease

Based on pathologic information available at the time of surgery, the risk for nodal metastasis may be estimated. Physicians who selectively perform nodal dissections frequently do so based on the presence of uterine risk factors that suggest the potential for nodal disease. In patients who did not undergo a nodal dissection at the time of hysterectomy, decisions to offer radiation therapy are commonly based on the estimation of risk for nodal disease based on uterine risk factors. In the surgical pathologic study GOG 33, pelvic and paraaortic nodal disease was more frequent with increasing grade (percentage of pelvic nodal metastases: 3% grade I, 9% grade II, 18% grade 3), depth of invasion (1% endometrium only, 5% inner one-third, 6% middle one-third, 25% outer one-third myometrial invasion), and LVSI (27% with LVSI, 7% without LVSI) (55). Pelvic and paraaortic nodal metastases were also more common with cervical involvement, when peritoneal cytology was positive, and when extra-nodal (adnexal, intraperitoneal sites) disease was found. In a multivariate model, grade, depth of invasion, and intraperitoneal disease were independent predictors of pelvic nodal disease. In a further analysis of patients participating in GOG 33, 47 of 48 patients with paraaortic nodal disease had one or more factors of palpably enlarged paraaortic nodes, grossly positive pelvic nodes, gross adnexal disease, or outer one-third invasion (57). Despite the use of pathology to help predict nodal disease, many believe that lymph node assessment is superior as it provides actual information on nodal status, as opposed to an estimate, which can then be used to tailor therapy. As previously discussed, patients at very low risk for nodal involvement may also be specified by uterine risk factors (size, grade, depth of invasion) (148–151).

Prognostic Factors

FIGO Stage

Prognostic factors may be used to categorize patients into high- and low-risk groups and to guide the use of adjuvant therapies. Understanding these factors also allows for the development of novel strategies to reduce risk of recurrence or alter patterns of disease failure. Overall, the patients at highest risk for recurrence and death have spread of disease outside of the uterus, which is reflected by FIGO stage (57). The prognostic utility of surgicopathologic stage has been confirmed in multiple studies of large numbers of patients, using both univariate and

multivariate analysis (55, 259–261). FIGO surgical stage is often the single strongest predictor of outcome for women with endometrial adenocarcinoma in studies using multivariate analyses. Although the FIGO clinical staging system of 1971 was generally useful, retrospective comparison of the two methods demonstrated the clear superiority of surgicopathologic staging over clinical staging in predicting outcome.

Patients with intraperitoneal or distant metastases (Stage IV) have the poorest prognosis with 5-year survival ranging from 20% to 25% (5). In GOG 122 comparing whole abdominal radiation therapy to doxorubicin/cisplatin chemotherapy as primary therapy for EC patients with less than 2 cm residual disease Stage III–IV, Stage IV (compared to Stage III) disease was an independent predictor of shorter PFS (HR, 2.29) and survival (HR, 1.9) (262). Gross intraperitoneal spread frequently indicates the presence of larger tumor burden as many patients with intraperitoneal disease also have adnexal and nodal disease. In GOG 33, 51% of patients with gross intraperitoneal spread had positive pelvic nodes, whereas only 7% without spread had positive pelvic nodes (55). Prognosis may be modified by the volume of residual disease after cytoreductive surgery (214–215).

Patients with nodal metastases (Stage IIIC disease) also have poorer prognosis compared to node-negative populations. FIGO data show 5-year survival to be 57% in Stage IIIC patients compared to 74% to 91% when nodes are negative (Stage I–II) (5). Patients with positive pelvic but negative paraaortic nodes have a better prognosis compared to those with paraaortic disease (57, 263, 264). For example, Hoekstra and colleagues reported a series of 85 patients with Stage IIIC disease who had a 5-year survival of 61% (264). Patients with positive pelvic nodes had a 5-year survival of 70% compared to 49% when paraaortic disease was present. In 2009, FIGO staging was revised for patients with positive pelvic nodes/negative paraaortic nodes who were reclassified as Stage IIIC1, and patients with any positive paraaortic node were classified as Stage IIIC2 (79). This change has been validated in two recent reviews (265, 266). Two retrospective series have also suggested that patients with nodal disease in addition to positive cytology, adnexa, or serosa have poorer PFS or survival compared to those patients with positive nodes alone (140, 263). Lymphadenectomy (139, 163–174), complete surgical resection of bulky nodes (267), and use of chemotherapy (164, 262, 265–268) have been suggested to improve outcomes in patients and modify the prognostic effect of nodal disease.

Patients with FIGO 1988 Stage IIIA disease represent a heterogeneous population having adnexal, peritoneal cytology, and/or serosal involvement, but with negative LN. Positive peritoneal cytology as the sole upstaging factor was dropped in the 2009 FIGO staging revisions as a stage-defining characteristic (79). In the GOG 33 study, 12% of all patients had positive cytology, and of these, 25% had positive pelvic nodes and 19% had metastases to paraaortic LN (55). Six percent of clinical Stage I–II patients have spread of tumor to the adnexa, and of these, 32% have pelvic node metastases compared with 8% pelvic node positivity if adnexal involvement is not present (55). Twenty percent have positive paraaortic node metastases, which is four times greater than if adnexal metastases were not present.

For patients who are completely staged and found to have no extrauterine disease, 4% to 6% of patients have positive cytology as an isolated finding (55). Published opinions are mixed about the significance of this finding (269, 270). In a review of the literature, Wethington categorized patients into groups based on low-risk uterine features (grade 1–2, <50% depth of invasion, no lymphovascular space invasion) with positive peritoneal cytology. In this group, positive cytology occurred in 11% of cases, and had a recurrence rate of 4%. Patients with higher-risk features plus positive cytology had a 32% risk of recurrence (271). Saga reported that positive peritoneal cytology alone in staged patients ($n = 32$) was associated with a 5-year survival of 87%; however, this was worse than the 97% survival seen in

cytology-negative patients (272). In a series of 57 patients with FIGO Stage IIIA (1988) disease, cytology appears to carry the same significance as adnexal involvement and was an independent predictor of prognosis (273).

Histologic Cell Types

The histologic classification of endometrial adenocarcinoma is important not only because it facilitates the recognition of lesions as carcinoma, but also because the cell type has consistently been recognized as being important in predicting the biologic behavior and probability of survival. Endometrioid adenocarcinoma accounts for the majority of tumors in the uterine corpus and carries a relatively favorable prognosis. Consequently, the virulence of other cell types is usually related to endometrioid adenocarcinoma.

Adenocarcinoma with squamous differentiation is similar to typical endometrioid adenocarcinoma with respect to the distribution by age and frequency of nodal metastasis, and is associated with a slightly increased probability of survival. *Villoglandular carcinoma* has a biologic behavior similar to that of endometrioid adenocarcinoma (228, 274). *Serous carcinoma* has been considered an aggressive histologic type, with OS rates varying from 40% to 60% at 5 years (5, 238, 275). *Clear-cell carcinoma* also has a highly aggressive behavior, with 5-year survival rates of 30% to 75% (276, 277). One of the problems with using histology as a marker for prognosis is that serous cancers are more likely to have spread at presentation than endometrioid tumors. Patients with serous or clear-cell tumors present with Stage III–IV disease in 41% and 33%, respectively, compared to 14% with endometrioid type (5). Studies suggest that 40% to 70% of serous tumors will have extrauterine spread at presentation; therefore, complete surgical staging is warranted in this tumor type (146). Given this level of disease spread, it is not surprising that unstaged/clinical Stage I serous patients appear to have similar prognosis to Stage III–IV endometrioid types. Once patients with serous or clear-cell tumors are appropriately allocated into the correct stage, the importance of histology appears to be less (278–281). For example, Creasman et al. evaluated FIGO data and showed that patients with Stage I serous tumors had comparable outcomes to those with Stage I, grade 3 endometrioid tumors. Five-year survival for Stage IB and IC serous tumors was 81% and 55% compared to 84% and 66% for grade 3 tumors (281). In advanced and recurrent EC patients participating in phase 3 GOG chemotherapy trials, response rate to chemotherapy was not associated with histologic type, and serous tumor type was not independently associated with PFS (16).

Grade

The degree of histologic differentiation has been considered to be an indicator of tumor spread. The GOG and other studies have confirmed that as grade becomes less differentiated, there is a greater tendency for deep myometrial invasion and, subsequently, higher rates of pelvic and paraaortic lymph node involvement (55, 282). Survival has also been consistently related to histologic grade, and in a GOG study of more than 600 women with clinical Stage I or occult Stage II endometrioid adenocarcinoma, the 5-year relative survival was as follows: grade 1, 94%; grade 2, 84%; grade 3, 72% (57). In patients with early-stage EC participating in the PORTEC trial, the risk of cancer-related death for patients with grade 3 tumors was 4.9 compared to grade 1–2 tumors (127).

Myometrial Invasion

Deep myometrial invasion is one of the more important factors correlated with a higher probability of extrauterine tumor spread, treatment failure, and recurrence, and with diminished

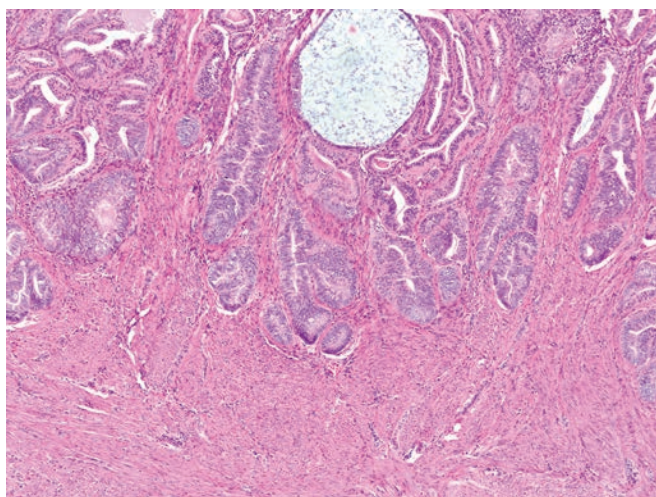


FIGURE 22.11. Myometrial invasion by endometrial adenocarcinoma may be accompanied by a desmoplastic reaction, but often no such reaction is present, as in this case.

probability of survival (Fig. 22.11) (121, 283). In a GOG study of over 400 women with clinical Stage I and occult Stage II endometrioid adenocarcinoma, the 5-year relative survival was 94% when tumor was confined to the endometrium, 91% when tumor involved the inner third of the myometrium, 84% when the tumor extended into the middle third, and 59% when the tumor invaded into the outer third of the myometrium (57). Even in node-negative patients, deep myometrial invasion retains prognostic information. For example, Mariani et al. reported that for Stage I (node-negative) patients, deep invasion (>66% myometrial invasion) was an independent predictor for recurrence and distant site of failure (284).

Lymphovascular Space Invasion

Several studies have suggested that lymphatic space invasion (LVSI) is a strong predictor of recurrence and death, and is independent of depth of myometrial invasion or histologic differentiation (Fig. 22.12) (285). In a retrospective series of 628 surgically staged patients, the presence of high intermediate

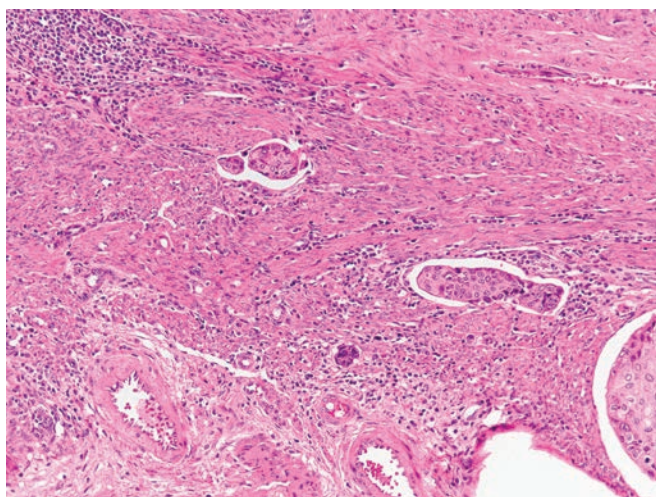


FIGURE 22.12. Lymphatic invasion by endometrial adenocarcinoma. Nests of neoplastic cells occupy the lumen of an endothelial lined space. Since artifactual retraction of stroma around tumor may simulate lymphatic spaces, true lymphatic invasion is best assessed in the myometrium adjacent to the tumor.

risk uterine (H-IR) characteristics and LVSI were associated with nodal metastases (285–287). The odds ratio (OR) for nodal disease was 4.4 with H-IR factors, and 11 for LVSI. In this series, LVSI and H-IR features were independently associated with PFS and survival. Zaino et al. (261) found that LVSI was a statistically significant indicator of death from tumor in early clinical stage but not early surgical stage endometrial adenocarcinoma. This suggests that lymphatic invasion helps to identify patients likely to have spread to LN or distant sites, but that its importance is diminished for those in whom thorough sampling of nodes has failed to identify metastasis. Vascular space invasion or capillary-like space (CLS) involvement with tumor exists in approximately 15% of uteri containing adenocarcinoma (55, 286). Pelvic LN are positive in 27% of cases, which is four times more often if malignant cells are found in the CLS than if absent. The risk of paraaortic node metastases when LVSI was present was 19%, which is a six-fold increase over negative CLS involvement (55). Lymphovascular invasion is identified in 35% to 95% of serous carcinomas of the endometrium, where it has generally been associated with an elevated risk of tumor recurrence or death from disease (275).

Patterns of Failure

Another way to approach pathologic information is to understand the pathologic relationships that predict particular patterns of failure. For example, in patients with pathologic negative-node, Stage I EC, pelvic sidewall recurrences are rare, and failures occur most frequently at the vaginal cuff or at distant sites (121, 288, 289). High-risk Stage I patients who do not undergo nodal dissections have both pelvic sidewall and distant sites of failure, even with routine use of radiation therapy (138). Patients with node-positive disease frequently have recurrences at distant sites, with rare intra-abdominal failures (140, 141, 264). Patients with Stage IV/intraperitoneal disease most commonly fail in the peritoneal cavity. The implications of patterns of failure data are that we may choose our postoperative therapies better by defining patterns of failure for a particular stage distribution or based on the presence of risk factors. The Mayo Clinic group has advocated this approach following a review of patterns of failure data from their group (284, 290–293). For example, these investigators suggested that hematogenous, lymphatic, and peritoneal failures could be predicted based on pathologic factors, and that therapy should be directed to reduce failures at these sites depending on pathologic information (56). Whether their finding can be validated in a prospective manner, or if existing therapies effectively control disease at particular sites needs to be evaluated.

GENERAL MANAGEMENT

Results of Standard Therapy and Their Sequelae

Early uncontrolled trials suggested that progestin therapy after surgery or irradiation was associated with a decreased risk of recurrence in patients with disease confined to the uterus (294). However, large prospective, randomized trials failed to show a survival advantage (295–297). Radiation therapy has been and remains the standard adjuvant treatment modality for most patients at risk for recurrence. This standard continues to evolve, however. An older, poorly designed adjuvant cytotoxic chemotherapy showed no benefit for patients treated with single-agent doxorubicin and arrested interest in adjuvant chemotherapy for many years (298). By 2006, two prospective trials comparing

radiation therapy to chemotherapy demonstrated similar outcomes for patients treated with chemotherapy or radiation therapy (297, 298). Adjuvant chemotherapy improved PFS and survival in patients with advanced-stage disease compared to whole abdominal radiotherapy, suggesting an important role for first-line therapy that includes chemotherapy (262). Current research focuses on whether outcomes may be improved by adding chemotherapy either sequentially or concomitantly with radiation.

ADJUVANT RADIATION THERAPY

Radiation therapy continues to play an important role in the management of EC, although its role is evolving. It is used adjvantly, as definitive treatment for patients who are medically inoperable, for local recurrence, and for palliation. Historically, patients were treated with preoperative intracavitary brachytherapy with or without external beam radiotherapy followed by hysterectomy. This approach has not been completely abandoned but is used infrequently and usually only in patients with gross cervical involvement. Today, most patients undergo primary surgery; then, depending on final pathological review, the need for radiotherapy is determined. Radiation can be delivered with external beam irradiation with or without brachytherapy. Brachytherapy can be delivered by interstitial treatment, where needles are placed into the tissues at risk under general anesthesia and postoperatively loaded with radioactive sources. More commonly, brachytherapy is intracavitary where a device is inserted into an anatomic cavity such as in the uterus or vagina. Brachytherapy doses can be delivered with low-dose-rate ^{137}Cs sources (LDR), high-dose-rate ^{192}Ir sources (HDR), and with ^{192}Ir pulse dose rate (PDR). With LDR, the patient is admitted to the hospital for insertion and delivery, and is usually at bed rest for delivery. This method exposes other personnel to irradiation, is often more costly, and places the patient at risk for deep venous thrombosis and other medical complications. HDR is typically done as an outpatient and avoids radiation exposure to additional personnel, although frequently, more sessions are required. PDR also spares treating personnel radiation exposure, but requires hospital admission.

Early-Stage Disease

Most of the data on adjuvant radiation in EC pertain to patients with early-stage (I–II) disease, as this is the most common presentation. The role of radiation in this group of patients, however, has been undergoing significant scrutiny in the last 10 years. The questions to be resolved are elucidating the benefits of radiation, clarifying which patients will be best served by this additional therapy, and determining the most appropriate radiation strategy.

Benefit of Adjuvant Radiation

Two prospective, randomized trials compared surgery alone to surgery and postoperative external beam radiation. The first trial was conducted by the GOG (study 99) where 392 patients with Stage IB–IIB EC who underwent total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO) and pelvic/para-aortic lymph node sampling were randomized to observation ($n = 202$) or postoperative pelvic radiation ($n = 190$) to a total dose of 50.4 Gy in 28 fractions (121). The study was designed to allow for an 80% chance of detecting a 58% decrease in the recurrence hazard rate and a 56% decrease in the death hazard rate. Recurrence free interval (RFI) was the primary endpoint

with all-cause survival as well as recurrence-free survival as secondary endpoints. With a median follow-up of 68 months, the 4-year survival rate was 92% in the radiation arm compared with 86% in the observation arm (Relative hazard [RH], 0.86; $p = 0.557$). The estimated 2-year cumulative incidence of recurrence was 3% versus 12% in favor of the irradiation arm (RH, 0.42; $p = 0.007$), indicating that radiation decreased the hazard rate of recurrence by the required 58%. Specifically, the rate of vaginal recurrence, the most frequent area of recurrence, was 6.4% (13 out of 202) in the surgery alone arm compared to 1.05% (2 out of 190) in the radiation arm. Of interest, these two patients in the surgery arm that recurred were randomized to radiation but refused it. In addition, the estimated risk of death from any cause was 14% less in the RT arm, but was nonsignificant. More than half of the deaths were from causes other than treatment or endometrial carcinoma, and the paper points out that it was therefore not adequate to detect an OS difference, a point often forgotten by many physicians. The subgroup termed HIR accounted for two-thirds of the cancer-related deaths and recurrences, and has become the population for further study in currently open trials. The definition of HIR by GOG is determined by the combination of age and risk factors, including grades 2 or 3, outer 1/3 myometrial invasion and lymphovascular space invasion. Patients are considered to be HIR if they are ≥ 70 with one risk factor, ≥ 50 with two risk factors, or ≥ 18 with all risk factors. The absolute benefit was a 19% decrease in cumulative recurrence in this HIR subgroup. These patients have higher risk factors than the majority low-risk GOG 99 population, including grades 2 or 3 disease, outer third myometrial invasion, more advanced age, and lymphovascular space invasion. In this HIR patient population, the 4-year cumulative recurrence was 27% without irradiation compared to 13% with irradiation. In contrast, for the low-risk population there was a 6% versus 2% recurrence rate in unirradiated compared to the irradiated enrollees. The currently open GOG 0249 randomizes this HIR population between cuff brachytherapy followed by three cycles of carboplatin and paclitaxel versus pelvic irradiation with either 3D conformal therapy or IMRT to 4,500–5,040 cGy in 25–28 fractions with an optional boost with defined high-risk factors to further refine the roles of chemotherapy and radiotherapy.

The second trial was the PORTEC study where 714 patients with Stage IB grade 2,3 and IC grade 1,2 were randomized after TAH/BSO without lymph node sampling to observation ($n = 360$) or pelvic radiation ($n = 354$) to a total dose of 46 Gy in 23 fractions (127). With a median follow-up of 52 months, the 5-year vaginal/pelvic recurrence rate was 4% in the radiation arm compared to 14% in the observation arm ($p < 0.001$). The corresponding 5-year survival rates were 81% and 85%, respectively ($p = 0.37$). In patients with HIR features by the PORTEC definition (where intermediate risk factors were outer-half invasion, grade 3, or greater than 60 years of age, but excluded deeply invasive high-grade tumors, and where patients were deemed HIR with two of the three factors), the recurrence was reduced from 23% to 5% with adjuvant irradiation. It should be noted here that this is different from the GOG HIR definition, and likely a much lower-risk population. An update with a median follow-up of 13.3 years has been recently published (301). The actuarial 15-year locoregional recurrence was statistically different at 6% versus 15% for those with adjuvant irradiation compared to observation with no statistical difference in OS or failure-free survival, distant metastases, or secondary cancers. Most recurrences in the observation arm were vaginal (11% of the 15%).

An additional trial, PORTEC II, was completed as a follow-up study (128). The study population was HIR PORTEC patients. As in PORTEC I the patients underwent a TAHBSO without lymph node dissection and were randomized to 46 Gy in 23 fractions of external beam irradiation or vaginal brachytherapy

alone, with either 21 Gy in three fractions of HDR therapy or 30 Gy in one LDR fraction. Four hundred and twenty seven patients were enrolled in this noninferiority trial designed with the primary endpoint of vaginal recurrence. The research question was whether vaginal brachytherapy was as effective at controlling vaginal recurrence as external beam, with fewer toxic effects and improved quality of life. Secondary endpoints were locoregional recurrence, distant metastases, and overall- and disease-free survival, and quality of life. At a median follow-up of 45 months the estimated 5-year vaginal recurrence rates were 1.8% for brachytherapy alone and 1.6% for external irradiation. The nodal failure rate was significantly different at 3.8% for the brachytherapy-alone arm and 0.5% for external beam irradiation. Distant metastases, disease-free survival, and OS were similar in both arms. Eighty percent of the patients had deeply invasive disease, and over 90% had grades 1 or 2 disease. In fact, with pathologic review, the 48% who were enrolled as grade 1 disease increased to 78.6% of the study population. Final pathology reviewed revealed that 14% of the patients did not fit pathologic eligibility for the trial, but by report, the outcome was unchanged with these patients excluded. It should not be a surprise that vaginal external beam controlled the vaginal recurrence rate as well as vaginal brachytherapy, especially if the patients were even more low risk than intended. In addition, it is not surprising that the pelvic failure rate was low given the relatively low-risk nature of this population. Gastrointestinal toxicity and quality of life were significantly improved in the vaginal brachytherapy arm compared to the external arm (302, 303). The currently enrolling PORTEC 3 trial randomizes high-risk patients between external irradiation alone and external irradiation with concurrent and adjuvant chemotherapy. The patients eligible for PORTEC 3 include patients with Stage IB grade 3 with lymphovascular space invasion, IC grade 3, Stages IIIA-C, or Stage IB-III with papillary serous/clear cell.

The ASTEC/EN.5 trial was actually two trials with separate randomizations combined as one intergroup trial between the United Kingdom Medical Research Council (MRC) and the National Cancer Institute of Canada (NCIC) (175). This trial examined women with IA grade 3 disease and all grades of IB, and stages I or II papillary serous or clear-cell carcinoma. A lymph node dissection was not required and positive cytology was not an exclusion criteria. Positive pelvic nodes were allowed in the ASTEC trial. Patients were randomized to external beam radiation or observation, although vaginal brachytherapy was at the institution's choice, even in the observation arm. The primary outcome measure was OS, and 905 women were enrolled from 112 centers and 7 countries. With a median follow-up of 58 months there was noted to be no statistical survival difference between the two arms, and the site of the first failure was distantly in both arms, approximately 7%. The vaginal and pelvic failure rates were 3.7% versus 1.5% and 2.6% versus 1.1% for observation (with 53% receiving cuff therapy) and pelvic irradiation, respectively (175).

Despite the fact that adjuvant radiation consistently significantly improved locoregional control, most of the debate focuses on the lack of improvement in OS. Obviously, the endpoint of OS is the gold standard for any randomized trial in cancer, but when dealing with early-stage EC, the data should be interpreted with caution. First, in GOG 99, the primary endpoint was not OS but rather PFS, which was significantly better in the radiation arm (121). Second, because of the relatively high incidence of other comorbidities such as hypertension, DM, and obesity as well as other cancers, the chance of dying from an intercurrent illness is as high, if not higher, than dying from EC. In the radiotherapy (RT) arm of the PORTEC trial (127), the 8-year mortality rate from EC was 9.6% compared to 14.4% from other causes and 5.3% from other cancers. In the no-RT arm, the corresponding rates were 7.5%, 10.6%, and 5.3%. Similar data that emerged from GOG 99 were that approximately half of the

deaths were due to causes other than EC or treatment. This led the authors of GOG 99 to state the following: "With this number of intercurrent deaths in both arms, even if RT reduces the risk of EC-related deaths, the size of this trial is not adequate to reliably detect an OS difference." Thus, it is clear that the competing causes of death in this group of patients who have a low mortality rate to start with make OS a very elusive endpoint to attain. Third, even in patients who die from EC, the most common cause is distant rather than local relapse. In the PORTEC trial, the 8-year mortality rate from local versus distant relapse was 1.1% and 7.9%, respectively, in the RT group, and 2% and 5.2% in the surgery-alone group (127). In the PORTEC 2 trial, vaginal control was the endpoint, but OS was the endpoint in the ASTEC/EN.5 trial (128, 175). In the PORTEC 2 study, 62% and 48% died from intercurrent disease in the external and brachytherapy arms, respectively, and 38% versus 52% died of endometrial carcinoma in the irradiation arm and brachytherapy arm, respectively. In the ASTEC/EN.5 trial, 36% of the deaths were felt not to be disease or treatment related. Therefore, it is unrealistic to expect a local treatment modality such as radiation to alter this pattern of relapse. Note that in the GOG 99 and PORTEC I trials, most of the patients did not have poor prognostic features, thus making it difficult to demonstrate any survival advantage to adjuvant radiation. In PORTEC 2 most (80%) of the patients had deeply invasive carcinoma, but grade 3 deeply invasive tumors were excluded from the trial. In the ASTEC/EN.5 trial, 75% were deeply invasive, but 65% were grades 1 or 2. When the impact of adjuvant radiation in GOG 99 was assessed in the subset of patients with high-risk features (based on age, grade, depth of myometrial invasion, and presence of lymphovascular invasion), the death rate was somewhat lower in the radiation arm (RH, 0.73; 90% confidence interval [CI], 0.43–1.26). The PORTEC 2 study included higher risk patients than PORTEC 1, but was powered as a noninferiority study examining the utility of vaginal brachytherapy to prevent local recurrences. Lee et al., in their analysis of the SEER data, also showed an OS advantage to pelvic radiation for patients with IC grade 1 and grade 3/4 ($p < 0.001$) EC over those treated with surgery alone in their examination of over 21,000 patients. This survival advantage of adjuvant pelvic radiation was significant even in patients who had surgical lymph node staging (304). All of these issues need to be considered when assessing the benefit of adjuvant radiation. Such debate is not new in the field of oncology, but it is important to note that other oncologists treating cancers of the breast or rectum, to name a few, when faced with similar results from prospective, randomized trials, have recognized the importance of a multimodality approach in achieving local and regional control as well as survival.

Type of Radiation

There are two types of radiation (intravaginal brachytherapy or pelvic external beam radiation) that could be used either alone or in combination for early-stage EC. Over the last three decades, the debate about the type of radiation to use has undergone a full circle. In the 1970s and mid-1980s, there was a shift from intravaginal brachytherapy alone to pelvic radiation plus intravaginal brachytherapy. Then, in the late 1980s and early 1990s, there was a shift toward pelvic radiation alone. More recently, and with the increase in surgical lymph node staging, there has been resurgence in the use of intravaginal brachytherapy alone. A recent article by Patel et al. documented this by probing the SEER data base examining the treatment of FIGO Stage I and II endometrial carcinoma over the years 1995–2005 (305). They examined the treatment of 9815 patients and found that the proportion of those receiving vaginal brachytherapy alone increased from 12.9% to 32.8% as the use of external beam alone decreased from 56.1% to 45.7% over the same time

period. The use of both modalities together also decreased from 31.0% to 21.4% as well.

Intravaginal Brachytherapy Alone or Combined With Pelvic Radiation. In a historically important trial, Aalders et al. (306) reported on 540 patients with Stage IB–IC EC who underwent TAH/BSO without lymph node sampling, and postoperative intravaginal brachytherapy to 60 Gy to the vaginal mucosa. The patients then were randomized to observation ($n = 277$) or to supplemental pelvic radiation to 40 Gy ($n = 263$). A significant reduction in local recurrence rates was seen with the addition of pelvic radiation (1.9% vs. 6.9%; $p < 0.01$). With regard to OS, there was no significant difference between the two arms of the study, but in the subset of patients with grade 3 disease and deep myometrial penetration, there was a survival advantage (cause-specific survival) of 18% versus 7% in favor of the pelvic radiation arm (306). The data from this trial contributed to the shift in treatment policy from intravaginal brachytherapy alone to external beam pelvic radiation with or without a brachytherapy boost. As outlined above, in the ASTEC/EN.5 trial over 50% of the observation arm received vaginal brachytherapy as well. Given that this is the most common site of pelvic failure, and the low morbidity of this modality, this paradigm is becoming more common. Greven et al. (307) reviewed the experience of two institutions in order to compare the outcome of the two approaches. In that study, there were 270 patients with Stage I–II EC: 173 were treated with postoperative pelvic radiation alone and 97 with a combination of intravaginal and pelvic radiation (307). The corresponding 5-year pelvic control and DFS rates were 96% versus 93% ($p = 0.32$) and 88% versus 83% ($p = 0.41$). This study as well as others called into question whether the addition of vaginal radiation is needed (308–310). Some studies suggested increased toxicity with the combined approach (308). A recent examination of the SEER database examined 3395 EC patients with stages IA, IB, and II disease. Most patients (62.7%) received external beam alone, and 37.3% received both external and brachytherapy. It was noted that the addition of brachytherapy did not statistically improve survival. A number of other reports (311, 312), however, suggest that vaginal vault radiation can be added to pelvic radiation with minimal morbidity and a very low rate of recurrences. Some institutions choose to treat to 45 Gy plus a brachytherapy boost, and others choose 50.4 Gy without a boost unless higher risk features exist, such as close or positive vaginal margins, extensive lymphovascular space invasion, or cervical involvement. As chemotherapy becomes increasingly common as part of the treatment paradigm, the former regimen may spare more bone marrow and bowel. Given that in all randomized studies thus reported (GOG 99, PORTEC 1 and 2, and ASTEC/EN.5), the vaginal recurrence rate with irradiation ranges between 1% and 2%; any study to examine whether brachytherapy should be added to external beam radiotherapy would require far too many patients than the question warrants.

Intravaginal Brachytherapy Alone. With the increase in surgical lymph node staging, the use of postoperative intravaginal brachytherapy alone regained its appeal, the rationale being that full surgical lymph node staging could potentially eliminate the need for pelvic radiation, whereas vaginal brachytherapy could still address the risk of vaginal cuff recurrence, as demonstrated in PORTEC 2. Several additional reports in the past 10 years also demonstrated a very low rate of recurrence either in the vagina or in the pelvis with such an approach (118, 176, 313, 314).

From the above discussion, it is clear that the options available for patients with early-stage endometrioid EC are numerous. Perhaps it is better to consider different options based on the following factors identified as risk factors for recurrence – age, grade, depth of invasion, lymphovascular space invasion, histology – and consider as well if a nodal dissection was accomplished.

Cancer Limited to the Mucosa (Formerly Stage IA, Grades 1 and 2)

The risk of pelvic lymph node positivity (54) is $\leq 3\%$, and the 5-year PFS rate in this group is of the order of 95% to 98%. It is unlikely that postoperative pelvic external beam radiation would add anything to the final outcome (311, 315). The role of intravaginal radiation in these patients is also of questionable benefit because of an almost negligible risk of vaginal recurrence with surgery alone. Straughn et al. reported no vaginal recurrence in 103 patients with Stage IA grade 1,2 treated with surgery alone (288). This is no longer a discreet stage in the 2010 FIGO staging system.

Cancer Limited to the Mucosa, Grade 3

In GOG 33, there were only eight patients with Stage IA grade 3 disease, making it difficult to draw any meaningful conclusion (55). There were no relapses in the three patients receiving postoperative radiation as compared with one failure in the five patients who received no postoperative therapy. The risk of lymph node metastasis in this group of patients is negligible. Straughn et al. reported on eight patients with Stage IA grade 3 disease treated with surgery alone, with two of the patients developing isolated vaginal recurrence (288). Again this subgroup is not formally staged in the new FIGO staging system, and observation is often favored unless other high-risk features exist such as advanced age, papillary serous or clear-cell variants, or extensive disease.

Low Risk—Stage I A, B Grades 1,2. The outcome of patients who have lymph node dissection and no adjuvant radiation seems to be very good based on prospective (GOG99) and retrospective series. Straughn et al. reported on 296 patients with IB grade 1,2 and found only nine (3%) vaginal recurrences and one (0.3%) pelvic recurrence (288). Horowitz et al. reported on 62 patients who had surgical lymph node staging and received adjuvant intravaginal brachytherapy. There was one (1.6%) vaginal recurrence and no pelvic recurrence (313). In comparison, data published by Alektiar et al. reported on 233 patients with IB grade 1,2 showed a vaginal recurrence rate of only 1% and pelvic recurrence of 2% using postoperative intravaginal brachytherapy alone without routine surgical lymph node staging (316). In addition, Sorbe et al. reported on 110 patients without retroperitoneal lymph node sampling with IB grade 1,2 who were part of a prospective, randomized trial evaluating two different intravaginal brachytherapy doses; the rate of vaginal recurrence was 0.9% and the rate of pelvic recurrence was 1.8% (317). These patients also often fit the GOG 99, PORTEC 1, and PORTEC 2 trials, with or without lymphadenectomy. Thus, it seems reasonable to suggest that either observation or intravaginal brachytherapy (irrespective of surgical staging) is a reasonable option. But when deciding on whether adjuvant radiation is needed, it is important to address three issues. First, older patients tend to have higher rates of relapse. In the study by Straughn et al., eight of the ten vaginal/pelvic recurrences were in patients ≥ 60 years old (288), which was confirmed in the randomized trials. Second, patients with lymphovascular invasion (LVI) have a higher chance of vaginal recurrence as demonstrated by Mariani et al. (291) who reported on 508 patients with Stage I EC treated with surgery alone (152 out of 508 were Stage IA). The presence of LVI increased the vaginal relapse rate from 3% to 7% ($p = 0.02$) as was confirmed by the GOG 99 trial among others. Recent publications of high intermediate and high-risk Stage I–III endometrial carcinoma patients suggest LVSI to be an independent prognostic factor for relapse and survival (285, 318). Third, often the indications for adjuvant radiation are rather arbitrarily based on the amount of myometrial invasion defined in thirds and on whether the tumor is grade 1 versus 2. Yet the amount of myometrial invasion in this group of patients and whether an endometrial cancer

is assigned as grade 1 as opposed to 2 in general do not appear to be significant predictors of outcome (319, 320). It is reasonable to offer patients with IA grades 1 and 2 without LVI and less than 60 years old observation or intravaginal radiation while those with LVI or ≥ 60 years old are offered intravaginal radiation. Those patients that fit the HIR group from GOG 99 are offered the open GOG 0249 trial (≥ 70 with one risk factor, ≥ 50 with 2, or any age with 3 high-risk factors. Factors considered high risk are more than 50% invasion, grade 2 or 3, and lymphovascular space invasion). It is worth noting here that the most likely area of recurrence is the vaginal vault, and brachytherapy is a low morbidity treatment. When that is taken into consideration, if one is undecided whether to offer brachytherapy, remember that it is a far less intensive treatment than treatment of recurrent disease.

Intermediate to High-Intermediate Risk Stage IB Grade 3 to IC Grades 1, 2, 3, Stage II

Up until the last 10 years, most data in the literature on this group of patients were based on pelvic radiation either alone or in combination with intravaginal brachytherapy (309, 311). Since 1988 and the increase in surgical lymph node staging in the United States, a shift occurred with regard to the role of radiation for Stage IB grade 3 and even in Stage IC disease. For some time the treatment decision between whole pelvis radiotherapy and cuff brachytherapy alone was primarily based on whether the patient had surgical lymph node staging. If the decision is made that a node dissection is necessary, and that has recently been called into question for all early-stage patients, an adequate lymph node sampling/dissection should, at a minimum, meet the GOG guidelines of sampling the obturator, external iliacs, internal iliacs, common iliacs, and paraaortic lymph node stations, and the minimum number of nodes sampled should be ≥ 10 .

Surgically Staged Patients. For patients with Stage IB grade 3 disease the retrospective data on intravaginal brachytherapy alone after surgical staging were encouraging (Table 22.14). The average rate of vaginal recurrence and pelvic recurrence was reported as 1.3% for both. This compares favorably with the data from the PORTEC I trial where the 5-year rates for vaginal and pelvic recurrence, in the subset of patients with Stage IB grade 3 disease treated with pelvic radiation ($n = 35$), were 0% and 3%, respectively. A multi-institutional review of 220 patients with Stage IC EC by Straughn et al. compared adjuvant radiation to no radiation in patients with negative nodes on surgical staging (289). The investigators concluded that adjuvant radiation is not needed even though the 5-year DFS was 74.5% for those treated with surgery alone compared to 92.5% for those treated with adjuvant radiation ($p = 0.0134$). It is unlikely that observation alone, even in those patients with full surgical staging, will be the best approach when cuff brachytherapy carries low

Table 22.15 Outcome for IC Endometrial Cancer Grade 1–3 after Surgical Lymph Node Staging and Intravaginal Radiation Therapy Alone

Study	No. of Patients	Median F/U	Vaginal rec	Pelvic rec
Horowitz (2002)	50	65 mo	2% (1/50)	4% (2/50)
Rittenberg (2003)	53	32 mo	0%	1.8% (1/53)
Solheim (2005)	40	23 mo	0%	0%
Alektiar (2007)	40	46 mo	5% (2/40)	2.5% (1/40)
Total	183	—	1.6% (3/183)	2.1% (4/183)

F/U, follow-up; rec, recurrence.

morbidity and can greatly decrease the 18% statistically significant difference in DFS from a retrospective study in which most likely those patients with the worst prognostic features were the ones who received radiation.

Several investigators have shown the feasibility of such an approach, with an average vaginal recurrence rate of 1.6% and pelvic control rate of 2.1% (Table 22.15). Thus, intravaginal brachytherapy alone after surgical staging in patients with IB grade 3 and IC EC seems to provide better local/regional control than surgery alone and, in a properly selected patient population, very few pelvic failures (121, 313, 321, 322). In patients that fit the GOG HIR criteria the appropriate treatment may be determined by the open trial GOG 0249 which randomizes this population between cuff brachytherapy followed by chemotherapy (carboplatin/paclitaxel for 3 cycles) or pelvic radiotherapy (IMRT or 3Dconformal) plus an optional cuff brachytherapy boost for high-risk features. Note that lymph node dissection is optional in this trial. In addition, while lymph node dissection is not allowed, further information may be gained by the PORTEC 3/EN.7 trial, which is randomizing (1988 staging) Stage IB grade 3 with LVSI, Stage IC or IIA grade 3, Stage IIB, Stage IIIA or IIIC, or stages IB–III serous or clear-cell endometrial carcinomas between pelvic radiotherapy alone to 48.6 Gy and the same pelvic radiotherapy with two cycles of concurrent cisplatin plus 4 adjuvant cycles of carboplatin/paclitaxel. In the PORTEC trial, the cuff boost is given with cervical invasion. In the absence of hard data, the risks of pelvic failure must be gauged and determination made if they are sufficient to undergo the risk of pelvic therapy versus vaginal cuff therapy alone. Useful in this regard is the PORTEC trial for Stage IC grade 3 tumors. These 99 patients were not randomized, but were followed prospectively, and all received pelvic irradiation. Again, no lymph node evaluation was done. The locoregional recurrence rate in this high-risk group of patients, without a node dissection, was 12%, with only 5% vaginal, despite adjuvant irradiation. Note that papillary serous and clear-cell were not identified separately in this trial so the percentage of these high-risk pathologies is not known, and given the very high distant failure rate, 31%, this is noted to be a very high-risk group (138).

With the publication of the two randomized trials, ASTEC and CONSORT, questioning the benefit for lymphadenectomy, many gynecologic oncologists in the United States have chosen to evaluate the nodes only in those patients most at risk for metastatic disease—deeply invasive, high-grade, high-risk histology, older patients, and those with lymphovascular space invasion or a combination of factors. Examining the trials where routine lymphadenectomy is performed demonstrates the risk for all Stage I patients to be approximately 10% (55, 131, 132), but

Table 22.14 Outcome for Stage IB Grade 3 Endometrial Cancer after Surgical Lymph Node Staging and Intravaginal Radiation Therapy Alone

Study	No. of Patients	Median F/U	Vaginal rec	Pelvic rec
Fanning (2001)	21	52 mo	0%	0%
Horowitz (2002)	31	65 mo	0%	0%
Alektiar (2007)	21	46 mo	4.8% (1/21)	4.8% (1/21)
Total	73	—	1.3% (1/73)	1.3% (1/73)

F/U, follow-up; rec, recurrence.

selecting the patients at highest risk for disease, while it may not change survival, can certainly guide further treatment paradigms.

No Surgical Lymph Node Staging. In those patients with combinations of high-risk features such as grade 3, high-risk histologies, LVSI, advanced age, and deep myometrial invasion, intravaginal brachytherapy may not be adequate therapy. In the Aalders et al. randomized trial, the rate of local recurrence in the subset of patients with IB grade 3 to IC was 9.3% (13 of 137) for those treated with brachytherapy alone compared to 1.3% (2 of 146) for those treated with brachytherapy and external radiation (306). This is not surprising since no lymph node sampling was done in that trial. Weiss et al. reported on 61 patients with Stage IC EC who were treated with postoperative pelvic radiation alone. With a median follow-up of 69.5 months, there was only one recurrence in the pelvis (1.6%). Their review of the published data from the literature on patients with Stage IC showed a pelvic recurrence of 1.04% in 240 patients treated with pelvic radiation alone compared to 0.97% in 301 patients treated with pelvic and intravaginal radiation. Their conclusion was that pelvic radiation alone is sufficient, and efforts should focus instead on trying to reduce the risk of distant relapse in this group of patients (323). In addition, the results of the GOG 0249 and PORTEC 3 trial may help us segregate these patients into low risk, who may be appropriate for observation or cuff brachytherapy alone, or high risk, who may need more aggressive therapy, including a combination of irradiation and chemotherapy.

Stage II. It is important to recognize the distinction between gross and occult cervical involvement in EC. Gross cervical involvement increases the risk of parametrial extension as well as spread to pelvic LN in a fashion similar to primary cervical cancer. Patients with gross cervical involvement from EC could undergo radical hysterectomy and pelvic lymph node dissection or preoperative radiation including pelvic radiation and intracavitary brachytherapy followed by simple hysterectomy. For occult cervical involvement, the treatment often consists of simple hysterectomy with or without lymph node surgical staging and adjuvant radiation. The type of radiation most often utilized is pelvic radiation and intravaginal brachytherapy. Pitson et al. reported on 120 patients treated with such a combination (324). The 5-year DFS rate was 68%, and the rate of pelvic relapse was 5.8% (7 of 120).

There are also emerging data on the role of intravaginal brachytherapy alone in patients with occult cervical involvement who also had surgical lymph node staging. The rate of pelvic recurrence in four such series ranged from 0% to 6%, but the data need confirmation on a larger number of patients and longer follow-up (313, 325, 326). Another important distinction to make in Stage II EC is the difference between glandular versus stromal invasion. The new staging system now combines these two entities into Stage II and does not make the distinction (79). Intravaginal brachytherapy alone could be used for surgically staged patients with mucosal involvement alone (313, 327), whereas those with disease invading into the stroma, with close margins or with a significant amount of cervical disease, should be treated with pelvic radiation with or without intravaginal brachytherapy boost until trial results demonstrate a better option.

Advanced-Stage Disease

Radiation

The outcome of patients with isolated adnexal involvement (Stage IIIA) treated with pelvic radiation is fairly good, although the studied patient numbers are small. Connell et al. reported on 12 patients treated with postoperative pelvic radiation with a 5-year DFS of 70.9%. The weighted average of 5-year disease-free and OS rates from literature review in that study were

78.6% and 67.1%, respectively (328). Patients with isolated serosal involvement (Stage IIIA) do worse than those with isolated adnexal involvement. Ashman et al. reported on 15 patients with isolated serosal involvement who were treated with pelvic radiation (329). The 5-year DFS was only 41.5%. If pelvic node involvement (IIIC1) is the only major risk factor, treatment with postoperative pelvic radiotherapy can yield a 60% to 72% long-term survival rate in these patients (141, 330, 331), but distant failure is a problem that new trials evaluating chemotherapy will hopefully change. Patients with Stage IIIC2 disease, by virtue of paraaortic node involvement, represent a particularly high-risk group. Following surgery, these patients are generally treated with extended field radiation to encompass the pelvis and the paraaortic regions. With this aggressive approach, several investigators have reported 30% to 40% survival rates in small patient populations (332). The question of whether it is safe to omit radiation even after adequate surgical lymph node staging in patients with IIIC2 EC was addressed in a study from the Mayo Clinic. Mariani et al. reported on 122 patients with node-positive disease; at 5 years the risk of pelvic recurrence was 57% after inadequate lymph node dissection and/or no RT compared to 10% with adequate lymph node dissection (>10 pelvic nodes and ≥ 5 paraaortic nodes) and radiation. This difference was statistically significant on univariate ($p < 0.001$) and multivariate analysis ($p = 0.03$), indicating the need for postoperative radiation even after adequate surgical staging (174). The recognition that a significant number of patients with Stage III disease fail in the abdomen (291, 330) has prompted a number of investigators to evaluate whole abdominal radiotherapy in these patients (333, 334) and after a small GOG trial a randomized trial was undertaken (335).

Chemoradiation

In the GOG 122 trial, there were 396 patients with Stage III and optimally debulked Stage IV disease who were randomized to whole abdomen radiation ($n = 202$) or to doxorubicin-cisplatin chemotherapy ($n = 194$). With a median follow-up of 74 months, there was significant improvement in both progression-free (50% vs. 38%; $p = 0.007$) as well as OS (55% vs. 42%; $p = 0.004$), respectively, in favor of chemotherapy (262). To elucidate the right approach for these patients, however, a closer look at these data is warranted. First, the overall absolute rate of relapse was 54% in the radiation arm compared to 50% in the chemotherapy arm, a small difference if any, yet the corresponding 5-year PFS rates were 38% and 50% ($p = 0.007$), respectively. Why the discrepancy? The answer is that the 5-year PFS rate for the radiation arm was 38% while the chemotherapy arm has two separate 5-year rates. The first one, called unadjusted, was 42%, which is not that significantly different from the 38% rate with radiation, and the second, called “adjusted for stage,” was 50%, which was significantly different from the radiation arm. This led us to the second issue: Was the adjustment for stage warranted? The answer is no. Numerically, there were more patients with lymph node involvement in the chemotherapy than the radiation arm, but having positive LN was not an independent predictor of poor outcome in this study. Therefore, the adjustment was not warranted, and if any adjustment was needed, it should have gone to the radiation arm since there were more patients with positive cytology in this arm, a factor with a HR of 1.8 (95% CI, 0.89–1.55) in predicting poor outcome. Third, what should be made of the significant difference in OS? There were 15 deaths unrelated to EC or protocol treatment in the radiation arm compared to only 6 in the chemotherapy arm, raising a question about whether the two arms of the study were truly balanced. Finally, the pelvic recurrence rate was lower in the radiotherapy arm, which indicates that perhaps both modalities could be used for the advantages they provide – locoregional control for irradiation and distant control for chemotherapy. Another randomized trial comparing adjuvant radiation to chemotherapy

(doxorubicin-cisplatin-cyclophosphamide) in patients with Stage I–III was recently reported and showed no difference in outcome between the two arms (387). With a median follow-up of 95.5 months, the 5-year DFS was 63% in both arms ($p = 0.44$) and the 5-year OS rates were 69% in the radiation arm compared to 66% in the chemotherapy arm ($p = 0.77$). What those two trials show is that chemotherapy at a minimum is equivalent to radiation in this group of patients and ought to be used, not alone, but rather in combination with radiation. Greven et al. reported the results of Radiation Therapy Oncology Group (RTOG) 9708 on 44 patients with Stage I–III EC who were treated with pelvic radiation and intravaginal brachytherapy given concurrently with cisplatin 50 mg/m² on days 1 and 28 of radiation followed by four cycles of cisplatin (50 mg/m²) and paclitaxel (Taxol) (175 mg/m²). The 4-year disease-free and OS for those with Stage III disease (66% of patients) was 72% and 77%, respectively (336).

As the follow-up study to GOG 122, GOG 184 was launched. The combination of irradiation and chemotherapy was used to control disease and was done in a sequential fashion to limit toxicity. Five hundred and fifty two Stage III and IV patients were enrolled (after 66 patients were enrolled, those with upper abdominal disease were excluded) and received tumor volume directed irradiation (51% received 5040 cGy pelvis irradiation alone, and 49% received 4320–4350 cGy of extended field for positive paraaortic disease, or undissected paraaortics) and were then randomized to cisplatin/adriamycin or cisplatin/adriamycin/paclitaxel (337). Growth factors were allowed and 80% of the patients were able to complete the assigned chemotherapy regimen following full dose radiotherapy. The locoregional recurrence rate (any failure in the pelvis, vagina or paraaortics as first failure) was 10%, which compares favorably with GOG 122 (isolated failures: 13% in WAI arm and 18% in chemotherapy arm), Greven's (187) study of 105 irradiated patients with IIIC disease with a pelvic failure rate of 21%, and Mundt's two series; one that described 30 patients with Stage IIIC treated with postoperative pelvic irradiation with an infield failure rate of 23%, and a second trial of 43 high-risk Stage I–IV endometrial carcinoma patients treated with chemotherapy alone who experienced a 21% actuarial rate of pelvic recurrence as their first or only site of recurrence (338, 339). The distant failure rate in these trials was unacceptably high, ranging from 26% to 55%. The PORTEC 3 trial described above and the open GOG 0258 address treatment in this advanced population. In the GOG 0258 trial, stages III or IVA are randomized between volume directed postoperative irradiation with concurrent cisplatin followed by 4 cycles of carboplatin/taxol or 6 cycles of carboplatin/taxol alone.

SPECIAL SITUATIONS

Positive Cytology Without Adnexal or Serosal Involvement

In this subset of patients, the presence of other adverse features such as aggressive histologies or deep myometrial invasion should be determined first as this is noted but no longer part of the official staging system. The argument to remove it from the staging is that without other factors, cytology alone has unclear prognostic value (340). The literature regarding the benefits of treatment in this setting is mixed; even if treatment is beneficial, the appropriate modality still has to be defined. Based on the concept that the entire peritoneal cavity is at risk, intraperitoneal radioactive colloidal ³²P had been used by some with results that were better than in historic controls (341), but carries significant toxicity. Eltabbakh et al. reported on 27 patients with FIGO grade 1,2

and <50% myometrial invasion who were treated with intra-vaginal brachytherapy and megestrol acetate (Megace). None of the patients relapsed or died from their disease. Megace was given for 1 year, and at the end of therapy, 24 patients underwent second-look laparoscopy and peritoneal cytology. In 23 patients, the cytology was negative, and the remaining patient with persistent positive cytology received an additional year of Megace after which cytology was confirmed to be negative (342). Given this, as an isolated risk factor, vaginal brachytherapy with Megace is likely the only radiation regimen to be recommended.

Definitive Radiation for Inoperable Disease

Patients with medically inoperable Stage I–II uterine cancer are usually treated in a fashion similar to those with cervical cancer by using intracavitary applicators with or without pelvic radiation. For patients with clinical Stage I grade 1 or 2 and no or minimal evidence of myometrial invasion or lymph node metastasis on MRI, intracavitary brachytherapy alone may be sufficient provided the uterus is of such a size and shape that it can be fully covered with the brachytherapy irradiation. There are several applicator choices with one or two tandems (depending on uterus size) and either a cylinder or ovoids. The American Brachytherapy Society Guidelines have recommended either dosing in the uterus 2 cm from the tandem, and treating the upper several cm of vagina, or, in the age of image guidance, dosing to the uterine serosa (343). When pelvic radiation is added to brachytherapy, the dose is usually 45 to 50 Gy supplemented with intracavitary brachytherapy. Rouanet et al. (344) treated 250 patients with endometrial cancer using LDR brachytherapy, which yielded a 5-year disease-specific survival of 76.5%. An alternative brachytherapy approach would be to use the Hymen or Simon afterloading system, which consists of multiple Teflon tubes that are inserted into the uterine cavity. With such a treatment approach, Grigsby et al. (345) reported that the 5-year PFS rate of patients with clinical Stage I disease treated with a combination of external and intracavitary radiotherapy was 94% for grade 1 disease, 92% for grade 2 disease, and 78% for grade 3 disease. High-dose-rate brachytherapy is increasingly used and demonstrates equivalent control (346). Nguyen (346) and Niazi (347) reported on patients with clinical Stage I–II disease treated with HDR alone or with external irradiation, and the disease-specific survival was 76% at 8 years, and 91% at 15 years, respectively. Note that many of these patients, by virtue of being medically inoperable, will die of other causes than their early-stage uterine carcinoma. Intriguingly, Fishman published a study comparing the operable with the inoperable and found that those inoperable patients who did not die of intercurrent disease had a similar median 5-year survival (348). Kucera et al. studied a larger population of 228 and using HDR alone found a disease-specific survival of 85% at 5 years and 75% at 10 years (349). For several of these studies, image guidance was not available, and the expectation is that dosing the radiation in the appropriate area will increase control and disease-specific survival. Although uncommonly seen, Stage IIIB patients are definitively treated with irradiation including external beam and intracavitary/interstitial brachytherapy, as they are not surgical candidates (350).

RADIATION THERAPY TECHNIQUES

Intravaginal Brachytherapy

Intracavitary vaginal brachytherapy is designed to deliver dose to the vaginal surface and underlying lymphatic channels at risk

of harboring residual disease. Choo et al. demonstrated that 95% of vaginal lymphatic channels lie within 5 mm of the vaginal mucosa and therefore this modality is well-suited to deliver this dose effectively and more safely than with external beam irradiation (351). Intravaginal brachytherapy can be delivered using LDR to 60 Gy prescribed to the vaginal mucosa or 30 to 35 Gy prescribed to 0.5 cm depth from the vaginal mucosa using either ovoids for the upper several cm of the vagina or a cylinder, which allows the length treated to be tailored to the clinical situation. Very rarely, the whole length of the vagina needs to be treated, and should be considered for those with close or positive margins, extensive lymphovascular invasion, or very high-risk histologies. HDR brachytherapy guidelines have been established and published for dose and fractionation, although the most common is 700 cGy for 3 fractions treated at 5 mm depth according to a survey published by Small et al. (352).

External Beam Radiation

Pelvic Radiation

Most patients are treated in the postoperative setting. At the time of simulation, the small bowel may be opacified using oral contrast, a vaginal marker is used to define the vaginal cuff, and the rectum may be opacified with barium or CT-compatible contrasts. Patients may be placed in the prone position to displace the small intestines from the radiation field or placed on a prone treatment board that allows the abdominal wall and contents to be displaced anteriorly through a hole in the board, to allow displacement out of the pelvis (353). The target volumes are the obturator, external, internal, and lower common iliac nodes, and the proximal two-thirds of the vagina. High-energy linear accelerators (15 MV) are preferred because of their sparing of the skin and subcutaneous tissue when the treatment is a four-field box or when three-dimensional conformal therapy (3DCF) is used. The ideal beam arrangement with the conventional four-field pelvic-box technique places the superior border at L5-S1, the inferior border at the bottom of the obturator foramina or at least 3 to 4 cm below the vaginal apex, and the lateral border 1–2 cm beyond the widest point of bony pelvis. For the lateral fields, the anterior border is in front of the pubis symphysis to allow external iliac coverage and the posterior border covers S1/S2. The superior and inferior borders are the same for the anterior and posterior fields. All fields are treated daily to a dose of 1.8 Gy. A total dose of 50.4 Gy is given to sterilize microscopic disease, or 45 Gy when combined with intravaginal brachytherapy. Three-dimension conformal field (3DCF) therapy uses the same beam arrangement, but a planning CT scan is used to outline both tissues at risk and normal tissues. Blocks are placed based on the contours that allow more accurate targeting and sparing of more normal tissues. Recent evidence demonstrates decreased acute and late toxicity to the bowel when intensity modulated radiation therapy (IMRT) is used (Figure 22.13). Mundt et al. demonstrated a significant reduction in acute and chronic gastrointestinal toxicity when IMRT was compared to conventional radiation (354–357). IMRT, compared to the four-field box or 3DCF therapy, uses the power of computers to shape the radiation dose to tissues at risk of harboring microscopic disease and minimize normal tissue dose. Both 3DCF therapy and IMRT use small collimator “leaves” to finely shape the beam. These “leaves” are mobile and block portions of the generated x-rays. If the collimator “leaves” move while the radiation beam is on and vary the beam intensity, areas of tumor and normal tissue can receive a spectrum of doses, hence the term “intensity modulated.” Papers have been published on the use of IMRT in postoperative uterine and cervical carcinoma, vulvar carcinoma, whole abdominal radiotherapy, vaginal carcinoma, and intact cervical carcinoma. However, because of the daily variation in

bladder and rectal filling, and the resultant mobility of the upper vagina, the use of IMRT should be undertaken with caution, and experience with contouring, planning, and delivery is essential (358, 359). The introduction of new technology such as tomotherapy (a linear accelerator linked to an on-line CT scanner), cyberknife (a linear accelerator capable of fiducial imaging to target radiation), and cone-beam CT (CT scan mounted to the linear accelerator) for image-guided radiotherapy (IGRT) assists in daily target and normal tissue localization. Randomized, prospective data comparing this to traditional therapy are lacking but ongoing trials are evaluating risks, effectiveness, and cost.

Extended Field

This technique is mainly used for patients with documented positive paraaortic nodes or patients at risk of disease but without surgical evaluation. Either 3DCF irradiation or IMRT can be utilized (360). Attention should always be paid to the kidney dose when paraaortic fields are utilized, especially with increased use of chemotherapy in these patients. The lower border is the same as in pelvic radiation, but the upper border is extended in some patients as high as the T12–L1 interspace. The typical dose is 45.0 Gy at 1.8 Gy per fraction or 1.5 Gy per fraction if patients develop acute gastrointestinal toxicity.

Whole Abdomen Radiation (WART)

WART is uncommonly used since the publication of GOG 122. The standard approach is AP/PA open fields with five half-value layer (HVL) kidney blocks placed over the PA field only (if the patient is lying supine) from the start of the treatment. The dose is usually 30.0 Gy at 1.5 Gy per fraction followed by a 19.8 Gy boost to the pelvis at 1.8 Gy per fraction. The upper border is usually placed 1 cm above the diaphragm, and the lateral borders should extend beyond the peritoneal reflections. The lower border is usually at the bottom of the obturator foramen.

Complications of Radiation

Pelvic Radiation

In GOG 99, the risk of Grade 3 or 4 complications was 14% with RT versus 6% without. In the PORTEC I randomized trial (121), the overall (grades 1 to 4) rate of late complications was 26% in the RT group compared to 4% in the observation group ($p < 0.0001$). Most of the late complications in the RT group, however, were grades 1,2 (22%), and only 3% were grades 3,4. It is also important to note that many patients in this trial were treated with AP/PA fields in which the overall rate of complications was 30% compared to 21% for those treated with the four-field box ($p = 0.06$), and even lower for IMRT. The recent 15-year update notes that second malignancies were diagnosed in 16% of the observation patients and 22% of the irradiation patients, a difference that was insignificant. In PORTEC II, grades 1 and 2 gastrointestinal side effects were significantly higher with external beam (delivered using CT planning and with multifield or 3DCF techniques) than with vaginal brachytherapy (53.8% vs. 12.6%), but grades 3 and 4 were not reported, which is curious, suggesting it was very low and likely not significantly different between the arms. Late grade 3 gastrointestinal effects were reported in 2% of those receiving EBRT versus less than 1% in those with VBT. Alternatively, grade 3 atrophy (marked atrophy with or without narrowing or shortening) was reported in less than 1% of those with EBRT and 2% with VBT. There were no grade 4 or 5 toxicities in either arm. In more advanced disease trials, we see a similar pattern. In GOG 122, those with at least one grade 3 and 4 hematologic toxicity between the arms of WART or chemotherapy were 14% versus 88%, respectively.

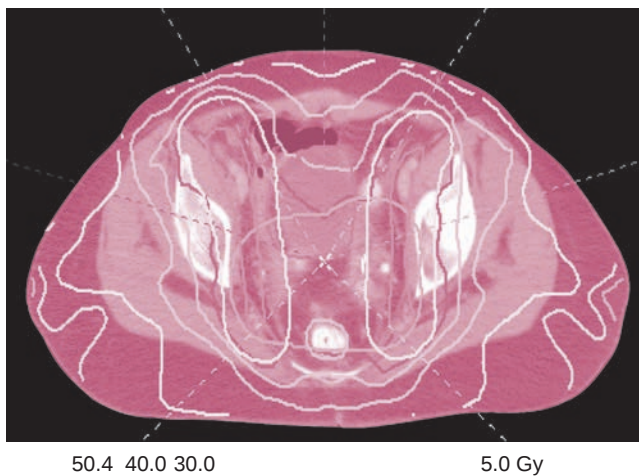


FIGURE 22.13. Pelvic IMRT demonstrating the sparing of bladder and bowel.

Grade 3 or 4 acute gastrointestinal toxicity was 13% versus 20% in the WART and chemotherapy arms, respectively. Late grades 3 or 4 gastrointestinal or genitourinary toxicity between the arms were 13% and less than 1% for WART, and 20% and 3% for chemotherapy, respectively. Many investigators were surprised that the chemotherapy arm had increased acute and late gastrointestinal effects when compared to WART. Statistical analyses of these results were not reported (262). In GOG 184, where everyone received whole pelvis radiation and 49% received pelvis and paraaortic irradiation, the rate of late grade 3 or higher treatment-related gastrointestinal events was only 5% (337). Acutely pelvic irradiation can cause fatigue, cystitis, diarrhea, skin erythema and breakdown, and vaginitis. Adding a paraaortic field can add nausea and gastritis to the list. VCB is very well tolerated, and complaints during treatment are rare other than discomfort with placement of the device. Late toxicities include intra-abdominal scarring, chronic cystitis or enteritis, bowel obstruction requiring surgery, rectal telangiectasias, and, more unusually, bone weakening with fracture, fistula formation, kidney or spinal cord damage, second malignancies, menopause if the ovaries are in the field, and with WART liver toxicity. With vaginal brachytherapy, vaginal atrophy, narrowing, dryness, and agglutination are possible.

Radiation Therapy for Local Recurrence

Radiation therapy can be curative in a select group of patients with small vaginal recurrences who have not received prior radiation. The 5-year local control rate ranges from 42% to 65%, and the 5-year OS rate from 31% to 53% (361). Creutzberg

et al. reported on survival after relapse from the PORTEC randomized trial (362). In patients who were initially randomized to surgery alone ($n = 46$ out of 360), the 5-year survival after vaginal relapse was 65%. But before adopting salvage radiation as a treatment policy for all early-stage EC, a few aspects of this trial need to be addressed. First, the 5-year survival rate from the PORTEC trial is much higher than what is reported in the literature. Most likely, the vaginal recurrences in this trial were detected very early, unlike patients in the community. The extent and size of local recurrence in EC are very significant predictors of outcome (361). Second, this high rate of salvage pertains only to isolated vaginal recurrence. The rate of survival at 3 years for pelvic recurrence in the PORTEC trial was 0%. Third, although the trial does not mention any data on complications, it is not unrealistic to expect a higher complication rate than what is normally seen with adjuvant radiation. With salvage radiation, external beam RT and brachytherapy are often combined, and the doses of radiation required are much higher than those used with adjuvant radiation. A study from the University of Texas MD Anderson Cancer Center by Jhingran et al. clearly highlights these issues (363). They reported on 91 patients who were treated with definitive radiation for isolated vaginal recurrence. The 5-year local control and OS rates were 75% and 43%, respectively. The median dose of radiation was 75 Gy, which often included external radiation and brachytherapy. The rate of grade 4 complications (requiring surgery) was 9%. Thus, when talking with a patient about adjuvant radiation versus radiation reserved for salvage, these issues need to be addressed and compared to the excellent local control and low morbidity obtained with adjuvant irradiation. The currently open GOG 0238 trial randomizes patient with recurrence of endometrial carcinoma limited to the pelvis and vagina to concurrent cisplatin/irradiation versus standard irradiation alone.

SYSTEMIC THERAPIES

Endocrine Therapy

Hormonal agents have been found to be valuable, particularly in the patient with recurrent disease, and reviews of their use have been extensively published. Response rates to a variety of endocrine agents, including progestins, antiestrogens, and aromatase inhibitors are presented in Table 22.16 (364–369). The overall response to progestins is approximately 25%. However, some trials demonstrate lower response rates, usually in the range of 15% to 20%. These studies generally used more rigorous response criteria and had multi-institutional participation. A higher dose of progestin does not appear to increase the response rate. In one randomized trial of 200 mg/d versus 1,000 mg/d of

Table 22.16 Response to Endocrine Therapy

Hormonal Agent	References	Average Dose	Response Rate (%)	Range (%)
Hydroxyprogesterone caproate (Delalutin)	(464,465)	1–3 g IM q wk	29	9–34
Medroxyprogesterone acetate (Provera)	(462)	200–1,000 mg IM q wk or po qd	22	14–53
Megestrol acetate (Megace)	(465)	40–800 mg po qd	20	11–56
Tamoxifen (Nolvadex)	(470,471)	20–40 mg po qd	10	0–53
Goserelin acetate	(486)	3.6 mg SC q mo	11	NA
Anastrozole (SERM)	(469)	1 mg po qd	9	NA
Arzoxifene (SERM)	(466)	20 mg po qd	31	NA

IM, intramuscularly; NA, not applicable; SC, subcutaneously; SERM, selective estrogen receptor modulator.

medroxyprogesterone acetate (MPA), the overall response rate was actually 25% versus 15% favoring the low-dose arm (370). The time to treatment failure and median OS of the low-dose versus high-dose regimens, respectively, were 3.2 versus 2.5 months and 11.1 versus 7.0 months, all showing no advantage for an increased dose. Prognostic factors related to response were performance status, grade, and progesterone receptor (PR) level. The response rate was only 8% in poorly differentiated tumors. A phase 2 trial of high-dose megestrol (800 mg orally daily) in 63 patients was associated with a response rate of 24% overall, which is similar to lower-dose regimens with doses of 40 mg po qid. As in the majority of studies with hormonal agents, response rates were statistically higher in patients with grade 1 or 2 lesions (37%) versus grade 3 lesions (8%); $p = 0.02$. In addition to grade, a long DFS (exceeding 2 or 3 years) and positive estrogen or PR status have all been associated with an increased frequency of response (Table 22.17) (364, 367, 370). Age, location of metastatic disease, number of metastatic sites, prior therapy, and weight have also been analyzed by several investigators, but they have not been convincingly linked with response.

Tamoxifen has been investigated in patients with recurrent disease in several studies (369, 370). Results have varied, but in general, response rates have been modest in untreated patients. A GOG study evaluated 68 patients with advanced or recurrent disease receiving tamoxifen at 20 mg po bid and showed an overall response rate of 10% (90% CI, 5.7–17.9). The median PFS was short at 1.9 months (90% CI, 1.7–3.2 months) and the OS was 8.8 months (90% CI, 7.0–10.1 months). One small randomized phase 2 study comparing megestrol acetate to megestrol acetate with tamoxifen showed no advantage in response rate for the combination, with response rates of 20% versus 19%, respectively (371). The lack of synergistic response is supported by observations of endometrial carcinoma treated in a nude mouse model. Tumors treated with medroxyprogesterone or tamoxifen plus medroxyprogesterone were devoid of PR during the growth inhibitory and regrowth phase of the tumor resulting

from receptor down-regulation (372). The possibility of alternating tamoxifen with megestrol acetate in order to exploit the recruitment of PRs by tamoxifen is an interesting strategy. The GOG performed a phase 2 study with 56 patients with advanced or recurrent EC who had not previously received chemotherapy or hormonal manipulation (373). Patients were treated with megestrol acetate at 160 mg/d for 3 weeks alternating with tamoxifen 40 mg po qid for 3 weeks. An overall response rate of 27% (90% CI, 17.3–38.4) with a 21.4% complete response rate was seen, with the duration of response exceeding 20 months in 8 of 15 responders. The response rate was 38% for patients with grade 1 disease and 22% for those with grade 3 disease. In another phase 2 GOG study, a similar patient population was treated with tamoxifen 40 mg po daily plus alternating weekly cycles of medroxyprogesterone acetate 200 mg po daily (374). Of the 58 evaluable patients, the response rate was 33% (6 complete, 13 partial). Although these phase 2 results are intriguing, a randomized study would be required to determine if alternating hormones is superior to single-hormone approaches. Positive receptor status has been associated with improved disease-free and OS rates (375, 376). These data indicate that the receptor status provides important biologic information and that receptor-positive tumors tend to be better differentiated and slower growing than their receptor-negative counterparts. Chemotherapy had no effect on hormone receptor capacity in a nude mouse model of xenografted EC. Other factors, such as changes in vaginal cytology during treatment (377), and results in the subrenal capsule chemosensitivity assay (378) and in the nude mouse model (379) may help predict response to progestins.

Several studies have evaluated gonadotropin-releasing hormone analogs in patients with metastatic EC. Gallagher et al. (380) noted one complete and five partial responses to leuprolide or goserelin in 17 patients (35% response; 95% CI, 13%–58%) with metastatic disease. Of note, the duration of remission ranged from 7 to 30 months, and 14 of the 17 patients had been previously treated with progestins. Another report described four responses in seven postmenopausal patients with EC treated with goserelin (381). *In vitro* studies in human EC cell lines have suggested that such growth inhibition may have been due to apoptosis (382). The GOG studied goserelin at 3.6 mg subcutaneously monthly in 40 patients with advanced or recurrent disease. Seventy-one percent of patients had received prior radiotherapy. There were two complete (5%) and three partial (7%) responses with an overall response rate of 11% (95% CI, 4%–27%). Goserelin is felt to have limited activity in this patient population, and no additional single-agent studies are planned (365).

Investigation is under way in patients with uterine cancer to evaluate the activity of SERMs. These agents have ER-antagonist activity in breast and uterine tissues, and ER-agonist activity in bone. The first reported study to date is from the GOG and evaluated anastrozole at 1 mg po daily orally in 23 unselected patients (i.e., 9 patients had grade 2 tumors and 14 patients had grade 3 tumors). A partial response rate of 9% was seen (90% CI, 3%–23%). It is noted that the partial response rate of 9% in this study is similar to the 8% reported in grade 3 patients treated with standard progestins (375). Another study evaluated the investigational SERM arzoxifene in 37 patients. Twenty-six patients were ER positive and 22 were PR positive. A response rate of 31% (95% CI, 25%–51%) was seen in this selected patient population with a median duration of response of 13.9 months (366). Additional study of these agents in patients with well-differentiated tumors is warranted.

Study	Treatment	Grade	N	RR
Podratz (1985)	Various progestins	1	10	40%
		2	71	15%
		3	73	2%
Lentz (1996) (371a)	MA 800 mg/d	1	14	37% (grade 1–2)
		2	17	
		3	27	8%
Thigpen (1999)	MPA 200 mg/d vs. 1,000 mg/d	1	59	37%
		2	113	23%
		3	127	9%
Whitney (2004)	Tam 40 mg/d + alternating weekly MPA 200 mg/d	1	15	Overall RR 33%
		2	17	
		3	27	
Fiorica (2004)	MA 160 mg/d × 3 wk, alternating with Tam 40 mg/d × 3 wk	1	16	38%
		2	17	24%
		3	22	22%

Note: MA, megestrol acetate; MPA, medroxyprogesterone acetate; RR, response rate; Tam, tamoxifen.

Endometrial Cancer and Cytotoxic Chemotherapy

Recent data illustrating the utility of chemotherapy have expanded the role of chemotherapy to include not only metastatic disease but also surgically staged advanced disease. The role of chemotherapy

in the management of high-risk early-stage disease remains investigational and is currently the focus of several clinical trials.

Early-Stage High-Risk Uterine Cancer

Despite the ability for surgical staging to define a low-risk patient population for most patients with negative pelvic and paraaortic LN, certain subgroups of patients with Stage I–II EC have been shown to have a higher risk of recurrence. These patients may benefit from postoperative adjuvant therapy with radiation, chemotherapy, or the combination of the two. In two prospective trials comparing pelvic radiation to chemotherapy, comparable outcomes were seen between the arms (299–300).

Hogberg et al. (383) reported the results of two randomized studies (NSGO-EC-9501/EORTC-55991 and MaNGO-ILIADE-III) examining the role of sequential adjuvant chemotherapy and radiotherapy. The two randomized clinical trials included patients with Stage I–III EC with no residual tumor and prognostic factors consistent with high-risk disease. These patients were randomly assigned to either adjuvant radiotherapy with or without sequential chemotherapy. The authors reported that in the NSGO/EORTC study, the combined modality treatment was associated with a 36% reduction in the risk for relapse or death (HR, 0.064; 95% CI, 0.41–0.99; $p = 0.04$). A similar HR was reported in the MaNGO study (HR, 0.61) but no significant significance was appreciated. In the combined analysis of these two trials, the estimate of risk for relapse or death was similar, with an HR of 0.69 (CI, 0.46–1.03; $p = 0.07$). Careful examination of the two independent studies reveals that the majority of patients in the NSGO-EC-9501/EORTC-55991 trial had Stage I disease

while patients in the MaNGO ILIADE-III had predominantly Stage IIB–IIIC disease. Overall, these results should be interpreted with caution given the heterogeneity of the population studied.

The role of radiation therapy alone or in combination with chemotherapy is currently investigated in the GOG–249, phase III clinical trial that compares the outcomes of pelvic irradiation versus VCB followed by paclitaxel/carboplatin in patients with high-risk early-stage endometrial carcinoma. RTOG 0921 is a phase II trial of postoperative intensity modulated radiation therapy with concurrent cisplatin and bevacizumab followed by four cycles of platinum and taxane.

Adjuvant and Advanced Disease

Chemotherapy for adjuvant and advanced disease has been evaluated in multiple clinical trials. Trials have compared chemotherapy to radiation therapy as well as to other chemotherapeutic regimens. For historical purposes, Table 22.18 highlights a comprehensive list of clinical trials.

The initial combinations to be explored included the use of cyclophosphamide with doxorubicin (384–386) followed by the addition of cyclophosphamide and doxorubicin to cisplatin (CAP) (387–390) and doxorubicin to cisplatin (AP) (391–395). Given the lack of additional benefit with a three-drug combination, the AP regimen became the “standard” to which more contemporary approaches were compared. It is important to note that the majority of these trials enrolled a heterogeneous patient population. Despite the lack of prospective data tailored to individual disease stage, these trials have provided constructive insights to the management of patients with advanced disease.

Table 22.18 Combination Chemotherapy

Reference	Drug	Dose (mg/m ²)	Schedule	Chemotherapy	<i>n</i>	CR + PR (%)
<i>Cyclophosphamide-Doxorubicin-Cisplatin (CAP)</i>						
(390)	CYC DOX CIS	500 50 50	q 4 wk	No	18	55 (56)
(387)	CYC DOX CIS	400 40 40	q 3 wk	No	16	05 (31)
(388)	CYC DOX CIS	500 50 50	q 4 wk	No	87	1227 (45)
(389)	CYC DOX CIS	500 50 50	q 3 wk	5	17	35 (47)
<i>Doxorubicin-Cisplatin</i>						
(393)	DOX CIS	50 50	q 3 wk	No	9	12 (33)
(395)	DOX CIS	50 50	q 4 wk	No	20	210 (60)
(393)	DOX CIS	60 60	q 4 wk	4/16	16	67 (81)
(391)	DOX CIS	60 ^a 60	q 4 wk	No	30	612 (60)
<i>Cyclophosphamide-Doxorubicin</i>						
(385)	CYC DOX	500 37.5	q 3 wk	No	11	32 (45)
(386)	CYC DOX	400–500 40–50	q 4 wk	No	26	08 (31)

Table 22.18 (Continued) Combination Chemotherapy

Reference	Drug	Dose (mg/m ²)	Schedule	Chemotherapy	n	CR + PR (%)
(517)	CYC DOX	500 50	q 3 wk	No	105	1519 (32)
(384)	CYC DOX	600 50	q 3 wk	No	13	15 (46)
<i>Other</i>						
(423)	DOX CIS VLB VCR VM-26	30 50 5 1.5 100	q 34 wk	No	42	310 (31)
	CIS CYC DOX VCR FU	60 500 40 1.5 500 (d2,3)	q 3 wk	No	44	914 (52)
			q 3 wk	No	2	5 (50)
(424)	MTX VLB DOX CIS	30 (d1,15,22) 3 (d2,15,22) 30 (d2) 70 (d2)	q 4 wk	No	25	15 (60)
<i>Randomized Trials—Chemotherapy</i>						
(517)	DOX vs. CYC DOX	—	q 3 k	No No	90 105	(24) (32)
(394)	DOX vs. DOX CIS	60 60 50	q 3 wk	No No	122 101	(27) (45)
(399)	DOX CIS vs. DOX PAC	60 50 50 150	q 3 wk	No	157 157	40 (15 + n/a 35) 43 (17 + 26)
(400)	DOX CIS vs. DOX CIS PAC	60 50 45 50 160			133 133	33 (7 + n/a 26) 57 (22 + 35)

CIS, cisplatin; CR, complete response; CYC, cyclophosphamide; DOX, doxorubicin; FU, fluorouracil; MTX, methotrexate; PAC, paclitaxel; PR, partial response; VCR, vincristine; VLB, vinblastine; VM-26, teniposide.

^aCircadian timed regimen doxorubicin at 0600 (6 AM) and cisplatin at 1800 (6 PM) hours.

Chemotherapy versus Radiation Therapy

GOG 122 compared whole abdominal radiation therapy to doxorubicin/cisplatin chemotherapy in patients with *Stage III–IV disease who underwent surgical assessment and had a maximum of 2 cm of disease postoperatively* (262). The results demonstrated an improved PFS and OS in patients with chemotherapy, with the reduction in recurrences largely due to reduced abdominal and distant sites of disease. The Japanese GOG 2033 trial (300) randomized 385 women with *stages IC–III endometrioid adenocarcinomas* to WPR therapy versus chemotherapy using the regimen cisplatin, doxorubicin and paclitaxel. PFS at 5 years was 83.5% versus 81.8 %. However, in a subgroup analysis of patients with Stage IC over the age of 70 with grade 3 endometrioid tumors or Stage II or IIIA, chemotherapy was associated with improvement over pelvic radiation therapy both in terms of PFS (83.8% vs. 66.2%, respectively, $p = 0.024$) and OS (89.7% vs. 73.6 %, respectively, $p = 0.006$).

GOG 184 (337) randomized 552 women with *Stage III disease debulked to a maximum residual of 2 cm or less* followed

by volume-directed radiation therapy to doxorubicin and cisplatin (AP) or doxorubicin/cisplatin and paclitaxel (TAP). At 3 years the proportion of patients alive and free from recurrence was similar (62% AP versus 64% TAP). The overall hazard for recurrence or death of TAP compared to AP was 0.90 (95% CI, 0.69–1.17). In women with gross residual disease at the time of enrollment, TAP was associated with a 50 % reduction in the risk of relapse or death (HR, 0.50; 95% CI, 0.26–0.92).

Chemotherapy

Given the phase II activity of single-agent taxanes (396–398), the GOG conducted a randomized trial (GOG 163) (399) *for patients with primary Stage III and IV or recurrent EC with measurable disease* comparing doxorubicin and cisplatin to doxorubicin with 24-hour paclitaxel and granulocyte colony-stimulating factor (G-CSF). There were no significant differences in response rate (40% vs. 43%), PFS (median 7.2 vs. 6.0 months), or OS (median 12.6 vs. 13.6 months) for arms 1 and 2, respectively.

The disadvantage of GOG-163 was the lack of platinum in the taxane-containing arm. The addition of a taxane was subsequently studied in GOG-177 (400) (*patients with primary Stage III and IV or recurrent EC with measurable disease*). GOG 177 utilized doxorubicin (60 mg/m² or 45 mg/m² in patients with prior radiotherapy) with cisplatin (50 mg/m²) as the standard arm versus paclitaxel (160 mg/m²) with doxorubicin (45 mg/m²) and cisplatin (50 mg/m²) and G-CSF as the investigational regimen. The primary objective was to determine if the addition of paclitaxel improved response rate, and progression-free and OS. Two hundred and seventy-three patients were enrolled, and the study was balanced for history of prior RT (50% vs. 46%), serous carcinoma (15% vs. 19%), stage, grade, and body surface area (BSA). Grade 3 and 4 platelet toxicity was higher in the three-drug arm (21% vs. 2%), but other hematologic toxicity was ameliorated with G-CSF: absolute neutrophil count (ANC) was 36% versus 50%, and neutropenic fever was 3% versus 2%. Nonhematologic grade 3, 4 toxicity was higher in the three-drug arm: gastrointestinal 59% versus 39% and metabolic 25% versus 13%. Response rates were better with the triplet: complete response 22% versus 7%, partial response 36% versus 27%, and overall response rate (RR) 57% versus 34%. Median PFS was 8.3 versus 5.3 months ($p < 0.0005$) and median OS was 15.3 versus 12.1 months ($p = 0.024$). Responses were similar in serous (48%) versus nonserous histology (45%). Overall, paclitaxel doxorubicin cisplatin (TAP) chemotherapy increased 12-month survival to 59% compared to 50% with AP with an HR of 0.75 (0.56 to 0.998). Although the TAP regimen produced an improvement in response rate and PFS, survival was minimally increased, and it is associated with greater toxicity. The combination of paclitaxel and carboplatin as a doublet has also been evaluated in a variety of phase 2 trials and retrospective studies with response rates in the 43% to 80% range (401, 402).

GOG 209, a randomized trial comparing doxorubicin, cisplatin, and paclitaxel (TAP) with carboplatin and paclitaxel (TC), (*Stage III, IV or recurrent disease*) was recently reported. TC was not inferior to TAP in terms of PFS (median PFS of TAP vs. TP: 13.5 vs. 13.3 months; HR, 1.03) and OS (40.3 vs. 36.5 months; HR: 1.05) based on interim analysis results. Overall, the toxicity profile favored TC with less sensory neuropathy (sensory neuropathy > Grade 1: 26% vs. 19%, $p < .01$) (403).

Sequence of Therapeutic Modalities

With the current data in mind, the sequence of therapy in patients with advanced surgically resected disease remains in question. Various approaches have been delineated. A RTOG phase II study (RTOG 9708) (336) was conducted to assess the feasibility, safety, toxicity, and patterns of recurrence and survival when chemotherapy was combined with adjuvant radiation for patients with high-risk EC. Pathologic requirements included grade 2 or 3 endometrial adenocarcinoma with either greater than 50% myometrial invasion, cervical stromal invasion, or pelvic-confined extra uterine disease. Radiation included 45 Gy in 25 fractions to the pelvis along with cisplatin (50 mg/m²) on days 1 and 28. Vaginal brachytherapy was performed after the external beam radiation. Four courses of cisplatin (50 mg/m²) and paclitaxel (175 mg/m²) were given at 4-week intervals following completion of radiotherapy. Forty-six patients were accrued to the study. Median follow-up was a median of 4.3 years. At 4 years, pelvic, regional, and distant recurrence rates were 2%, 2%, and 19%, respectively. OS and DFS rates at 4 years were 85% and 81%, respectively. Four-year rates for survival and DFS for Stage III patients were 77% and 72%, respectively. There were no recurrences for patients with Stage IC, IIA, or IIB. Local-regional control was reported to be excellent following combined modality treatment in all patients suggesting additive effects of chemotherapy and radiation. Distant metastases continued to occur in more advanced-stage patients.

Secord et al. (404) reported a multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced EC. A multicenter retrospective analysis of patients with surgical stages III and IV EC from 1993 to 2007 was conducted. Inclusion criteria included a comprehensive staging procedure including hysterectomy, bilateral salpingo-oophorectomy, +/- selective pelvic/aortic lymphadenectomy, and treatment with adjuvant chemotherapy and radiation. One hundred and nine patients with advanced-stage EC were identified who received postoperative adjuvant therapies; 41% ($n = 45$) received chemotherapy followed by radiation and then further chemotherapy (CRC), 17% ($n = 18$) radiation followed by chemotherapy (RC), and 42% ($n = 46$) chemotherapy followed by radiation (CR). There was no difference in the frequency of adverse effects due to either chemotherapy ($p = 0.35$) or radiotherapy ($p = 0.14$), dose modifications ($p = 0.055$), or delays ($p = 0.80$) between the various sequencing modalities. There was a significant difference between adjuvant treatment groups for both OS (log rank $p = 0.011$) and PFS (log rank $p = 0.025$), with those receiving CRC having a superior 3-year OS (88%) and PFS (69%) compared to RC (54% and 47%) or CR (57% and 52%). After adjusting for stage, age, grade, race, histology, and cytoreduction status, the OS HR for therapy was 5.74 (95% CI, 1.96–16.77) for RC and 2.60 (95% CI, 1.01–6.71) for CR, compared to CRC, $p = 0.003$. When the analysis was restricted to optimally cytoreduced patients, those who were treated with RC were at higher risk for disease progression (HR, 3.53; 95% CI, 1.29–9.71; $p = 0.024$) and death (HR, 7.24; 95% CI, 2.25–23.37; $p = 0.001$) than patients who received sequential CRC. The authors reported that sequential CRC was associated with improved survival in women with advanced-stage disease compared to other sequencing modalities with a similar adverse effect profile.

Metastatic/Recurrent Disease

The role of chemotherapy in the recurrent/metastatic setting remains palliative, and minimizing side effects is of equal importance when selecting a regimen. Previously discussed were the trials enrolling patients with metastatic disease, namely GOG 163, 177, and GOG 209 (389, 390, 393). As the role of chemotherapy in the postoperative setting has expanded, the choices in the recurrent/metastatic setting have shifted and, in some cases, narrowed. A variety of single cytotoxic agents that have been tested are presented in Table 22.19. Options and choices are dependent on prior treatment and, in some cases, disease-free interval. The most commonly used single agents today based on response rates of at least 20% include cisplatin, carboplatin, doxorubicin, epirubicin, ifosfamide, docetaxel, paclitaxel, and topotecan.

The response rate to **cisplatin** dosages of 50 to 60 mg/m² given every 3 weeks was similar in patients with prior (25%) (387, 405) and no prior chemotherapy (21%) (406–408). **Carboplatin** given in dosages of 300 to 400 mg/m² every 4 weeks has been associated with response rates of 29% (409–410), which is similar to cisplatin. **Doxorubicin** in dosages of 55 to 60 mg/m² has been associated with an overall response rate of 26% (411, 412), and **epirubicin** with a response rate of 26% (413). **Liposomal doxorubicin** was reported in a GOG study of 46 patients receiving 50 mg/m² every 4 weeks with an overall response rate of 9.5% (95% CI, 2.7%–26%) (414). It is important to note that 32 patients had received prior doxorubicin therapy. A second study evaluated its efficacy in 19 patients without prior chemotherapy treatment and resulted in a 21% response rate (415). Of the antimetabolites, **5-fluorouracil** was given in dosages of 15 mg/kg for 5 consecutive days and then every other day until dose-limiting toxicity occurred. It has displayed a 21% response rate in 34 patients, whereas **methotrexate** (416) and **mercaptopurine** (417) have been inactive. **Vincristine** given on

a weekly schedule was associated with a response rate of 18% in 33 untreated patients (418), but dose-limiting neurotoxicity was substantial. In a phase 2 trial of **paclitaxel** conducted by the GOG (396), 28 patients with recurrent or advanced EC received a dose of 250 mg/m² every 21 days. Patients who had received prior pelvic irradiation were treated at an initial dose of 200 mg/m². Complete responses were noted in four patients (14%) and partial responses in six (21%), for an overall response rate of 36%. A more contemporary GOG study evaluated paclitaxel at 200 mg/m² (175 mg/m² with prior radiotherapy) every 3 weeks in pretreated patients showing an overall response rate of 27.3% (95% CI, 15.0%–42.8%). The median duration of response was 4.2 months with an OS of 10.3 months (398). A similar study showed a response rate of 43% (95% CI, 6%–80%) in patients who had all previously been treated with platinum-based therapy (419). A multicenter trial recently reported showed a response

rate of 21% with PFS of 12 weeks and OS of 43 weeks in 35 patients receiving weekly **docetaxel** at 35 mg/m² (397). **Topotecan** was evaluated in a phase 2 trial of untreated advanced or recurrent EC administered initially at 1.5 mg/m² every day for 5 days every 3 weeks. The trial was suspended for toxicity, but reopened and completed at 1 mg/m² q day for 5 days (or 0.8 mg/m²/d for patients with prior radiotherapy). An overall response rate of 20% was seen with median duration of response of 8.0 months and OS of 6.5 months (420). A subsequent smaller study by Traina et al. using weekly topotecan dosing of 2.5 to 4.0 mg/m² on a 2 of 3 weeks schedule followed by 1 week off showed one partial response for 54 weeks with two patients having stable disease for 15 weeks each. Only two patients required dose reduction for toxicity using the weekly schedule (421).

Epothilones are a novel class of nontaxane microtubule-stabilizing agents that are currently approved for the management

Table 22.19 Single-Agent Trials

Agent (Reference)	n	Prior Treatment	No. of CR + PR	(%)	95% CI
<i>Alkylating Agents</i>					
Cyclophosphamide (425)	37	Some	4	11	3–25
Chlorambucil (425)	11	NS	0	0	0–28
Ifosfamide (426, 427)	56	Some	4 + 4	14	6–26
Hexamethylmelamine (428)	54	Few	2 + 7	17	8–29
<i>Cisplatin</i>					
No prior Rx (408)	63	No	3 + 10	21	11–33
Prior chemo (405, 406)	64	Yes	3 + 13	25	15–37
Carboplatin (409, 410)	82	No	5 + 18	28	19–39
<i>Anthracyclines/Anthraquinones</i>					
Doxorubicin (393, 394)	161	No	18 + 24	26	19–34
Epirubicin (413)	27	No	2 + 5	26	11–46
Liposomal doxorubicin (414, 415)	42	Yes	0 + 4	9.5	2.7–22.6
Pirarubicin (429)	28	7	2 + 0	7	1–30
Mitoxantrone (430–432)	46	32	0 + 2	4	1–15
<i>Antimetabolites</i>					
Fluorouracil (425)	34	NS	7	21	9–38
Methotrexate (416)	33	No	1 + 1	6	2–20
6-Mercaptopurine (417)	10	NS	0	0	0–31
<i>Vincas/Epipodophyllotoxins</i>					
Vincristine (418)	38	5	1 + 5	16	6–31
Vinblastine (433)	48	Most	1 + 3	8	2–20
Etoposide (VP-16) (434)	29	Yes	0 + 1	3	1–29
Teniposide (VM-26) (435)	22	17	0 + 2	9	1–26
<i>Topoisomerase I Inhibitor</i>					
Topotecan (420, 421)	42	No	3 + 5	20	Nr
<i>Taxanes</i>					
Paclitaxel (396–398)	44	Yes	3 + 9	27.3	15–42.8
Docetaxel (397)	35	No	3 + 4	21	Nr
Ixabepilone (422)	50	Yes	1 + 5	12	Nr

95% CI, the 95% confidence interval for complete and partial response; CR, complete response; NS, not stated; Nr, not reported; PR, partial response.

of advanced breast cancer. Ixabepilone was recently reported to have an objective response rate of 12% with a PFS of 2.9 months and a stable disease and a stable disease rate for at least 8 weeks of 60% (422).

Regardless of the available choices, responses to each successive line of therapy are short lived. As such, focus has centered on the molecular basis of EC and potential targeted agents.

GENTETIC CHANGES IN ENDOMETRIAL CANCER AND TARGETED THERAPY

The molecular background of EC provides a platform that lends itself to targeted therapeutics in patients with advanced or recurrent disease. Biological agents targeting such molecular components are currently under development in numerous clinical trials. Focus has centered on specific histologic subtype- and/or biomarker-driven patient stratification. Evidence suggests that not only are type I and II endometrial tumors distinct entities with diversified genotypic and phenotypic profile (Table 22.20),

but also patients within each subtype may differ molecularly. Hence, efforts have focused on the application of personalized therapies by utilizing biomarkers able to discriminate patients' dominant profile (11, 436).

The **PI3K/AKT/mTOR pathway** represents a major signaling pathway downstream of several growth factor receptor kinases (e.g., epidermal growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor, and insulin growth factor receptor) and is well known to have a pivotal role in cell survival and growth (437). The PI3K/AKT/PTEN pathway is the most commonly altered pathway in type I EC (438). Activation of PI3K leads to the phosphorylation of a secondary messenger to form PIP3 (phosphatidylinositol 3,4,5-triphosphate). This process is regulated by PTEN, which dephosphorylates PIP3 to PIP2. Activation of PI3K, resulting in PIP3, subsequently leads to AKT activation. AKT promotes cell growth, proliferation, reduces apoptosis, and increases angiogenesis. Two important regulators of the process include the mammalian target of rapamycin complexes mTORC 1 and 2.

The most common mechanisms of PI3K activation are loss of the phosphatase and tensin homolog (PTEN) tumor suppressor protein function, and activating mutations in catalytic PI3K

Table 22.20 Molecular Aberrations of Endometrial Cancer (EC) by Type

Molecular Aberration	Type I (Endometrioid) EC (%)	Type II (Nonendometrioid) EC (%)	Aberrant Pathway
PTEN loss	80–83	5	PI3K/AKT/mTOR pathway
PIK3CA			
Mutation	24–40	20	PI3K/AKT/mTOR pathway
Amplification	2–14	46	
PIK3R1 mutation	43	12	PI3K/AKT/mTOR pathway
AKT mutation	3	0	PI3K/AKT/mTOR pathway
KRAS mutation	10–30	0–10	Ras-Raf-Mek-Erk pathway
MSI	15–45	0–5	–
β -catenin (CTNNB1) mutation	14–50	0	Wnt/ β -catenin/LEF-1 pathway
E-cadherin loss	5–50	60–90	Wnt/ β -catenin/LEF-1 pathway
TP53 mutation	10–20	90	Tumor suppression
p16 loss	8	45	Cyclin D/CDK4-CDK6/RB
HER2			
Overexpression	3–10	32–43	Cell-surface receptor
Amplification	1	17–29	
FGFR-2 mutation	12–16	1	Cell-surface receptor
EGFR			
Overexpression	46	34	
Mutation	Unknown	0	
IGFIR overexpression	78	Unknown	Cell-surface receptor
Chromosomal Instability STK15, BUB1, CCNB2 LOH at multiple loci			–
EphA2 overexpression	48	Unknown	Transmembrane protein
EpCAM overexpression	Unknown	96	Transmembrane protein
HIF1a overexpression	25%	80%	Gene transcription nuclear protein
ARID1A mutation	29–40	18–26	Transcription-regulating process

subunit, p110 α , which is encoded by the PIK3CA gene. Cells that are deficient in PTEN may have a resulting activation of the PI3K pathway. The function of the tumor-suppressor gene *PTEN* includes inhibition of cell migration, spreading, and adhesion (439, 440). The *PTEN* gene is located on chromosome 10q23, and about 40% of endometrial carcinomas display loss of heterozygosity of chromosome 10q23, which suggests the involvement of *PTEN* in this disease (439, 441). *PTEN* mutations in 30% to 50% of endometrial carcinoma tumors make this the most frequent genetic alteration known in this disease (442, 443). Genes for the catalytic subunit of PI3K (PI3KCA) are frequently amplified (2–14% type I ECs, 46% type II) or mutated (30% type I–II) in EC, leading to constitutive activation (11).

mTOR is a conserved serine/threonine kinase that lies downstream of the phosphatidylinositol 3 kinase/PTEN/AKT pathway and is composed of two subunits, mTORC1 and mTORC2. Activated AKT phosphorylates mTOR directly or indirectly by phosphorylating TSC2 (Tuberous sclerosis complex 2), which in turn stimulates mTORC1. Subsequently, mTORC1 phosphorylates several transcription factors, namely S6K-1 (ribosomal S6 kinase-1) and 4E-BP1 eukaryote translation initiation factor 4E binding protein-1), thereby leading to the synthesis of proteins involved in proliferation and survival. The second subunit mTORC2 is much less defined, but may mediate activation of AKT in response to mTORC1 inhibitors (444).

The frequency of dysfunction and importance of the PI3K pathway in EC made this a predominate disease site targeted by inhibitors of this pathway (445). PI3K/AKT/mTOR pathway inhibitors undergoing active clinical investigation in EC are highlighted in Table 22.21 (446, 661–675). Of all the available inhibitors, the rapalogs temsirolimus (CCI-779®; Wyeth), ridaforolimus (deforolimus; AP23573®, MK-8669; Merck), and everolimus (RAD001®; Novartis), which specifically inhibit mTORC 1, are the compounds more extensively tested in EC clinical trials thus far (447).

Preliminary results of a phase II trial (448) of **temsirolimus** in recurrent or metastatic EC (chemotherapy naïve, with up to 1 prior line of hormonal therapy) demonstrated encouraging results with 5 confirmed partial responses (26%) out of 19 evaluable patients. Three of the partial responses were in patients with papillary serous tumors. Evaluation of a second cohort, women who must have had treatment with one prior regimen of cytotoxic chemotherapy, revealed an RR of 7% (2/27). Overall, temsirolimus activity was seen in all histologic subgroups and grades regardless of PTEN loss. The most frequent drug-related toxicities were fatigue, mucocutaneous irritation (acne-like maculopapular rashes, mucositis, stomatitis, and diarrhea), and pneumonitis. Grade 3 toxic effects were rare and included lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, and hyperlipidemia. Temsirolimus has also been studied in combination with paclitaxel/carboplatin and has demonstrated good tolerability in a phase I trial (449), prompting the initiation of a phase II study. A recently reported GOG study combining temsirolimus with alternating hormones, megestrol acetate and tamoxifen, was closed secondary to high levels of venous thrombosis and insufficient additional activity to warrant further study (450). Temsirolimus is currently being explored in combination with other cytotoxic and biological agents, such as carboplatin/paclitaxel, pegylated liposomal doxorubicin, bevacizumab, AMG386, and AZD2171.

Two phase II clinical trials (451, 452) have demonstrated clinical response to intravenous **ridaforolimus** (12.5 mg/day for five days every other week) in chemotherapy-treated patients (451). A PR rate of 7.7% and an SD rate of 58% to oral ridaforolimus in chemotherapy-naïve patients (452) was also noted. In one study (453), patients with unresectable Stage III or IVA or metastatic disease were randomized to oral ridaforolimus (40 mg for 5 days/week) versus medroxyprogesterone (200 mg/d) or megestrol (60 mg/d). Interim analysis of the first 114 patients

Table 22.21 PI3K/AKT/mTOR Signaling Pathway Inhibitors

1. PI3K inhibitors—target p110 exclusively either as pan-p110 inhibitors and isoform-specific inhibitors (mostly ATP competitors)

Wortmannin (SL-2052; Tocris Bioscience)
LY294002 (SelleckBio)
XL147 (SAR245408; Exelixis)
NVP-BKM120 (Novartis)
GDC-0941 (Piramed/Genentech, Slough)
PX-866 (Oncothyreon)
PWT33597 (Pathway Therapeutics)
CAL-101 (Calistoga Pharmaceuticals)
ZSTK474 (SelleckBio)

2. Dual PI3K and mTOR inhibitors—target all catalytic isoforms of PI3K together with mTORC1 and mTORC2

NVP-BEZ235 (Novartis)
NVP-BGT226 (Novartis)
GDC-0980 (Genentech)
XL765 (SAR245409; Exelixis)
GSK 1059615 (GlaxoSmithKline)
SF1126 (Semafore Pharmaceuticals)
PF-04691502 (Pfizer)
PKI-587 or PF-05212384 (Pfizer)

3. AKT inhibitors—target serine/threonine kinase AKT (lipidbased phosphatidyl inositol analogues, ATP mimetics or allosteric inhibitors)

MK-2206 (Merck & Co)
GSK690693 (GlaxoSmithKline)
MKC-1 (EntreMed)
Perifosine (Keryx Biopharmaceuticals)
GSK2141795 (GlaxoSmithKline)
GSK2110183 (Octagon Research Solutions)
GDC-0068 (Genentech)
LY2780301 (Eli Lilly)
Inositol-1,3,4,5,6 pentakisphosphate (IP5)—(2-O-Bn-InsP5)
VQD-002 (API-2)

4. mTOR inhibitors—the rapalogs (synthetic rapamycin derivatives) target the FKBP12 binding protein, and directly the mTORC1 +/- mTORC2 complex

Rapamycin
Temsirolimus (CCI-779; Wyeth)
Everolimus (RAD001; Novartis)
Ridaforolimus (AP23573, formerly known as deforolimus—ARIAD; Merck & Co)
ATP-competitive mTORC1 and mTORC2 inhibitors
AZD8055 (Astra Zeneca)
OSI-027 (OSI Pharmaceuticals)

Ref. 518–522.

demonstrated a median PFS of 36 months for ridaforolimus and 1.9 months for progestin therapy (HR 0.53, $p = 0.008$) with grade 3/4 toxicities of hyperglycemia (19%) and anemia (9%). A trial investigating the combination of ridaforolimus with carboplatin/paclitaxel is underway. In a recent phase II trial (454), 35 heavily pre-treated patients with recurrent endometrioid EC received oral **everolimus** at a dose of 10mg daily. Results were encouraging, with 43% and 21% of patients achieving SD at 8 and 16 weeks, respectively. Most common drug-related toxicities included abdominal pain (28%), nausea and vomiting (21%), fatigue, anemia, and lymphopenia. An attempt to correlate response to the molecular status of the primary tumor failed to reveal any significant predictive marker, although a trend for K-RAS mutation correlation with therapy resistance was noticed (455). A study of everolimus and letrozole in pre-treated recurrent EC achieved a response rate of 21%, including one CR and three PRs. Furthermore, four patients had SD and seven still remain on treatment (456).

Microsatellite instability (MSI) is found in 20%–45% of type I tumors (0–5% type II tumors), and is caused by inactivation of DNA repair genes such as MLH1, MSH2, MSH6, and PMS2 (457, 458). Tumors with MSI have instability (insertions and deletions) in the simple repeated sequences found in coding and noncoding elements of many genes. Resulting frameshift mutations may inactivate some genes including PTEN. MSI was first described in HNPCC. One of the most common extracolonic tumors associated with this disease is EC, and MSI has been demonstrated in both hereditary and sporadic tumors (459). MSI in EC has been reported to be between 9% and 43% (460–462). In 71% to 92% of sporadic endometrial carcinoma, MSI has been found to be associated with hypermethylation of the *bMLH1* promoter region, whereas it seems to be less common in the promoter region of *bMSH2* (463). It is likely that methylation of the promoter region is an important mechanism of *bMLH1* gene inactivation in endometrial carcinoma (449) and a precursor to MSI. Too few studies have been done to reach any conclusion regarding the importance of MSI as a prognostic factor in EC, although defects in MMR systems may alter responsiveness to chemotherapy or radiation (465). Deletions or mutations of the *PTEN* gene, and MSI due to hypermethylation of the promoter for the mismatch repair gene *bMLH1*, are both relatively common and early events in the development of a significant proportion of type I endometrioid adenocarcinomas. In contrast, these molecular alterations do not appear to be critical in the pathogenesis of serous or clear-cell carcinoma. However, mutations in the p53 gene are found with high frequency not only in invasive serous carcinoma but also in EIC (247, 466), the noninvasive precursor of serous carcinoma, suggesting that a different pathway is followed in the development of the second type of endometrial adenocarcinoma.

TP53 is a tumor-suppressor gene, the product of which is a protein involved in the regulation of the cell cycle at the G1 checkpoint, permitting replication of cells that have acquired various mutations. Mutations of the p53 gene often result in a protein with a longer half-life, which accumulates in the cell. Up-regulation of wild-type (i.e., nonmutated) p53 may occur after DNA damage and also results in overexpression that is detectable by immunohistochemistry. This appears to be an early event in the development of serous carcinoma, but it is a late event in endometrioid carcinomas for which it serves as an indicator of poor prognosis. In addition to the very frequent overexpression of p53 protein in serous carcinoma (467), it has also been related to a higher FIGO stage, clear-cell histology, higher histologic grade, and increased depth of myometrial invasion (467, 468). Lundgren et al. (469) studied p53 in relation to clinicopathologic variables in 376 consecutive patients with EC stages I–IV. p53 overexpression was found to be a strong significant factor with regard to relapse-free survival in univariate analysis, but it failed to retain its significance when submitted to multivariate analysis.

In contrast, p53 mutations are not often found in type I, low-grade endometrioid tumors (470). This suggests that different subgroups of ECs have different genetic pathways. Much more work is needed to understand the genetic mechanics at play and to translate this into use within the clinical and therapeutic field.

EGFR/Her/ErbB family is composed of four structurally similar tyrosine kinase – functioning receptors: EGFR (epidermal growth factor receptor, HER1), ErbB2 (HER2/neu), ErbB3 (HER3) and ErbB4 (HER4). Their activation triggers a cascade of events ultimately leading to cell proliferation and survival (471). This molecular family has garnered a great deal of interest given that it activates important downstream pathways including VEGF, PI3K/AKT and Ras/Raf/MEK (472). EGFR family-directed therapies include both small molecule tyrosine kinase inhibitors (e.g. erlotinib, gefitinib and lapatinib) and anti-EGFR monoclonal antibodies (e.g. cetuximab and trastuzumab). Yet, despite EGFR overexpression in both EC subtypes (473), and favorable preclinical studies using EGF receptor antagonists (474), clinical trials in unselected EC population have shown little promise.

HER2/neu is a proto-oncogene, the product of which is a transmembrane growth factor receptor, p185erb-2, which shares some homology with the epidermal growth factor receptor. It is normally expressed at low levels in the cycling endometrium. HER2/neu is frequently over expressed or amplified in 10–30% of type I and 40–80% of type II ECs (475), and has been associated with advanced stage (476), decreased differentiation, aggressive cell types particularly including the clear-cell type (479), and deep myometrial invasion. The significance of HER2/neu amplification or over expression as a predictor of survival is somewhat unclear, with no apparent association of overexpression to outcome being identified in several studies (467, 478, 480), but a statistically significant relationship in most others (477–481, 482) even after adjusting for other known risk factors (477). In addition to its potential utility as an indicator of poor prognosis, systemic therapy using antibodies directed against the HER2/neu protein has been investigated for patients with tumors that express the protein at high levels. **Trastuzumab** (Herceptin®, Genentech) monotherapy failed to demonstrate significant activity in the recent GOG 181-B study (483). No responses were achieved, although 12 of 34 women experienced stabilization. Given the higher rates of HER2 overexpression seen in type II tumors, assessment of trastuzumab combined with carboplatin/paclitaxel in serous papillary tumors is underway.

Erlotinib (Tarceva®, GenenTech) (150 mg/day orally) was evaluated in 32 assessable women with chemotherapy-naïve, recurrent or metastatic EC (484). One prior line of hormonal therapy was permitted. The overall response rate was 13% (12.5% with confirmed PR lasting 2 to 36 months and 47% with SD with a median duration of 3.7 months). The treatment was very well tolerated with elevated transaminases being the only grade 4 toxicity. EGFR expression was noted to be positive in 19 patients and negative in 9 patients. Three of the 19 patients with overexpression (16%) had a PR. There were no EGFR mutations identified, and there was no correlation with gene amplification and response. Given the poor overall response rate of 4% and SD of 27% of **gefitinib** (Iressa®, AstraZeneca) (500 mg/day) in the GOG 229-C trial (485) no further studies have been undertaken. EGFR mutations, as well as expression of EGFR, phosphor-EGFR, phosphor-ERK were examined in tumors but did not correlate with clinical response. A phase II study of **cetuximab** (Erbixux®, Bristol-Myers Squibb) in progressive or recurrent EC was recently completed and its results are eagerly waited. The novel dual EGFR and HER2 tyrosine kinase inhibitors, **lapatinib** (Tykerb®, GSK), was evaluated in the phase II GOG 229-D study. Although no data have been published by this trial, second stage accrual was not

opened, likely indicating low clinical activity. Clinical trials focusing on preselected patients are ongoing (e.g., **BIBW 2992** [afatinib], an oral ErbB family blocker that covalently binds and irreversibly blocks all kinase-competent ErbB family members, and **ARRY 380**, an orally active, reversible and selective ErbB-2/HER2 inhibitor) while much effort is currently focused on effective combinations of EGFR with other agents that can overcome the molecular “escape” pathways for EGF receptor antagonists.

The **RAS/RAF/MEK pathway** is involved in several crucial cellular functions including angiogenesis, cell cycle regulation, proliferation and survival. The activation of RAS proto-oncogenes through either point mutations or gene amplification has been identified in various malignant tumors. Mutations in the *K-ras* oncogene have been reported in endometrioid cancer and also in endometrial hyperplasia, suggesting that *K-ras* activation may be an early event in the development of endometrioid malignancy. In most studies, the presence of *K-ras* mutations has not been related to stage, grade, depth of invasion, or survival (486, 487). *K-ras* mutations may activate the PI3K pathway independent of traditional signaling (488, 489). This pathway is under the direct control of upstream cell-surface growth receptors that are often affected in EC. Beside the relatively high prevalence of *K-ras* mutations identified in EC (Table 22.20), recent data has also illustrated an interesting negative feedback loop involving pS6K. Ramjaun and colleagues recently reported that this pathway is activated in the presence of AKT blockade (490). MEK inhibitors and RAF kinase small molecule inhibitors are currently being investigated. The GOG has explored a single-agent phase II trial of the oral MEK inhibitor **selumetinib** (AZD6244) in patients pre-treated with recurrent or persistent EC. Although adequate response rates were achieved, frequent and severe side effects have halted this trial. Clinical trials under development have now focused on the simultaneous blockade of components of both Ras/Raf/MEK and PI3K/AKT/mTOR pathways (490).

Angiogenesis mediates the growth of several solid tumors including that of endometrial cancer. Overexpression of VEGF has been associated with poor prognostic factors in EC such as deep myometrial invasion and lymph node metastasis (491, 492). VEGF expression seems highly variable depending on histologic subtype and disease stage, with early-stage well-differentiated lesions expressing the highest levels (493). To date, treatment of recurrent EC with antiangiogenic agents has revealed mixed results.

The most significant developments in this class of agents have centered on suppressing the VEGFR ligand. **Bevacizumab** (Avastin®, Roche) (15 mg IV every 3 weeks) was investigated in GOG-229E, a study in patients with recurrent or persistent measurable EC after receiving one or two prior cytotoxic regimens (494). Of fifty-two evaluable patients, 13.5% had objective response (one CR and six PRs) while 40.4% of patients survived progression-free for at least 6 months. Median PFS and OS were 4.2 and 10.5 months, respectively. Although no GI perforations or fistulas occurred, two episodes of grades 3/4 hemorrhage and thromboembolism were reported. Bevacizumab is currently being evaluated in a three-arm randomized phase II GOG study (86P) with patients randomly assigned to carboplatin/paclitaxel/bevacizumab, carboplatin/paclitaxel/temsirolimus, and carboplatin/ixabepilone/bevacizumab. Other trials under evaluation include first-line intensity-modulated irradiation/cisplatin/bevacizumab followed by carboplatin/paclitaxel.

Tyrosine kinase receptor inhibitors are among the various targeted therapeutics under investigation. These agents target several receptors allowing for the pharmacological disruption of several independent pathways. **Sunitinib malate** (Sutent®, Pfizer) is an oral small-molecule, multitargeted tyrosine kinase inhibitor that targets several receptor tyrosine kinases. In one study (495), 20 evaluable patients with recurrent or metastatic EC, previously treated with at most one chemotherapy regimen,

received 50 mg sunitinib daily for 4 consecutive weeks followed by 2 weeks off. Three patients (15%) achieved PR and five (25%) achieved stabilization of the disease, four of which were for more than 6 months. Median time to progression and OS were 2.5 and 19.0 months respectively.

Unfortunately, the antiangiogenic and antiproliferative properties of **sorafenib** (Nexavar®, Bayer) (495) and **thalidomide** (Thalomid®, Celgene) (496) did not lead to significant objective responses in the corresponding phase II clinical trials and were deemed not clinically interesting enough to justify further study. New antiangiogenic agents undergoing phase II clinical trials in pretreated EC include the angiokinase inhibitors **brivanib**, **cediranib**, **E7080**, **BIBF1120**, and the VEGF-Trap **aflicercept** (GOG 229-F).

Metformin is a biguanide drug that is widely used for the treatment of type II diabetes. Several studies have suggested that this agent can reduce cancer incidence among hyperglycemic patients. Since the first case report describing metformin-induced regression of AEH in one patient nonrespondent to progesterone therapy, a continuously growing body of evidence has brought metformin to the foreground of therapies against EC. Not only does this antidiabetic agent improve the negatively associated EC metabolic profile (insulin resistance, obesity, estrogen excess) (498, 499), but it also exhibits activity against EC cells through antiproliferative, proapoptotic, antiangiogenic, and antimetastatic properties (500–502). Metformin is commonly thought of as an insulin sensitizer resulting in an improvement in insulin resistance, followed by a reduction in circulating insulin levels. Metformin inhibits complex I activity in the mitochondria leading to the activation of its downstream target, AMPK, which regulates multiple signaling pathways controlling cellular proliferation, including inhibition of the mTOR pathway (503). Given the interrelationship between these two pathways, metformin is thought to behave as a novel mTOR inhibitor and has been shown to dramatically decrease proliferation in a number of different human cancer cell lines *in vitro* (504). Hanna et al. demonstrated a synergistic relationship between paclitaxel and metformin against human EC cell lines (505). A prospective trial is currently being conducted evaluating metformin's effect in patients with EC without concurrent diabetes.

The Poly (adenosine diphosphate ribose) polymerase (PARP). is a family of nuclear, multifunctional enzymes that mediates the recruitment of the DNA repair machinery through the base-excision repair (BER) pathway (506). The anti-neoplastic effect of PARP inhibitors stems from their ability to enhance the genomic instability of tumor cells by simultaneously targeting DNA repair pathways and exploiting their intrinsic deficiencies in the homologous recombination (HR) pathway through the phenomenon of synthetic lethality (506). PTEN loss is considered a component of BRCA-ness phenotype. It impedes repair of DNA double-strand breaks via homologous recombination, thereby creating cellular susceptibility to PARP inhibition (507). Preclinical data have shown a correlation between *in vitro* sensitivity to PARP inhibition and mutated PTEN status in EC cell lines (508), providing a strong rationale for testing PARP inhibitors in EC, especially type I, which harbors PTEN functional loss in 80% of cases. There is a variety of PARP inhibitors in clinical development, including olaparib, veliparib, and iniparib. A phase I study evaluating olaparib observed a dramatic clinical response in one BRCA mutation negative patient with metastatic EC. After 6 weeks of treatment, complete resolution of symptoms as well as radiologic response of visceral metastases were noted (509). Iniparib (BSI-201) has been studied in the treatment of recurrent carcinosarcoma of the uterus in combination with carboplatin and paclitaxel. The results of this study have not been formally reported. Further clinical evaluation of the potential utility of PARP inhibitors in EC is warranted.

MANAGEMENT OF PATIENTS WITH SEROUS AND CLEAR-CELL HISTOLOGIES

Serous cancer and, to a lesser extent, clear-cell ECs tend to spread in a fashion similar to ovarian cancer with a high propensity for upper abdominal relapse. Therefore, whole-abdomen radiation has been extensively studied historically in this group of patients (335). Given the mixed results with whole-abdomen radiotherapy, the recognized patterns of disease spread and failure, and the findings of GOG 122 (289) supporting an increased role for chemotherapy, chemotherapy has increasingly been used to treat these high-risk histologies. Based on the response rates of paclitaxel and carboplatin in other tumors of serous histology, trials investigating paclitaxel and carboplatin in UPSCs have reported response rates of 60% to 70% (510, 511). No randomized, prospective trials evaluating multi-modality therapy specifically for early- or late-stage uterine serous carcinomas have been reported. A single-institution phase 2 trial for advanced-stage uterine papillary serous histology administered paclitaxel and platinum-based chemotherapy for three cycles followed by volume-directed radiation therapy. Patients then received an additional three cycles of chemotherapy. The most common toxicity was hematologic and occurred during chemotherapy following radiation therapy. The PFS for the nine women treated is 46.4 months (512). A similar study administered four cycles of platinum with paclitaxel or epirubicin followed by whole pelvic and vaginal brachytherapy. The 5-year OS for this group was 58.9% (513).

With regard to Stage I disease, the available data for designing a treatment plan are retrospective. A study of 74 Stage I patients with UPSC between 1987 and 2004 who underwent complete staging at Yale University was reported (514). Patients were divided into those who had no residual cancer in the hysterectomy specimen versus those who did. Stage IA patients who had residual in the hysterectomy specimen and who were treated with platinum-based chemotherapy had no recurrences ($n = 7$) versus 6 of 14 (43%) who did not receive treatment. Of 15 patients with Stage IB disease, there were no recurrences in the treated group, but 10 of 13 nontreated patients (77%) recurred. Platinum-based chemotherapy was associated with improved progression-free ($p < 0.01$) and OS ($p < 0.05$). Furthermore, no patient who received radiation to the vaginal cuff recurred at the cuff versus 6 of 31 (19%) of those who did not receive vaginal cuff irradiation (514). Recognizing the limits of retrospective studies, these data support the potential benefit of a regimen of platinum-based chemotherapy with cuff irradiation in patients with UPSC. Randomized, prospective data are needed to accurately define the best approach in these patients.

In 2009, the SGO produced a review of the management of women with serous EC (515). It was noted that as extra-uterine spread was common, even in the setting of minimally invasive/noninvasive disease, surgical staging should be routinely performed. In addition, platinum-based chemotherapy should be considered in both early-stage and advanced-stage patients. The role of radiation in these patients by itself or in combination

with chemotherapy remains uncertain, and is being addressed by the GOG 249 and GOG 258 protocols. In addition, the SGO also sponsored a review of clear-cell carcinoma of the uterus, which supported routine staging, and consideration of post-operative chemotherapy (516). The rarity of these tumor types has made histology-based clinical trials difficult to perform. It is hoped that as a better understanding of the molecular pathways evolves in EC, treatment based on histology may become more common. At the present time, using standard chemotherapy regimens, there are no data to support different therapies based on histology alone (16).

FUTURE DIRECTIONS

In 2001, the National Cancer Institute convened an expert panel to develop a national 5-year plan for research priorities in gynecologic cancers. The resulting report, Priorities of the Gynecologic Cancer Progress Review Group (PRG), specified that understanding tumor biology was the central key toward controlling gynecologic cancers. Now, nearly a decade later, some hope for a better understanding of EC at a genetic and molecular level is being realized. The GOG 210 study, a prospective surgical pathologic study that created an annotated tissue repository from over 6000 patients with more than 36,000 specimens serves as a resource for discovery and validation of predictive and prognostic biomarkers. In addition, the Genome Atlas Project has nearly completed an analysis of 500 ECs (endometrioid and serous types) with array-based analyses and second-generation sequencing, which will provide information on genome copy number, gene expression profiles, methylation status, and whole exome sequencing, and will completely sequence 10% of all cases. It is expected that the knowledge from these datasets will drive clinical research and patient care for the next decade. Increasingly, we can expect that therapies offered to our patients will be based on a more complete understanding of pathways, and that therapies may be matched to address specific genetic changes.

Summary

EC is the most common gynecologic malignancy, and an understanding of presentation, surgical management, and treatment options is required for gynecologic oncologists. Surgical therapy is a mainstay of EC, with lymphadenectomy and laparoscopy increasingly integrated. A thorough knowledge of the relationships between uterine factors and extrauterine disease spread is essential. Surgical staging defines extent of disease and largely defines risk of recurrence. Pelvic radiation is associated with better local control, but no improvement in survival for patients with Stage I–II EC is seen in randomized trials. Chemotherapy is increasingly integrated into up-front management of advanced-stage EC and may have a role in early-stage disease. Combination therapy with radiation and chemotherapy is under evaluation. Targeted agents hold promise; however, a better understanding of molecular and genetic changes is required to improve efficacy.

REFERENCES

1. American Cancer Society. *Cancer Facts and Figures 2012*. Atlanta, GA: American cancer Society; 2012.
2. Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. *Obstet Gynecol*. 1984;64:417–420.
3. Norris HJ, Tavassoli FA, Kurman RJ. Endometrial hyperplasia and carcinoma: diagnostic consideration. *Am J Surg Pathol*. 1983;7: 839–847.
4. Trimble EL, Harlan LC, Clegg L, et al. Pre-operative imaging, surgery, and adjuvant therapy for women diagnosed with cancer of the corpus uteri in community practice in the US. *Gynecol Oncol*. 2005;96:741–748.
5. Creasman W, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. *Int J Gynecol Obstet*. 2006;95(suppl. 1):S105–S143.

6. Kitchener H, Trimble EL. Endometrial cancer state of the science meeting. *Int J Gynecol Cancer*. 2009;19:134–140.
7. Curtin J, Clarke-Pearson DL. *Pathways to Progress in Women's Cancer. A Research Agenda Proposed by the Society of Gynecologic Oncology*. Chicago, IL: SGO; 2012.
8. Naumann RW, Coleman R. The use of adjuvant radiation therapy in early endometrial cancer by members of the Society of Gynecologic Oncologists in 2005. *Gynecol Oncol*. 2007;105:7–12.
9. Singh M, Zaino R, Filiaci V, et al. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2007;106(2):325–333.
10. Engelsens I, Akslen LA, Salverson HB. Biologic markers in endometrial cancer treatment. *APMIS*. 2009;117:693–707.
11. Dedes K, Wetterskog D, Ashworth A, et al. Emerging therapeutic targets in endometrial cancer. *Nat Rev Clin Oncol*. 2011;8:261–271.
12. Ries LAG, Eisner CL, Kosary, et al., eds. *SEER Cancer Statistics Review, 1973–1997*. National Cancer Institute. NIH Pub #00-27 89. Bethesda, MD: NIH;2000:171–181.
13. Parkin DM, Whelan SL, Ferlay J, et al., eds. *Cancer Incidence in Five Continents*. Vol. VII. IARC Sci. Pub. No. 143. Lyon, France: IARC;1997.
14. Yap S, Matthews R. Racial and ethnic disparities in cancer of the uterine corpus. *J Nat Med Assoc*. 2006;98:1930–1933.
15. Maxwell GL, Tian C, Risinger J, et al. Racial disparity in survival among patients with advanced/recurrent endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Cancer*. 2006;107:2197–2205.
16. McMeekin DS, Filiaci V, Thigpen JT, et al. Importance of histology in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2007;106:16–22.
17. Ferguson S, Olshen A, Levine D, et al. Molecular profiling of endometrial cancers from African American and Caucasian women. *Gynecol Oncol*. 2006;101:209–213.
18. Watson P, Lynch H. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. *Cancer*. 1993;71:677–685.
19. Lu K, Dinh M, Kohlman W, et al. Gynecologic cancer as a “sentinel cancer” for women with hereditary nonpolyposis colorectal cancer syndrome. *Obstet Gynecol*. 2005;105:569–574.
20. Berends M, Wu Y, Sijmons R, et al. Toward new strategies to select young endometrial cancer patients for mismatch repair gene mutation analysis. *J Clin Oncol*. 2003;23:4364–4370.
21. Schmeler K, Lynch H, Chen L, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med*. 2006;354:261–269.
22. Hornreich G, Beller U, Lavie O, et al. Is uterine serous papillary carcinoma a *BRCA1*-related disease? Case report and review of the literature. *Gynecol Oncol*. 1999;75:300–304.
23. Levine D, Lin O, Barakat R, et al. Risk of endometrial cancer associated with *BRCA* mutation. *Gynecol Oncol*. 2001;80:395–398.
24. Beiner M, Fich A, Rosen B, et al. The risk of endometrial cancer in women with *BRCA1* and *BRCA2* mutations. A prospective study. *Gynecol Oncol*. 2007;104:7–10.
25. Barak F, Milgrom R, Laitman Y, et al. The rate of predominant Jewish mutations in the *BRCA1*, *BRCA2*, *MSH2*, *MSH6* genes in unselected Jewish endometrial cancer patients. *Gynecol Oncol*. 2010;119:511–515.
26. Bokhman JV. Two pathologic types of endometrial carcinoma. *Gynecol Oncol*. 1983;10:237–246.
27. Kovalev S, Marchenko ND, Gugliotta BG, et al. Loss of p53 function in uterine papillary serous carcinoma. *Hum Pathol*. 1998;29:613–619.
28. Cao QJ, Belbin T, Socci N, et al. Distinctive gene expression profiles by cDNA microarrays in endometrioid and serous carcinomas of the endometrium. *Int J Gynecol Pathol*. 2004;23:321–329.
29. Akhmedkhanov A, Zeleniuch-Jaquotte A, Toniolo P. Role of exogenous and endogenous hormones in endometrial cancer. *Ann NY Acad Sci*. 2001;943:296–315.
30. Henderson BE, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis*. 2000;21:427–433.
31. McDonald TW, Malkasian GD, Gaffey TA. Endometrial cancer associated with feminizing ovarian tumor and polycystic ovarian disease. *Obstet Gynecol*. 1977;49:654–658.
32. Smith DC, Prentice R, Thompson DJ, et al. Association of exogenous estrogen and endometrial carcinoma. *N Engl J Med*. 1975;293:1164–1167.
33. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med*. 1975;293:1167–1170.
34. Grady D, Gebretsadik DT, Kerlikowske K, et al. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol*. 1995;85:304–313.
35. Schottenfeld D. Epidemiology of endometrial neoplasia. *J Cell Biochem Suppl*. 1995;23:151–159.
36. MacDonald PC, Edman CD, Hemsell DL, et al. Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. *Am J Obstet Gynecol*. 1978;130:448–455.
37. Weiss J, Saltzman B, Doherty J, et al. Risk factors for the incidence of endometrial cancer according to the aggressiveness of disease. *Am J Epidemiol*. 2006;164:56–62.
38. Elwood JM, Cole P, Rothman KJ, et al. Epidemiology of endometrial cancer. *J Natl Cancer Inst*. 1977;59:1055–1060.
39. O'Mara BA, Byers T, Schoenfeld E. Diabetes mellitus and cancer risk: a multisite case-control study. *J Chronic Dis*. 1985;38:435–441.
40. Parazzini F, La Vecchia C, Negri E, et al. Diabetes and endometrial cancer: an Italian case-control study. *Int J Cancer*. 1999;81:539–542.
41. Rutanen EM. Insulin-like growth factors in endometrial function. *Gynecol Endocrinol*. 1998;12:399–406.
42. Nagamani M, Stuart CA. Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. *Am J Obstet Gynecol*. 1998;179:6–12.
43. Killackey MA, Hakes TB, Pierce VK. Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. *Cancer Treat Rep*. 1985;69:237–238.
44. Fornander T, Cedermark B, Mattsson A, et al. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet*. 1989;21:117–120.
45. Fisher B, Costantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst*. 1994;86:527–537.
46. Magriples U, Naftolin F, Schwartz PE, et al. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol*. 1993;11:485–490.
47. Barakat RR, Wong G, Curtin JP, et al. Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. *Gynecol Oncol*. 1994;55:164–168.
48. van Leeuwen FE, Benraad J, Coebergh JW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet*. 1994;343:448–452.
49. Fornander T, Hellstrom AC, Moberger B. Descriptive clinicopathologic study of 17 patients with endometrial cancer during or after adjuvant tamoxifen in early breast cancer. *J Natl Cancer Inst*. 1993;85:1850–1855.
50. DeMichele A, Troxel A, Berlin J, et al. Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population based case-control study. *J Clin Oncol*. 2008;26:4151–4159.
51. Perez E. Appraising adjuvant aromatase inhibitor therapy. *Oncologist*. 2006;11:1058–1069.
52. Breast International Group 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353:2747–2757.
53. Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after 2 years of treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 study. *J Clin Oncol*. 2007;25:2664–2670.
54. Maxwell GL, Schildkraut J, Calingaert B, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. *Gynecol Oncol*. 2006;103:535–540.
55. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. *Cancer*. 1987;60:2035–2041.
56. Mariani A, Dowdy S, Keeney G, et al. High-risk endometrial cancer subgroups: candidates for target based adjuvant therapy. *Gynecol Oncol*. 2004;95:120–126.
57. Morrow CP, Bundy BN, Kumar RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stages I and II carcinoma of the endometrium. A Gynecologic Oncology Group study. *Gynecol Oncol*. 1991;40:55.
58. Rabban JT, Zaloudek CJ. Minimal uterine serous carcinoma: current concepts in diagnosis and prognosis. *Pathology*. 2007;39:125–133.
59. Nakagawa-Okamura C, Sato S, Tsuji I, et al. Effectiveness of mass screening for endometrial cancer. *Acta Cytol*. 2002;46:277–283.
60. Vuento MH, Maatela JI, Tyrkko JE, et al. A longitudinal study of screening for endometrial cancer by endometrial biopsy in diabetic females. *Int J Gynecol Cancer*. 1995;5:390–395.
61. ACOG Committee Opinion. Routine cancer screening. *Obstet Gynecol*. 2006;108:1611–1613.
62. Society of Gynecologic Oncologists. Practice guidelines: uterine corpus-endometrial cancer. *Oncology*. 1998;12:122–126.
63. Gorodeski IG, Geier A, Lunenfeld B, et al. Progesterone challenge test in postmenopausal women with pathological endometrium. *Cancer Invest*. 1988;6:481–485.
64. Hunter JE, Tritz DE, Howell MG, et al. The prognostic and therapeutic implications of cytologic atypia in patients with endometrial hyperplasia. *Gynecol Oncol*. 1994;55:66–71.
65. Kurman R, Kaminski P, Norris H. The behavior of endometrial hyperplasia. A long-term study of “untreated” hyperplasia in 170 patients. *Cancer*. 1985;56:403–411.
66. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a

- Gynecologic Oncology Group study. *Cancer*. 2006;106:812–819.
67. King A, Seraj IM, Wagner RJ. Stromal invasion in endometrial adenocarcinoma. *Am J Obstet Gynecol*. 1984;149:10–14.
 68. Randal TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium under age 40. *Obstet Gynecol*. 1997;90:434–440.
 69. Ushijima K, Yahata H, Yoshikawa H, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. *J Clin Oncol*. 2007;25:2798–2803.
 70. Runowicz CD. Gynecologic surveillance of women on tamoxifen: first do no harm. *J Clin Oncol*. 2000;18:3457–3458.
 71. ACOG Committee Opinion. Tamoxifen and uterine cancer. *Obstet Gynecol*. 2006;107:1475–1478.
 72. Gredmark T, Kvint S, Harvel G, et al. Histopathologic findings in women with post-menopausal bleeding. *Br J Obstet Gynaecol*. 1995;102:133–136.
 73. Feldman S, Cook F, Harlow B, et al. Predicting endometrial cancer among women who present with abnormal vaginal bleeding. *Gynecol Oncol*. 1995;56:376–381.
 74. Clark TJ, Mann CH, Shah N, et al. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. *Br J Obstet Gynaecol*. 2002;109:313–321.
 75. Dijkhuizen FP, Mol B, Brolmann H, et al. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. *Cancer*. 2000;89:1765–1772.
 76. Clark TJ, Voit D, Gupta J, et al. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia. A systematic quantitative review. *JAMA*. 2002;288:1610–1621.
 77. Bradley WH, Boente MP, Brooker D, et al. Hysteroscopy and cytology in endometrial cancer. *Obstet Gynecol*. 2004;104:1030–1033.
 78. Revel A, Tsafir A, Anteby SO, et al. Does hysteroscopy produce intraperitoneal spread of endometrial cancer cells? *Obstet Gynecol Surv*. 2004;59:280–284.
 79. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obstet*. 2009;105:109–110.
 80. Tabor A, Watt H, Wald N. Endometrial thickness as a test for endometrial cancer in women with post-menopausal vaginal bleeding. *Obstet Gynecol*. 2002;99:663–670.
 81. Smith-Bindman R, Kerlikowske K, Feldstein K, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *JAMA*. 1998;280:1510–1517.
 82. Conoscenti G, Mier YJ, Fischer-Tamaro L, et al. Endometrial assessment by transvaginal sonography and histological findings after D&C in women with post-menopausal bleeding. *Ultrasound Obstet Gynecol*. 1995;6:108–115.
 83. Goldstein R, Bree R, Benson C, et al. Evaluation of the woman with post-menopausal bleeding. Society of radiologists in ultrasound—sponsored consensus conference statement. *J Ultrasound Med*. 2001;20:1025–1036.
 84. deKroon CD, deBrock GH, Dieben SW, et al. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. *Br J Obstet Gynaecol*. 2003;110:938–947.
 85. Marziale P, Atlante G, Pozzi M, et al. 426 cases of stage I endometrial carcinoma: a clinicopathological analysis. *Gynecol Oncol*. 1989;32:278.
 86. Ozalp S, Yalcin OT, Polay S, et al. Diagnostic efficacy of the preoperative lymphoscintigraphy, Ga-67 scintigraphy, and computed tomography for the detection of lymph node metastasis in cases of ovarian or endometrial cancer. *Acta Obstet Gynaecol Scand*. 1999;78:155–159.
 87. Zerbe M, Bristow R, Grumbine F, et al. Inability of preoperative computed tomography scans to accurately predict the extent of myometrial invasion and extracorporeal spread in endometrial cancer. *Gynecol Oncol*. 2000;78:67–70.
 88. Signorelli M, Guerra L, Buda A, et al. Role of integrated FDG PET/CT in the surgical management of patients with high risk clinical early stage endometrial cancer: detection of pelvic nodal metastases. *Gynecol Oncol*. 2009;115:231–235.
 89. Savelli L, Testa A, Mabrouk M, et al. A prospective comparison of the accuracy of transvaginal sonography and frozen section assessment of myometrial invasion in endometrial cancer. *Gynecol Oncol*. 2012;124:549–552.
 90. Rockall AG, Sohaib SS, Harisinghani MG, et al. Diagnostic performance of nanoparticle enhanced magnetic resonance imaging in the diagnosis of lymph node metastases in patients with endometrial and cervical cancer. *J Clin Oncol*. 2005;23:2813–2821.
 91. Messiou C, Spencer JA, Swift SE. MR staging of endometrial cancer. *Clin Radiol*. 2006;61:822–832.
 92. Chung HH, Kang SB, Cho JY, et al. Accuracy of MR imaging for the prediction of myometrial invasion of endometrial cancer. *Gynecol Oncol*. 2007;104:654–659.
 93. Rockall AG, Meroni R, Sohaib SA, et al. Evaluation of endometrial carcinoma on magnetic resonance imaging. *Int J Gynecol Cancer*. 2007;17:188–196.
 94. Kalogera E, Scholler N, Powless C, et al. Correlation of serum HER4 with tumor size and myometrial invasion in endometrial cancer. *Gynecol Oncol*. 2011.
 95. Farias-Eisener R, Su F, Robbins T, et al. Validation of serum biomarkers for detection of early and late stage endometrial cancer. *Am J Obstet Gynecol*. 2010;202:73.e1–73.e5.
 96. Niloff JM, Klug TL, Schaezel E, et al. Elevation of serum CA 125 level in carcinomas of the fallopian tube, endometrium, and endocervix. *Am J Obstet Gynecol*. 1984;148:1057.
 97. Hsieh CH, Chang Chien CC, Lin H, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? *Gynecol Oncol*. 2002;86:28–33.
 98. Rose PG, Sommers RM, Reale FR, et al. Serial serum CA-125 measurements for evaluation of recurrence in patients with endometrial carcinoma. *Obstet Gynecol*. 1994;84:12–16.
 99. Nicklin J, Janda M, Gebksi V, et al. The utility of serum CA-125 in predicting extra-uterine disease in apparent early-stage endometrial cancer. *Cancer Int J*. 2011. doi:10.1002/ijc.26433.
 100. Heyman J. The so-called Stockholm Method and the results of treatment of uterine cancer at the radiumhemmet. *Acta Radiol*. 1935;16:129.
 101. Arneson AN, Stanbro WW, Nolan JF. The use of multiple sources of radium within the uterus in the treatment of endometrial cancer. *Am J Obstet Gynecol*. 1948;55:64–78.
 102. Nolan J, Arneson A. An instrument for inserting multiple capsules of radium within the uterus in the treatment of corpus cancers. *Am J Roentgenol*. 1943;49:504.
 103. Lewis GC Jr, Slack NH, Mortel R, et al. Adjuvant progestogen therapy in the primary definitive treatment of endometrial cancer. *Gynecol Oncol*. 1974;2:368–376.
 104. Gray LA. Lymph node excision in treatment of gynecologic malignancies. *Am J Surg*. 1964;108:660–108663.
 105. Lewis GC, Bundy B. Surgery for endometrial cancer. *Cancer*. 1981;48:568–574.
 106. Barakat RR, Lev G, Hummer A, et al. Twelve-year experience in the management of endometrial cancer: a change in surgical and postoperative radiation approaches. *Gynecol Oncol*. 2007;105:150–156.
 107. Morrow CP, Curtin JP. *Surgery for Ovarian Neoplasia in Gynecologic Cancer Surgery*. New York, NY: Churchill Livingstone Inc.; 1996:627–716.
 108. Soliman P, Frumovitz M, Spannuth W, et al. Lymphadenectomy during endometrial cancer staging: practice patterns among gynecologic oncologists. *Gynecol Oncol*. 2010;119:291–294.
 109. Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. *Fert Steril*. 2003;80:1315–1324.
 110. International Federation of Gynecology and Obstetrics: classification and staging of malignant tumors in the female pelvis. *Int J Gynaecol Obstet*. 1971;9:172.
 111. Tillmanns T, Kamelle S, Abudayyeh I, et al. Panniculectomy with simultaneous gynecologic oncology surgery. *Gynecol Oncol*. 2001;83:518–522.
 112. Wright J, Powell M, Herzog T, et al. Panniculectomy: improving lymph node yield in morbidly obese patients with endometrial neoplasms. *Gynecol Oncol*. 2004;94:436–441.
 113. Ramirez P, Frumovitz M, Bodurka D, et al. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. *Gynecol Oncol*. 2004;95:133–138.
 114. Baker J, Obermair A, Gebksi V, et al. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. *Gynecol Oncol*. 2012;125:263–270.
 115. Penner K, Dorigo O, Aoyama C, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. *Gynecol Oncol*. 2012;124:542–548.
 116. Massi G, Savino L, Susini T. Vaginal hysterectomy versus abdominal hysterectomy for treatment of stage I endometrial adenocarcinoma. *Am J Obstet Gynecol*. 1996;174:1320–1326.
 117. Bloss JD, Berman ML, Bloss LP, et al. Use of vaginal hysterectomy for the management of stage I endometrial cancer in the medically compromised patient. *Gynecol Oncol*. 1991;40:74–77.
 118. Orr JW, Holimon J, Orr P. Stage I corpus cancer: is teletherapy necessary. *Am J Obstet Gynecol*. 1997;176:777–789.
 119. Homesley HD, Kadar N, Barrett RJ, et al. Selective pelvic and periaortic lymphadenectomy does not increase morbidity in surgical staging of endometrial carcinoma. *Am J Obstet Gynecol*. 1992;167:1225–1230.
 120. Abu-Rustum N, Alektiar K, Iasonos A, et al. The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. *Gynecol Oncol*. 2006;103:714–718.
 121. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjuvant external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a

- Gynecologic Oncology Group study. *Gynecol Oncol.* 2004;92:744–751.
122. Goudge C, Bernhard S, Cloven N, et al. The impact of complete surgical staging on adjuvant treatment decisions in endometrial cancer. *Gynecol Oncol.* 2004;93:536–539.
 123. Sharma C, Deeutsch I, Lewin S, et al. Lymphadenectomy influences the utilization of adjuvant radiation treatment for endometrial cancer. *Am J Obstet Gynecol.* 2011;205:562.e1–562.e9.
 124. MacDonald OK, Sause W, Lee J, et al. Does oncologic specialization influence outcomes following surgery in early stage adenocarcinoma of the endometrium. *Gynecol Oncol.* 2005;99:730–735.
 125. Roland PY, Kelly FJ, Kulwicki C, et al. The benefits of a gynecologic oncologist: a pattern of care study for endometrial cancer treatment. *Gynecol Oncol.* 2004;93:125–130.
 126. Aalders JG, Thomas G. Endometrial cancer—revisiting the importance of pelvic and paraaortic lymph nodes. *Gynecol Oncol.* 2007;104:222–231.
 127. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post operative radiation therapy in endometrial carcinoma. *Lancet.* 2000;355:1404–1411.
 128. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC 2): an open label, non inferiority, randomized trial. *Lancet.* 2010;375:816–823.
 129. Trimble E, Kosary C, Park R. Lymph node sampling and survival in endometrial cancer. *Gynecol Oncol.* 1998;71:340–343.
 130. COSA-NZ-UK Endometrial Cancer Study Groups. Pelvic lymphadenectomy in high-risk endometrial cancer. *Int J Gynecol Cancer.* 1996;6:102–107.
 131. ASTEC Study Group. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomized study. *Lancet.* 2009;373:125–136.
 132. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy versus no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst.* 2008;100:1707–1716.
 133. Creasman WT, Mutch DE, Herzog TJ. ATEC lymphadenectomy and radiation therapy: are conclusions valid. *Gynecol Oncol.* 2010;116:293–294.
 134. Seamon LG, Fowler JM, Cohn DE. Lymphadenectomy for endometrial cancer: The controversy. *Gynecol Oncol.* 2010;117:6–8.
 135. Scholten A, van Putten WL, Beerman H, et al. Postoperative radiotherapy for stage I endometrial carcinoma: long term outcome of the randomized PORTEC trial with central pathology review. *Int J Radiation Oncol Biol Phys.* 2005;63:834–838.
 136. Nugent EK, Bishop EA, Mathews CA, et al. Do uterine risk factors or lymph node metastasis more significantly affect recurrence in patients with endometrioid adenocarcinoma. *Gynecol Oncol.* 2012;125:94–98.
 137. Kwon J, Qiu F, Saski R, et al. Are uterine risk factors more important than nodal status in predicting survival. *Obstet Gynecol.* 2009;114:736–743.
 138. Creutzberg C, van Putten W, Warlam-Rodenhuis C, et al. Outcome of high-risk stage IC, grade 3 compared with stage I endometrial carcinoma patients: the postoperative radiation therapy in endometrial carcinoma trial. *J Clin Oncol.* 2004;22:1234–1241.
 139. Onda T, Yoshikawa H, Mizutani K, et al. Treatment of node positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy. *Br J Cancer.* 1997;75:1836–1841.
 140. McMeekin DS, Lashbrook D, Gold M, et al. Analysis of FIGO stage IIIC endometrial cancer patients. *Gynecol Oncol.* 2001;81:273–278.
 141. Nelson G, Randall M, Sutton G, et al. FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. *Gynecol Oncol.* 1999;75:211–214.
 142. Arango HA, Hoffman MS, Roberts WS, et al. Accuracy of lymph node palpation to determine need for lymphadenectomy in gynecologic malignancies. *Obstet Gynecol.* 2000;95:553–556.
 143. Franchi M, Ghezzi F, Melpignano M, et al. Clinical value of intraoperative gross examination in endometrial cancer. *Gynecol Oncol.* 2000;76:357–361.
 144. Kim Y, Niloff J. Endometrial carcinoma: analysis of recurrence in patients treated with a strategy minimizing lymph node sampling and radiation therapy. *Obstet Gynecol.* 1993;82:175–180.
 145. Faught W, Krepart G, Loctocki R, et al. Should selective paraaortic lymphadenectomy be part of surgical staging for endometrial cancer. *Gynecol Oncol.* 1994;55:51–55.
 146. Goff B, Kato D, Schmidt R, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. *Gynecol Oncol.* 1994;54:264–268.
 147. Podratz KC, Mariani A, Webb M. Staging and therapeutic value of lymphadenectomy in endometrial cancer. *Gynecol Oncol.* 1998;70:163–164.
 148. Mariani A, Webb MJ, Keeney GI, et al. Low risk corpus cancer: is lymphadenectomy or radiotherapy necessary. *Am J Obstet Gynecol.* 2000;182:1506–1519.
 149. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. *Gynecol Oncol.* 2008;109:11–28.
 150. Convery PA, Cantrell LA, DiSanto N, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low grade endometrial cancer. *Gynecol Oncol.* 2011;123:65–70.
 151. Milam M, Java J, Walker JL, et al. Nodal metastasis risk in endometrioid endometrial cancer. *Obstet Gynecol.* 2012;119:286–292.
 152. Kang S, Kang WD, Chung HH, et al. Preoperative identification of Low-risk group for lymph node metastasis in endometrial cancer: a Korean GOG study. *J Clin Oncol.* 2012;30:1329–1334.
 153. Bernardini M, May T, Khalifa M, et al. Evaluation of two management strategies for preoperative grade 1 endometrial cancer. *Obstet Gynecol.* 2009;114:7–15.
 154. Doering DL, Barnhill DR, Weiser EB, et al. Intraoperative evaluation of depth of myometrial invasion in stage I endometrial adenocarcinoma. *Obstet Gynecol.* 1989;74:930–933.
 155. Goff BA, Riche LW. Assessment of depth of myometrial invasion in endometrial adenocarcinoma. *Gynecol Oncol.* 1990;38:46–48.
 156. Case AS, Rocconi RP, Straughn JM, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. *Obstet Gynecol.* 2006;108:1375–1379.
 157. Frumovitz M, Slomovitz BM, Singh DK, et al. Frozen section analyses as predictors of lymphatic spread in patients with early-stage uterine cancer. *J Am Coll Surg.* 2004;199:388–393.
 158. Cohn D, Huh D, Fowler J, et al. Cost-effectiveness analysis of strategies for the surgical management of grade 1 endometrial cancer. *Obstet Gynecol.* 2007;109:1388–1395.
 159. Mariani A, Webb M, Galli L, et al. Potential therapeutic role of paraaortic lymphadenectomy in node positive endometrial cancer. *Gynecol Oncol.* 2000;76:348–356.
 160. McMeekin DS, Lashbrook D, Gold M, et al. Nodal distribution and its significance in FIGO stage III endometrial cancer. *Gynecol Oncol.* 2001;82:375–379.
 161. Flanigan C, Mannel R, Walker J, et al. Incidence and location of paraaortic lymph node metastases in gynecologic malignancies. *J Am Coll Surg.* 1995;181:72–74.
 162. Abu-Rustum NR, Gomez J, Alektiar KM, et al. The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymphnodes. *Gynecol Oncol.* 2009;115:236–238.
 - 162a. Schorge JO, Molpus KL, Goodman A, Nikrui N, Fuller. The effect of postsurgical therapy on stage III endometrial carcinoma. *Gynecol Oncol.* 1996;115:236–238.
 - 162b. Otsuka I, Kubota T, Aso T. Lymphadenectomy and adjuvant therapy in endometrial carcinoma: role of adjuvant chemotherapy. *Br J Cancer.* 2002;87:236–238.
 163. Chuang L, Burke T, Tornos C, et al. Staging laparotomy for endometrial carcinoma: assessment of retroperitoneal lymph nodes. *Gynecol Oncol.* 1995;63:377–80.
 164. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of paraaortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet.* 2010;375:1165–1172.
 165. Hirahatake K, Hareyama H, Sakuragi N, et al. A clinical and pathologic study on paraaortic lymph node metastasis in endometrial carcinoma. *J Surg Oncol.* 1997;65:82–87.
 166. Kohler C, Tozzi R, Klemm P, et al. Laparoscopic paraaortic left-sided transperitoneal infrarenal lymphadenectomy in patients with gynecologic malignancies: techniques and results. *Gynecol Oncol.* 2003;91:139–148.
 167. Dowdy S, Aletti G, Cliby W. Extra-peritoneal laparoscopic paraaortic lymphadenectomy. A prospective cohort study of 293 patients with endometrial cancer. *Gynecol Oncol.* 2008;111:418–424.
 168. Kilgore L, Partidge E, Alvarez R, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol.* 1995;56:29–33.
 169. Girardi F, Petru E, Heydarfadaei M, et al. Pelvic lymphadenectomy in the surgical treatment of endometrial cancer. *Gynecol Oncol.* 1993;49:177–180.
 170. Cragan J, Havrilesky L, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. *J Clin Oncol.* 2005;23:3668–3675.
 171. Chan J, Cheung M, Huh W, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer.* 2006;107:1823–1830.
 172. Havrilesky LJ, Cragan J, Calingaert B, et al. Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. *Gynecol Oncol.* 2005;99(3):689–695.
 173. Bristow RE, Zahurak ML, Alexander CJ, et al. FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. *Int J Gynecol Cancer.* 2003;13:664–672.

174. Mariani A, Dowdy S, Cliby W, et al. Efficacy of systematic lymphadenectomy and adjuvant radiotherapy in node-positive endometrial cancer patients. *Gynecol Oncol*. 2006;101:200–208.
175. ASTEC/EN. 5 Study Group, Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomized trials): pooled trial results, systematic review, and meta-analysis. *Lancet*. 2009;373:137–46.
176. Mohan D, Samuels M, Selim M, et al. Long term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. *Gynecol Oncol*. 1998;70:165–171.
177. Khoury-Collado F, Abu-Rustum NR. Lymphatic mapping in endometrial cancer: a literature review of current techniques. *Int J Gynecol Cancer*. 2008;18:1163–1168.
178. Altgassen C, Muller N, Hornemann A, et al. Immunohistochemical workup of sentinel nodes in endometrial cancer improves diagnostic accuracy. *Gynecol Oncol*. 2009;114:284–287.
179. Nihura H, Okamoto S, Yoshinaga K, et al. Detection of micrometastases in the sentinel lymph nodes of patients with endometrial cancer. *Gynecol Oncol*. 2007;105:683–686.
180. Khoury-Collado F, Murray MP, Hensley ML, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. *Gynecol Oncol*. 2011;122:251–254.
181. Kang S, Yoo HJ, Hwang JH, et al. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. *Gynecol Oncol*. 2011;123:522–527.
182. Childers JM, Brzechffa P, Hatch K, et al. Laparoscopically assisted surgical staging of endometrial cancer. *Gynecol Oncol*. 1993;51:33–38.
183. Childers JM, Surwit EA. Combined laparoscopic and vaginal surgery for the management of two cases of stage I endometrial cancer. *Gynecol Oncol*. 1992;45:46–51.
184. Malur S, Possover M, Michels W, et al. Laparoscopic assisted vaginal hysterectomy versus abdominal surgery in patients with endometrial cancer—a prospective randomized trial. *Gynecol Oncol*. 2001;80:239–244.
185. Spirtos NM, Schlaerth J, Gross G, et al. Cost and quality of life analyses of surgery for early endometrial cancer: laparotomy versus laparoscopy. *Am J Obstet Gynecol*. 1996;174(6):1795–1799.
186. Walker J, Piedmonte MR, Spirtos N, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive staging of uterine cancer: GOG LAP2 study. *J Clin Oncol*. 2012;30:695–700.
187. Janda M, Gebski V, Brand A, et al. Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomized trial. *Lancet Oncol*. 2010;11:772–80.
188. Querleu D, Leblanc E, Castelain B. Laparoscopic pelvic lymphadenectomy in the staging of early carcinoma of the cervix. *Am J Obstet Gynecol*. 1991;164:579–581.
189. Nezhat CR, Burrell MO, Nezhat FR, et al. Laparoscopic radical hysterectomy with paraaortic and pelvic node dissection. *Am J Obstet Gynecol*. 1992;166:864–865.
190. Scribner D, Walker J, Johnson G, et al. Laparoscopic pelvic and paraaortic lymph node dissection: analysis of first 100 cases. *Gynecol Oncol*. 2001;82:498–503.
191. Malzoni M, Tinelli R, Cosentino F, et al. Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early stage endometrial cancer: a prospective randomized study. *Gynecol Oncol*. 2009;112:126–133.
192. Tozzi R, Malur S, Koehler C, et al. Laparoscopy versus laparotomy in endometrial cancer: first analysis of survival of a randomized prospective study. *J Minim Invasive Gynecol*. 2005;12:130–136.
193. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 study. *J Clin Oncol*. 2012;30:695–700.
194. Scribner D, Walker J, Johnson G, et al. Surgical management of early stage endometrial cancer in the elderly: is laparoscopy feasible? *Gynecol Oncol*. 2001;83:563–568.
195. Scribner D, Walker J, Johnson G, et al. Laparoscopic pelvic and paraaortic lymph node dissection in the obese. *Gynecol Oncol*. 2002;84:426–430.
196. Eltabbakh G, Shamonki M, Moody J, et al. Hysterectomy for obese women with endometrial cancer: laparoscopy or laparotomy. *Gynecol Oncol*. 2000;78:329–335.
197. O'Hanlan K, Dibble S, Fisher D. Total laparoscopic hysterectomy for uterine pathology: impact of body mass index on outcomes. *Gynecol Oncol*. 2006;103:938–941.
198. Boggess JF, Gehrig PA, Cantrell L, et al. A comparative study of 3 surgical methods for hysterectomy with staging for endometrial cancer: robotic assistance, laparoscopy, laparotomy. *Am J Obstet Gynecol*. 2008;199:360–369.
199. DeNardis SA, Holloway RW, Bigsby GE, et al. Robotically assisted laparoscopic hysterectomy versus total abdominal hysterectomy and lymphadenectomy for endometrial cancer. *Gynecol Oncol*. 2008;111:412–417.
200. Veljovich DS, Paley PJ, Drescher CW, et al. Robotic surgery in gynecologic oncology: program initiation and outcomes after the first year with comparison with laparotomy for endometrial cancer staging. *Am J Obstet Gynecol*. 2008;198:679.e1–679.e10.
201. Holloway RW, Ahmad S, DeNardis SA, et al. Robotically assisted laparoscopic hysterectomy and lymphadenectomy for endometrial cancer: analysis of surgical performance. *Gynecol Oncol*. 2009;115:447–452.
202. Seamon LG, Fowler JM, Richardson DL, et al. A detailed analysis of the learning curve: robotic hysterectomy and pelvic-aortic lymphadenectomy for endometrial cancer. *Gynecol Oncol*. 2009;114:162–167.
203. Lowe MP, Johnson PR, Kamelle SA, et al. A multi-institutional experience with robotic-assisted hysterectomy with staging for endometrial cancer. *Obstet Gynecol*. 2009;114:236–243.
204. Lim PC, Kang E, Park DH. Learning curve and surgical outcome for robotic-assisted hysterectomy with lymphadenectomy: case-matched controlled comparison with laparoscopy and laparotomy for treatment of endometrial cancer. *J Min Invas Gynecol*. 2010;17:739–748.
205. Seamon L, Cohn D, Richardson D, et al. Robotic Hysterectomy and pelvic-aortic lymphadenectomy for endometrial cancer. *Obstet Gynecol*. 2008;112:1207–1213.
206. Subramaniam A, Kim K, Bryant S, et al. A cohort study evaluating robotic versus laparotomy surgical outcomes of obese women with endometrial cancer. *Gynecol Oncol*. 2011;122:604–607.
207. Massi G, Savino L, Susini T. Vaginal hysterectomy versus abdominal hysterectomy for the treatment of stage I endometrial adenocarcinoma. *Am J Obstet Gynecol*. 1996;174:1320–1326.
208. Kornblith A, Huang H, Walker J, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic FIGO staging compared with laparotomy: a GOG study. *J Clin Oncol*. 2009;27:5337–5342.
209. Scribner D, Walker J, Johnson G, et al. Laparoscopic pelvic and paraaortic lymph node dissection: analysis of the first 100 cases. *Gynecol Oncol*. 2001;82:498–503.
210. Possover M, Krause N, Plaul K, et al. Laparoscopic paraaortic and pelvic lymphadenectomy: experience with 150 patients and review of literature. *Gynecol Oncol*. 1998;71:19–28.
211. Querleu D, Leblanc E, Cartron G, et al. Audit of preoperative and early complications of laparoscopic lymph node dissection in 1000 cancer patients. *Am J Obstet Gynecol*. 2006;195:1287–1292.
212. Reza M, Maeso S, Blasco JA. Meta-analysis of observational studies on the safety and effectiveness of robotic gynecologic surgery. *Br J Surg*. 2010;97:1772–1783.
213. Childers JM, Spirtos N, Brainard P, et al. Laparoscopic staging of the patient with incompletely staged early adenocarcinoma of the endometrium. *Obstet Gynecol*. 1994;83:597–600.
214. Bristow RE, Zerbe MJ, Rosenshein N, et al. Stage IVb endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. *Gynecol Oncol*. 2000;78:85–91.
215. Shih KK, Gardner G, Barakat R, et al. Surgical cytoreduction in stage IV endometrioid endometrial carcinoma. *Gynecol Oncol*. 2011;122:608–611.
216. Bristow R, Duska L, Montz F. The role of cytoreductive surgery in the management of stage IV uterine papillary serous carcinoma. *Gynecol Oncol*. 2001;81:92–99.
217. Kurman R, Norris H. Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma. *Cancer*. 1982;49:2547–2559.
218. Huang S, Amparo E, Fu Y. Endometrial hyperplasia: histologic classification and behavior. *Surg Pathol*. 1988;1:215–225.
219. Hunter JE, Tritz DE, Howell MG, et al. The prognostic and therapeutic implications of cytologic atypia in patients with endometrial hyperplasia. *Gynecol Oncol*. 1994;55:66–71.
220. Bergeron C, Nogales F, Masseroli M, et al. A multicentric European study testing the reproducibility of the WHO classification of endometrial hyperplasia with a proposal of a simplified working classification for biopsy and curettage specimens. *Am J Surg Pathol*. 1999;23:1102–1108.
221. Baak JP, Mutter G, Robboy S, et al. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. *Cancer*. 2005;103:2304–2312.
222. Mutter GL, Zaino R, Baak J, et al. Benign endometrial hyperplasia sequence and endometrial intraepithelial neoplasia. *Int J Gynecol Pathol*. 2007;26:103–114.
223. Silverberg S, Kurman R. *Tumors of the Uterine Corpus and Gestational Trophoblastic Disease*. Vol 3. Washington, DC: Armed Forces Institute of Pathology; 1992.
224. Zaino RJ, Silverberg SG, Norris HJ, et al. The prognostic value of nuclear versus architectural grading in endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Int J Gynecol Pathol*. 1994;13:29–36.
225. Zaino RJ, Kurman RJ, Diana KL, et al. The utility of the revised International Federation of

- Gynecology and Obstetrics histologic grading of endometrial adenocarcinoma using a defined nuclear grading system. *Cancer*. 1995;75:81–86.
226. Taylor R, Zeller J, Lieberman R, et al. An analysis of two versus three grades for endometrial carcinoma. *Gynecol Oncol*. 1999;74:3–6.
 227. Lax S, Ronntet B, Pizer E, et al. A binary grading system for uterine endometrioid carcinoma is comparable to FIGO grading for predicting prognosis and has superior interobserver reproducibility. *Mod Pathol*. 1999;12:118A.
 228. Zaino FJ, Kurman RJ, Brunetto VL, et al. Villo-glandular adenocarcinoma of the endometrium: a clinicopathologic study of 61 cases. *Am J Surg Pathol*. 1998;22:1379.
 229. Kusuyama J, Yoshida M, Imai H, et al. Secretory carcinoma of the endometrium. *Acta Cytol*. 1989;33:127.
 230. Christopherson WM, Alberhasky RC, Connelly PF. Carcinoma of the endometrium. I. A clinicopathologic study of clear-cell carcinoma and secretory carcinoma. *Cancer*. 1982;49:1511.
 231. Hendrickson MR, Kempson RL. Ciliated carcinoma—a variant of endometrial adenocarcinoma. A report of 10 cases. *Int J Gynecol Pathol*. 1983;2:1–12.
 232. Salazar OM, DePapp EW, Bonfiglio T, et al. Adenosquamous carcinoma of the endometrium. An entity with an inherently poor prognosis? *Cancer*. 1977;40:119–130.
 233. Silverberg SG, Bolin MG, DeGiorgi LS. Adenocarcinoma and mixed adenosquamous carcinoma of the endometrium. A clinicopathologic study. *Cancer*. 1972;30:1307–1314.
 234. Zaino R, Kurman R, Herbold D, et al. The significance of squamous differentiation in endometrial carcinoma. *Cancer*. 1991;68:2293–2302.
 235. Melhem MF, Tobon H. Mucinous adenocarcinoma of the endometrium: a clinicopathological review of 18 cases. *Int J Gynecol Pathol*. 1987;6:347.
 236. Maier RC, Norris HJ. Coexistence of cervical intraepithelial neoplasia with primary adenocarcinoma of the endocervix. *Obstet Gynecol*. 1980;56:361.
 237. McCluggage WG, Roberts N, Bharucha H. Enteric differentiation in endometrial adenocarcinomas: a mucin histochemical study. *Int J Gynecol Pathol*. 1995;14:250–254.
 238. Carcangiu ML, Chambers JT. Uterine papillary serous carcinoma: a study on 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. *Gynecol Oncol*. 1992;47:298–305.
 239. Chan JK, Loizzi V, Youssef M, et al. Significance of comprehensive surgical staging in noninvasive papillary serous carcinoma of the endometrium. *Gynecol Oncol*. 2003;90:181–185.
 240. Wheeler D, Bell K, Kurman R, et al. Minimal uterine serous carcinoma: diagnostic and clinicopathologic correlation. *Am J Surg Pathol*. 2000;24:797–806.
 241. Huh W, Powell M, Leath C, et al. Uterine papillary serous carcinoma: comparisons of outcomes in surgical stage I patients with and without adjuvant therapy. *Gynecol Oncol*. 2003;91:470–475.
 242. Havrilesky L, Alvarez Secord A, Bae-Jump V, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. *Gynecol Oncol*. 2007;105:677–682.
 243. Ambros RA, Sherman ME, Zahn CM, et al. Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. *Hum Pathol*. 1995;26:1260–1267.
 244. Sherman ME, Bitterman P, Rosenshein NB, et al. Uterine serous carcinoma. A morphologically diverse neoplasm with unifying clinicopathologic features. *Am J Surg Pathol*. 1992;16:600–610.
 245. Soslow R, Pirong E, Isacson C. Endometrial intraepithelial carcinoma with associated peritoneal carcinomatosis. *Am J Surg Pathol*. 2000;24:726–732.
 246. Spiegel G. Endometrial carcinoma *in situ* in postmenopausal women. *Am J Surg Pathol*. 1995;19:417–431.
 247. Zheng W, Khurana R, Farahmand S, et al. p53 immunostaining as a significant adjunct diagnostic method for uterine serous carcinoma. *Am J Surg Pathol*. 1998;22:1463–1473.
 248. Lax SE, Pizer ES, Ronnett BM, et al. Clear cell carcinoma of the endometrium is characterized by a distinctive profile of p53, Ki-67, estrogen, and progesterone receptor expression. *Hum Pathol*. 1998;29:551–558.
 249. Miller B, Umpierre S, Tornos C, et al. Histologic characterization of uterine papillary serous adenocarcinoma. *Gynecol Oncol*. 1995;56:425–429.
 250. Webb GA, Lagios MD. Clear cell carcinoma of the endometrium. *Am J Obstet Gynecol*. 1987;156:1486–1491.
 251. Tagsjo EB, Rosenberg P, Simonsen E. Primary squamous cell carcinoma of the endometrium. Case report. *Eur J Gynaecol Oncol*. 1993;14:308–310.
 252. Yamashina M, Kobara TY. Primary squamous cell carcinoma with its spindle cell variant in the endometrium. A case report and review of literature. *Cancer*. 1986;57:340–345.
 253. Hachisuga T, Sugimori H, Kaku T, et al. Glassy cell carcinoma of the endometrium. *Gynecol Oncol*. 1990;36:134–138.
 254. Kumar NB, Hart WR. Metastases to the uterine corpus from extravaginal cancers. A clinicopathologic study of 63 cases. *Cancer*. 1982;50:2163.
 255. Piura B, Glezerman M. Synchronous carcinomas of endometrium and ovary. *Gynecol Oncol*. 1989;33:261–264.
 256. Eifel P, Hendrickson M, Ross J, et al. Simultaneous presentation of carcinoma involving the ovary and uterine corpus. *Cancer*. 1982;50:163–170.
 257. Zaino RJ, Whitney C, Brady ME. Simultaneously detected endometrial and ovarian carcinomas: a clinicopathologic study of 74 cases. *Mod Pathol*. 1998;11:118.
 258. Ulbright T, Roth L. Metastatic and independent cancers of the endometrium and ovary. A clinicopathologic study of 34 cases. *Hum Pathol*. 1985;16:28–34.
 259. Gal D, Recio FO, Zamurovic D. The new International Federation of Gynecology and Obstetrics surgical staging and survival rates in early endometrial carcinoma. *Cancer*. 1992;69:200–202.
 260. Wolfson A, Sightler S, Markoe A, et al. The prognostic significance of surgical staging for carcinoma of the endometrium. *Gynecol Oncol*. 1992;45:142–146.
 261. Zaino RJ, Kurman RJ, Diana KL, et al. Pathologic models to predict outcome for women with endometrial adenocarcinoma. *Cancer*. 1996;77:1115–1121.
 262. Randall M, Filiaci V, Muss H, et al. Randomized phase III trial of WART versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a GOG study. *J Clin Oncol*. 2006;24:36–44.
 263. Mariani A, Webb M, Keeney G, et al. Stage IIIC endometrioid corpus cancer includes distinct subgroups. *Gynecol Oncol*. 2002;87:112–117.
 264. Hoekstra AV, Kim RJ, Small W, et al. FIGO stage IIIC endometrial carcinoma: Prognostic factors and outcomes. *Gynecol Oncol*. 2008;114:273–278.
 265. Todo Y, Kato H, Minobe S, et al. A validation study of the new revised FIGO staging system to estimate prognosis for patients with stage IIIC endometrial cancer. *Gynecol Oncol*. 2011;121:126–130.
 266. Werner HMJ, Trovik J, Marcinkiewicz J, et al. Revision of FIGO surgical staging in 2009 for endometrial cancer validates to improve risk stratification. *Gynecol Oncol*. 2012;125:103–108.
 267. Havrilesky LJ, Cragun J, Calingaert B, et al. Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. *Gynecol Oncol*. 2005;99:689–695.
 268. Takeshima N, Umayahara K, Fujiwara K, et al. Effectiveness of postoperative chemotherapy for paraaortic lymph node metastasis of endometrial cancer. *Gynecol Oncol*. 2006;102:214–217.
 269. Sutton GP. The significance of positive peritoneal cytology in endometrial cancer. *Oncology*. 1990;4:21–26.
 270. Kadar N, Homesley H, Malfetano J. Positive peritoneal cytology is an adverse risk factor in endometrial carcinoma only if there is other evidence of extruterine disease. *Gynecol Oncol*. 1992;46:145–149.
 271. Wethington S, Medel NIB, Wright JD, et al. Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: unraveling a mystery. *Gynecol Oncol*. 2009;115:18–25.
 272. Saga Y, Imai M, Joba T, et al. Is peritoneal cytology a prognostic factor of endometrial cancer confined to the uterus. *Gynecol Oncol*. 2006;103:277–280.
 273. Havrilesky L, Cragun J, Calingaert B, et al. The prognostic significance of positive peritoneal cytology and adnexal/serosal metastasis in stage IIIa endometrial cancer. *Gynecol Oncol*. 2007;104:401–405.
 274. Esteller M, Garcia A, Martinez-Palones JM, et al. Clinicopathologic features and genetic alterations in endometrioid carcinoma of the uterus with villoglandular differentiation. *Am J Clin Pathol*. 1999;111:336–342.
 275. Hendrickson M, Martinez A, Ross J, et al. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. *Am J Surg Pathol*. 1982;6:93–108.
 276. Aquino-Parsons C, Lim P, Wong F, et al. Papillary serous and clear cell carcinoma limited to endometrial curetings in FIGO stage 1a and 1b endometrial adenocarcinoma: treatment implications. *Gynecol Oncol*. 1998;71:83–86.
 277. Malpica A, Tornos C, Burke TW, et al. Low-stage clear-cell carcinoma of the endometrium. *Am J Surg Pathol*. 1995;19:769–774.
 278. Havrilesky L, Alvarez Secord A, Bae-Jump V, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. *Gynecol Oncol*. 2007;105:677–682.
 279. Alektiar A, McKee A, Lin O, et al. Is there a difference in outcome between stage I-II endometrial cancer of papillary serous/clear cell and endometrioid FIGO grade 3 cancer? *Int J Radiat Oncol Biol Phys*. 2002;54:79–85.
 280. Huh W, Powell M, Leath C, et al. Uterine papillary serous carcinoma: comparisons of outcomes in surgical stage I patients with and without adjuvant therapy. *Gynecol Oncol*. 2003;91:470–475.
 281. Creasman WT, Kohler M, Odicino F, et al. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the uterus. *Gynecol Oncol*. 2004;95:593–596.

282. Sutton GP, Geiser HE, Stehman FB, et al. Features associated with survival and disease-free survival in early endometrial cancer. *Am J Obstet Gynecol.* 1989;160:1385–1393.
283. Bucy GS, Mendenhall WM, Morgan LS, et al. Clinical stage I and II endometrial carcinoma treated with surgery and/or radiation therapy: analysis of prognostic and treatment-related factors. *Gynecol Oncol.* 1989;33:290.
284. Mariani A, Webb M, Keeney G, et al. Surgical stage I endometrial cancer: predictors of distant failure and death. *Gynecol Oncol.* 2002;87:274–280.
285. Guntupalli S, Zigelheim I, Kizer N, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. *Gynecol Oncol.* 2012;124:31–35.
286. Hanson M, van Nagell J, Powell D. The prognostic significance of lymph-vascular space invasion in stage I endometrial cancer. *Cancer.* 1985;55:1753–1757.
287. Inoue Y, Obata K, Abe K, et al. The prognostic significance of vascular invasion by endometrial carcinoma. *Cancer.* 1996;78:1447–1451.
288. Straughn JM, Huh W, Kelly J, et al. Conservative management of stage I endometrial carcinoma after surgical staging. *Gynecol Oncol.* 2002;84:194–200.
289. Straughn JM, Huh W, Orr J, et al. Stage IC adenocarcinoma of the endometrium: survival comparisons of surgically staged patients with and without adjuvant therapy. *Gynecol Oncol.* 2003;89:295–300.
290. Mariani A, Dowdy S, Keeney G, et al. Predictors of vaginal relapse in stage I endometrial cancer. *Gynecol Oncol.* 2005;97:820–827.
291. Mariani A, Webb M, Keeney G, et al. Endometrial cancer: predictors of peritoneal failure. *Gynecol Oncol.* 2003;89:236–242.
292. Mariani A, Webb M, Keeney G, et al. Predictors of lymphatic failure in endometrial cancer. *Gynecol Oncol.* 2002;84:437–442.
293. Mariani A, Webb M, Rao S, et al. Significance of pathologic patterns of pelvic lymph node metastases in endometrial cancer. *Gynecol Oncol.* 2001;80:113–120.
294. Kauppila A, Kujansuu E, Vihko R. Cytosol estrogen and progesterone receptors in endometrial carcinoma of patients treated with surgery, radiotherapy, and progestin. Clinical correlates. *Cancer.* 1982;50:2157–2162.
295. Macdonald RR, Thorogood J, Mason MK. A randomized trial of progestogens in the primary treatment of endometrial carcinoma. *Br J Obstet Gynaecol.* 1988;95:166–174.
296. Vergote I, Kjaerstad K, Abeler V, et al. A randomized trial of adjuvant progestogen in early endometrial cancer. *Cancer.* 1989;64:1011.
297. von Minckwitz G, Loibl S, Brunnert K, et al. Adjuvant endocrine treatment with medroxyprogesterone acetate or tamoxifen in stage I and II endometrial cancer—a multicentre, open, controlled, prospectively randomised trial. *Eur J Cancer.* 2002;38:2265–2271.
298. Morrow C, Bundy B, Homesley H, et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1990;36:166–171.
299. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs. radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer.* 2006;95(3):266–271.
300. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy vs. cisplatin-based combined chemotherapy in patients with intermediate and high-risk endometrial cancer: a JGOG study. *Gynecol Oncol.* 2008;108:236–233.
301. Creutzberg CL, Nout RA, Marnix L, et al. Fifteen year radiotherapy outcomes for the randomized PORTEC-1 trial for endometrial cancer. *Int J Rad Oncol Biol Phys.* 2011;81:631–638.
302. Nout RA, Putter H, Jürgenliemk-Schulz IM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. *J Clin Oncol.* 2009;27:3547–3556.
303. Nout RA, Putter H, Jürgenliemk-Schulz IM, et al. Five year quality of life of endometrial cancer patients treated in the randomized PORTEC-2 trial and comparison with norm data. *Eur J Cancer.* 2011. [Epub ahead of printing].
304. Lee CM, Szabo A, Shrieve DC, et al. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. *JAMA.* 2006;295(4):389–397.
305. Patel MK, Cote ML, Ali-Fehmi R, et al. Trends in the utilization of adjuvant vaginal cuff brachytherapy and/or external beam radiation treatment in stage I and II endometrial cancer: a surveillance, epidemiology, and end-results study. *Int J Radiat Oncol Biol Phys.* 2011. [Epub ahead of print].
306. Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol.* 1980;56:419–427.
307. Greven KM, D'Agostino RB Jr, Lanciano RM, et al. Is there a role for a brachytherapy vaginal cuff boost in the adjuvant management of patients with uterine-confined endometrial cancer? *Int J Radiat Oncol Biol Phys.* 1998;42:101–104.
308. Randall ME, Wilder J, Greven K, et al. Role of intracavitary cuff boost after adjuvant external irradiation in early endometrial carcinoma. *Int J Radiat Oncol Biol Phys.* 1990;19:49–54.
309. Rush S, Gal D, Potters L, et al. Pelvic control following external beam radiation for surgical stage I endometrial adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 1995;33:851–854.
310. Crosby MA, Tward JD, Szabo A, et al. Does brachytherapy improve survival in addition to external beam radiation therapy in patients with high risk stage I and II endometrial carcinoma? *Am J Clin Oncol.* 2010;33:364–369.
311. Kucera H, Vaura N, Weghouth K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. *Gynecol Oncol.* 1990;38:99–104.
312. Nori D, Merimsky O, Batata M, et al. Postoperative high dose-rate intravaginal brachytherapy combined with external irradiation for early stage endometrial cancer: a long-term follow-up. *Int J Radiat Oncol Biol Phys.* 1994;30:831–837.
313. Horowitz NS, Peters WA 3rd, Smith MR, et al. Adjuvant high dose rate vaginal brachytherapy as treatment of stage I and II endometrial carcinoma. *Obstet Gynecol.* 2002;99:235–240.
314. Anderson JM, Stea B, Hallum AV, et al. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2000;46:417–425.
315. Elliot P, Green D. The efficacy of postoperative vaginal irradiation in preventing vaginal recurrence in endometrial cancer. *Int J Gynecol Cancer.* 1994;4:84.
316. Alektiar KM, McKee A, Venkatraman E, et al. Intravaginal high-dose-rate brachytherapy for stage IB (FIGO grade 1, 2) endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2002;53:707–713.
317. Sorbe B, Staumits A, Karlsson L. Intravaginal high-dose-rate brachytherapy for stage I endometrial cancer: a randomized study of two dose-per-fraction levels. *Int J Radiat Oncol Biol Phys.* 2005;62(5):1385–1389.
318. Narayan K, Khaw P, Bernshaw D, et al. Prognostic significance of lymphovascular space invasion and nodal involvement in intermediate- and high-risk endometrial cancer patients treated with curative intent using surgery and adjuvant radiotherapy. *Int J Gynecol Cancer.* 2012;22:260–266.
319. Alektiar KM, McKee A, Lin O, et al. The significance of the amount of myometrial invasion in patients with stage IB endometrial carcinoma. *Cancer.* 2002;95:316–321.
320. Scholten AN, Creutzberg CL, Noordijk EM, et al. Long-term outcome in endometrial carcinoma favors a two—instead of a three—tiered grading system. *Int J Radiat Oncol Biol Phys.* 2002;52:1067–1074.
321. Solhjem MC, Petersen IA, Haddock MG. Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2005;62(5):1379–1384.
322. Rittenberg PVC, Lotocki RJ, Heywood MS, et al. High-risk surgical stage 1 endometrial cancer: outcomes with vault brachytherapy alone. *Gynecol Oncol.* 2003;89(2):288–294.
323. Weiss MF, Connell PP, Waggoner S, et al. External pelvic radiation therapy in stage IC endometrial carcinoma. *Obstet Gynecol.* 1999;93:599–602.
324. Pitson G, Colgan T, Levin W, et al. Stage II endometrial carcinoma: prognostic factors and risk classification in 170 patients. *Int J Radiat Oncol Biol Phys.* 2002;53:862–867.
325. Fanning J. Long-term survival of intermediate risk endometrial cancer (stage IG3, IC, II) treated with full lymphadenectomy and brachytherapy without teletherapy. *Gynecol Oncol.* 2001;82:371–374.
326. Ng TY, Nicklin JL, Perrin LC, et al. Postoperative vaginal vault brachytherapy for node-negative stage II (occult) endometrial carcinoma. *Gynecol Oncol.* 2001;81:193–195.
327. Rittenberg PVC, Lotocki RJ, Heywood MS, et al. Stage II endometrial carcinoma: limiting post-operative radiotherapy to the vaginal vault in node-negative tumors. *Gynecol Oncol.* 2005;98(3):434–438.
328. Connell PP, Rotmensch J, Waggoner S, et al. The significance of adnexal involvement in endometrial carcinoma. *Gynecol Oncol.* 1999;74:74–79.
329. Ashman JB, Connell PP, Yamada D, et al. Outcome of endometrial carcinoma patients with involvement of the uterine serosa. *Gynecol Oncol.* 2001;82:338–343.
330. Greven K, Corn B, Lanciano RM. Pathologic stage III endometrial carcinoma. *Cancer.* 1993;71:3697.
331. Mariani A, Webb MJ, Keeney GL, et al. Stage IIIC endometrioid corpus cancer includes distinct subgroups. *Gynecol Oncol.* 2002;87:12–17.
332. Rose PG, Cha SD, Tak WK, et al. Radiation therapy for surgically proven paraaortic node metastasis in endometrial carcinoma. *Int J Radiat Oncol Biol Phys.* 1992;24:229–233.
333. Gibbons S, Martinez A, Schary M, et al. Adjuvant whole abdominopelvic irradiation for high-risk endometrial carcinoma. *Int J Radiat Oncol Biol Phys.* 1991;21:1019–1025.

334. Martinez A, Podratz K. Results of whole abdomino-pelvic radiation with nodal boost for patients with endometrial cancer at high risk of failure in the peritoneal cavity. *Hematol Oncol Clin North Am*. 1988;2:431.
335. Sutton G, Axelrod J, Bundy B, et al. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2005;97(3):755–763.
336. Greven K, Winter K, Underhill K, et al. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol*. 2006;103(1):155–159.
337. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2009;112:543–552.
338. Mundt AJ, Murphy KT, Rotmensch J, et al. Surgery and postoperative radiation therapy in FIGO stage IIIC endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2001;50:1154–1160.
339. Mundt AJ, McBride R, Rotmensch J, et al. Significant pelvic recurrence in high risk pathologic stage I–IV endometrial carcinoma patients after chemotherapy alone: implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys*. 2001;50:1145–1153.
340. Milosevic MF, Dembo AJ, Thomas GM. The clinical significance of malignant peritoneal cytology in stage I endometrial carcinoma. *Int J Gynecol Cancer*. 1992;2:225–235.
341. Soper JT, Creasman WT, Clarke-Pearson DL, et al. Intraperitoneal chronic phosphate ^{32}P suspension therapy of malignant peritoneal cytology in endometrial carcinoma. *Am J Obstet Gynecol*. 1985;153:191–196.
342. Eltabbakh GH, Piver MS, Hempling RE, et al. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. *Int J Radiat Oncol Biol Phys*. 1997;38:373–380.
343. Nag S, Erickson B, Parikh S, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. *Int J Radiat Oncol Biol Phys*. 2000;48:779–790.
344. Rouanet P, Dubois JB, Gely S, et al. Exclusive radiation therapy in endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 1993;26:223–228.
345. Grigsby P, Kuske R, Perez CA, et al. Medically inoperable stage I adenocarcinoma of the endometrium treated with radiotherapy alone. *Int J Radiat Oncol Biol Phys*. 1986;13:483.
346. Nguyen TV, Peteret DG. High-dose-rate brachytherapy for medically inoperable stage I endometrial cancer. *Gynecol Oncol*. 1995;59:370–375.
347. Niazi TM, Souhami L, Portelance L, et al. Long term results of high dose rate brachytherapy in the primary treatment of medically inoperable stage I–II endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2005;63:1108–1113.
348. Fishman DA, Roberts KB, Chambers JT, et al. Radiation therapy as exclusive treatment for medically inoperable patients with stage I and II endometrioid carcinoma with endometrium. *Gynecol Oncol*. 1996;61(2):189–196.
349. Kucera H, Kucera TH, Kucera E, et al. Treatment of endometrial carcinoma with high-dose-rate brachytherapy alone in medically inoperable stage I patients. *Acta Obstet Gynecol Scand*. 1998;77:1008–1012.
350. Nicklin JL, Petersen RW. Stage 3B adenocarcinoma of the endometrium: a clinicopathologic study. *Gynecol Oncol*. 2000;78:203–207.
351. Choo JJ, Scudiere J, Bitterman P, et al. Vaginal lymphatic channel location and its implication for intracavitary brachytherapy radiation treatment. *Brachytherapy*. 2005;4:236–240.
352. Small W Jr, Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy*. 2012;1:58–67.
353. Ghosh K, Padilla LA, Murray KP, et al. Using a belly board device to reduce the small bowel volume within pelvic radiation fields in women with postoperatively treated cervical carcinoma. *Gynecol Oncol*. 2001;83:271–275.
354. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2002;52(5):1330–1337.
355. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys*. 2003;56(5):1354–1360.
356. Roeske JC, Lujan A, Rotmensch J, et al. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2000;48:1613–1621.
357. Lujan AE, Mundt AJ, Roeske JC, et al. Intensity-modulated radiotherapy as a means of reducing dose to bone marrow in gynecologic patients receiving whole pelvic radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003;57:516–521.
358. Buchali A, Koswig S, Dinges S, et al. Impact of the filling status of the bladder and rectum on their integral dose distribution and the movement of the uterus in the treatment planning of gynaecological cancer. *Radiother Oncol*. 1999;52:29–34.
359. Huh, SJ, Park W, Han Y. Interfractional variation in position of the uterus during radical radiotherapy for cervical cancer. *Radiother Oncol*. 2004;71:73–79.
360. Salama JK, Mundt AJ, Roeske J, et al. Preliminary outcome and toxicity report of extended-field, intensity-modulated radiation therapy for gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2006;65:1170–1176.
361. Wylie J, Irwin C, Pintilie M, et al. Results of radical radiotherapy for recurrent endometrial cancer. *Gynecol Oncol*. 2000;77:66–72.
362. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. *Gynecol Oncol*. 2003;89:201–209.
363. Jhingran A, Burke TW, Eifel PJ, et al. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. *Int J Radiat Oncol Biol Phys*. 2003;56:1366–1372.
364. Podratz KC, O'Brien PC, Malkasian GD Jr, et al. Effects of progestational agents in treatment of endometrial carcinoma. *Obstet Gynecol*. 1985;66:106–110.
365. Asbury RF, Brunetto VL, Lee RB, et al. Goserelin acetate as treatment for recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Am J Clin Oncol*. 2002;25:557–560.
366. McMeekin DS, Gordon A, Fowler J, et al. A phase II trial of arzoxifene, a selective estrogen response modulator, in patients with recurrent or advanced endometrial cancer. *Gynecol Oncol*. 2003;90:64–69.
367. Piver MS, Barlow JJ, Lurain JR, et al. Medroxyprogesterone acetate (Depo-Provera) vs. hydroxyprogesterone caproate (Delalutin) in women with metastatic endometrial adenocarcinoma. *Cancer*. 1980;45:268–272.
368. Rose PG, Brunetto VL, VanLe L, et al. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2000;78(2):212–216.
369. Thigpen T, Brady MF, Homesley HD, et al. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2001;19:364–367.
370. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Oncol*. 1999;17:1736–1744.
371. Pandya KJ, Yeap BY, Weiner LM, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group study (E4882). *Am J Clin Oncol*. 2001;24:43–46.
- 371a. Lentz SS, Brady MF, Major FJ, et al. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 1996;14:357–361.
372. Satyaswaroop PG, Clarke CL, Zaino RJ, et al. Apparent resistance in human endometrial carcinoma during combination treatment with tamoxifen and progesterin may result from desensitization following down-regulation of tumor progesterone receptor. *Cancer Lett*. 1992;62:107–114.
373. Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;92:10–14.
374. Whitney C, Brunetto V, Zaino R, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;92:4–9.
375. Geisinger K, Homesley H, Morgan T, et al. Endometrial adenocarcinoma. A multiparameter clinicopathologic analysis including the DNA profile and the sex steroid hormone receptors. *Cancer*. 1986;58:1518–1525.
376. Kauppila A. Oestrogen and progesterone receptors as prognostic indicators in endometrial cancer. A review of the literature. *Acta Oncol*. 1989;28:561–566.
377. Bonte J, Decoster JM, Ide P. Vaginal cytologic evaluation as a practical link between hormone blood levels and tumor hormone dependency in exclusive medroxyprogesterone treatment of recurrent or metastatic endometrial adenocarcinoma. *Acta Cytol*. 1977;21:218–224.
378. Stratton JA, Mannel RS, Rettenmaier MA, et al. Treatment of advanced and recurrent endometrial carcinoma: correlation of patient response to hormonal and cytotoxic chemotherapy and the response predicted by the subrenal capsule chemosensitivity assay. *Gynecol Oncol*. 1989;32:55–59.
379. Zaino RJ, Satyaswaroop PG, Mortel R. Hormonal therapy of human endometrial adenocarcinoma in a nude mouse model. *Cancer Res*. 1985;45:539–541.
380. Gallagher CJ, Oliver RT, Oram DH, et al. A new treatment for endometrial cancer with gonadotropin releasing-hormone analogue. *Br J Obstet Gynaecol*. 1991;98:1037.
381. De Vriese G, Bonte J. Possible role of goserelin, an LH-RH agonist, in the treatment of gynaecologic

- cological cancers. *Eur J Gynaecol Oncol*. 1993; 14:187–191.
382. Kleinman D, Douvdevani A, Schally AV, et al. Direct growth inhibition of human endometrial cancer cells by the gonadotropin-releasing hormone antagonist SB-75: role of apoptosis. *Am J Obstet Gynecol*. 1994;170:96–102.
 383. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. *Eur J Cancer*. 2010;46(13): 2422–2431.
 384. Campora E, Vidali A, Mammoliti S, et al. Treatment of advanced or recurrent adenocarcinoma of the endometrium with doxorubicin and cyclophosphamide. *Eur J Gynaecol Oncol*. 1990; 11(3):181–183.
 385. Muggia FM, Chia G, Reed LJ, et al. Doxorubicin-cyclophosphamide: effective chemotherapy for advanced endometrial adenocarcinoma. *Am J Obstet Gynecol*. 1977;128(3):314–319.
 386. Seski JC, Edwards CL, Gershenson DM, et al. Doxorubicin and cyclophosphamide chemotherapy for disseminated endometrial cancer. *Obstet Gynecol*. 1981;58(1):88–91.
 387. Edmonson JH, Krook JE, Hilton JF, et al. Randomized phase II studies of cisplatin and a combination of cyclophosphamide-doxorubicin-cisplatin (CAP) in patients with progestin-refractory advanced endometrial carcinoma. *Gynecol Oncol*. 1987; 28(1):20–24.
 388. Burke TW, Stringer CA, Morris M, et al. Prospective treatment of advanced or recurrent endometrial carcinoma with cisplatin, doxorubicin, and cyclophosphamide. *Gynecol Oncol*. 1991; 40(3):264–267.
 389. Dunton CJ, Pfeifer SM, Braitman LE, et al. Treatment of advanced and recurrent endometrial cancer with cisplatin, doxorubicin, and cyclophosphamide. *Gynecol Oncol*. 1991;41(2):113–116.
 390. Hancock KC, Freedman RS, Edwards CL, et al. Use of cisplatin, doxorubicin, and cyclophosphamide to treat advanced and recurrent adenocarcinoma of the endometrium. *Cancer Treat Rep*. 1986;70(6):789–791.
 391. Barrett RJ, Blessing JA, Homesley HD, et al. Circadian-timed combination doxorubicin-cisplatin chemotherapy for advanced endometrial carcinoma. A phase II study of the Gynecologic Oncology Group. *Am J Clin Oncol*. 1993; 16(6):494–496.
 392. Pasmantier MW, Coleman M, Silver RT, et al. Treatment of advanced endometrial carcinoma with doxorubicin and cisplatin: effects on both untreated and previously treated patients. *Cancer Treat Rep*. 1985;69(5):539–542.
 393. Seltzer V, Vogl SE, Kaplan BH. Adriamycin and cis-diamminedichloroplatinum in the treatment of metastatic endometrial adenocarcinoma. *Gynecol Oncol*. 1984;19(3):308–313.
 394. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. *J Clin Oncol*. 2004;22(19):3902–3908.
 395. Trope C, Johnsson JE, Simonsen E, et al. Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. *Am J Obstet Gynecol*. 1984;149(4):379–381.
 396. Ball HG, Blessing JA, Lentz SS, et al. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996;62(2):278–281.
 397. Gunthert AR, Ackermann S, Beckmann MW, et al. Phase II study of weekly docetaxel in patients with recurrent or metastatic endometrial cancer: AGO Uterus-4. *Gynecol Oncol*. 2007;104(1):86–90.
 398. Lincoln S, Blessing JA, Lee RB, et al. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2003;88(3):277–281.
 399. Fleming GF, Filiaci VL, Bentley RC, et al. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. *Ann Oncol*. 2004;15(8):1173–1178.
 400. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2004;22(11): 2159–2166.
 401. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol*. 2001; 19(20):4048–4053.
 402. Sovak MA, Dupont J, Hensley ML, et al. Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. *Int J Gynecol Cancer*. 2007;17(1):197–203.
 403. Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;125: 771–773.
 404. Secord AA, Havrilesky LJ, O'Malley DM, et al. A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer. *Gynecol Oncol*. 2009;114(3):442–447.
 405. Thigpen JT, Blessing JA, Lagasse LD, et al. Phase II trial of cisplatin as second-line chemotherapy in patients with advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group study. *Am J Clin Oncol*. 1984;7(3):253–256.
 406. Deppe G, Cohen CJ, Bruckner HW. Treatment of advanced endometrial adenocarcinoma with cis-dichlorodiammine platinum (II) after intensive prior therapy. *Gynecol Oncol*. 1980;10(1):51–54.
 407. Seski JC, Edwards CL, Herson J, et al. Cisplatin chemotherapy for disseminated endometrial cancer. *Obstet Gynecol*. 1982;59(2):225–228.
 408. Thigpen JT, Blessing JA, Homesley H, et al. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 1989;33(1):68–70.
 409. Green JB 3rd, Green S, Alberts DS, et al. Carboplatin therapy in advanced endometrial cancer. *Obstet Gynecol*. 1990;75(4):696–700.
 410. Long HJ, Pfeifle DM, Wieand HS, et al. Phase II evaluation of carboplatin in advanced endometrial carcinoma. *J Natl Cancer Inst*. 1988;80(4): 276–278.
 411. Horton J, Begg CB, Arseneault J, et al. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. *Cancer Treat Rep*. 1978;62(1):159–161.
 412. Thigpen JT, Buchsbaum HJ, Mangan C, et al. Phase II trial of adriamycin in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Cancer Treat Rep*. 1979;63(1):21–27.
 413. Calero F, Asins-Codoñer E, Jimeno J, et al. Epirubicin in advanced endometrial adenocarcinoma: a phase II study of the Grupo Ginecologico Espanol para el Tratamiento Oncologico (GGETO). *Eur J Cancer*. 1991;27(7):864–866.
 414. Muggia FM, Blessing JA, Sorosky J, et al. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2002;20(9):2360–2364.
 415. Escobar PF, Markman M, Zanotti K, et al. Phase 2 trial of pegylated liposomal doxorubicin in advanced endometrial cancer. *J Cancer Res Clin Oncol*. 2003;129(11):651–654.
 416. Muss HB, Blessing JA, Hatch KD, et al. Methotrexate in advanced endometrial carcinoma. A phase II trial of the Gynecologic Oncology Group. *Am J Clin Oncol*. 1990;13(1):61–63.
 417. Dvorak O. Cytembena treatment of advanced gynaecological carcinomas. *Neoplasma*. 1971; 18(5):461–464.
 418. Broun GO, Blessing JA, Eddy GL, et al. A phase II trial of vincristine in advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group Study. *Am J Clin Oncol*. 1993;16(1):18–21.
 419. Woo HL, Swenerton KD, Hoskins PJ. Taxol is active in platinum-resistant endometrial adenocarcinoma. *Am J Clin Oncol*. 1996;19(3):290–291.
 420. Wadler S, Levy DE, Lincoln ST, et al. Topotecan is an active agent in the first-line treatment of metastatic or recurrent endometrial carcinoma: Eastern Cooperative Oncology Group Study E3E93. *J Clin Oncol*. 2003;21(11):2110–2114.
 421. Traina TA, et al. Weekly topotecan for recurrent endometrial cancer: a case series and review of the literature. *Gynecol Oncol*. 2004;95(1):235–241.
 422. Dizon DS, Blessing JA, McMeekin DS, et al. Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: gynecologic oncology group trial 129-P. *J Clin Oncol*. 2009;27(19):3104–3108.
 423. Alberts DS, Mason NL, O'Toole RV, et al. Doxorubicin-cisplatin-vinblastine combination chemotherapy of advanced endometrial carcinoma: a Southwest Oncology Group Study. *Gynecol Oncol*. 1987;26(2):193–201.
 424. Long HJ 3rd, Langdon RM Jr, Cha SS, et al. Phase II trial of methotrexate, vinblastine, doxorubicin, and cisplatin in advanced/recurrent endometrial carcinoma. *Gynecol Oncol*. 1995; 58(2):240–243.
 425. Carbone PP, Carter SK. Endometrial cancer: approach to development of effective chemotherapy. *Gynecol Oncol*. 1974;2(2–3):348–353.
 426. Barton C, Buxton EJ, Blachledge G, et al. A phase II study of ifosfamide in endometrial cancer. *Cancer Chemother Pharmacol*. 1990;26(Suppl):S4.
 427. Sutton GP, Blessing JA, Homesley HD, et al. Phase II study of ifosfamide and mesna in refractory adenocarcinoma of the endometrium. A Gynecologic Oncology Group study. *Cancer*. 1994;73(5):1453–1455.
 428. Seski JC, Edwards CL, Copeland LJ, et al. Hexamethylmelamine chemotherapy for disseminated endometrial cancer. *Obstet Gynecol*. 1981;58(3):361–363.
 429. Chauvergne J, Fumoleau P, Cappelaere P, et al. Phase II study of pirarubicin (THP) in patients with cervical, endometrial and ovarian cancer: study of the Clinical Screening Group of the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer*. 1993; 29A(3):350–354.
 430. Boadle DJ, Tattersall MH. Phase II study of mitoxantrone in advanced or metastatic endometrial carcinoma. *Aust N Z J Obstet Gynaecol*. 1987;27(4):341–342.
 431. Hilgers RD, Von Hoff DD, Stephens RL, et al. Mitoxantrone in adenocarcinoma of the endometrium: a Southwest Oncology Group Study. *Cancer Treat Rep*. 1985;69(11):1329–1330.
 432. Muss HB, Bundy BN, DiSaia PJ, et al. Mitoxantrone for carcinoma of the endometrium:

- a phase II trial of the Gynecologic Oncology Group. *Cancer Treat Rep.* 1987;71(2):217–218.
433. Thigpen JT, Kronmal R, Vogel S, et al. A phase II trial of vinblastine in patients with advanced or recurrent endometrial carcinoma. A Southwest Oncology Group Study. *Am J Clin Oncol.* 1987; 10(5):429–431.
 434. Slayton RE, Blessing JA, Delgado G. Phase II trial of etoposide in the management of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *Cancer Treat Rep.* 1982;66(8):1669–1671.
 435. Muss HB, Bundy BN, Adcock L. Teniposide (VM-26) in patients with advanced endometrial carcinoma. A phase II trial of the Gynecologic Oncology Group. *Am J Clin Oncol.* 1991;14(1):36–37.
 436. Westin SN, Broaddus RR. Personalized therapy in endometrial cancer: Challenges and opportunities. *Cancer Biol Ther.* 2012;13(1):1–13.
 437. Yeramian A, Moreno-Bueno G, Dolcet X, et al. Endometrial carcinoma: molecular alterations involved in tumor development and progression. *Oncogene.* 2012.
 438. Naumann W. The role of the phosphatidylinositol 3-kinase (PI3K) pathway in the development and treatment of uterine cancer. *Gynecol Oncol.* 2011;123:411–420.
 439. Sansal I, Sellers W. The biology and clinical relevance of the *PTEN* tumor suppressor pathway. *J Clin Oncol.* 2004;22:2954–2963.
 440. Maxwell GL, Risinger JI, Gumbs C, et al. Mutation of the *PTEN* tumor suppressor gene in endometrial hyperplasias. *Cancer Res.* 1998;58:2500–2503.
 441. Peiffer SL, Herzog TJ, Tribune DJ, et al. Allelic loss of sequences from the long arm of chromosome 10 and replication errors in endometrial cancers. *Cancer Res.* 1995;55:1922–1926.
 442. Kong D, Suzuki A, Zou TT, et al. *PTEN1* is frequently mutated in primary endometrial carcinomas. *Nat Genet.* 1997;17:143–144.
 443. Tashiro H, Blazes MS, Wu R, et al. Mutations in *PTEN* are frequent in endometrial carcinoma but rare in other gynecological malignancies. *Cancer Res.* 1997;57:3935–3940.
 444. Meric-Bernstam F, Gonzalez-Angulo. Targeting the mTOR signaling network for cancer therapy. *J Clin Oncol.* 2009;27(13):2278–2287.
 445. Slomovitz BM, Wu W, Broaddus RR, et al. mTOR inhibition is a rational target for the treatment of endometrial cancer. *Proc Am Soc Clin Oncol.* 2004;22 [abstract 5076].
 446. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. *Nat Rev Cancer.* 2009;9(8):550–562.
 447. Dancy JE. Clinical development of mammalian target of rapamycin inhibitors. *Hematol Oncol Clin North Am.* 2002;16(5):1101–1114.
 448. Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol.* 2011;29(24):3278–3285.
 449. Kollmannsberger C, Hirte H, Siu LL, et al. Temsirolimus in combination with carboplatin and paclitaxel in patients with advanced solid tumors: a NCIC-CTG, phase I, open-label dose-escalation study (IND 179). *Ann Oncol.* 2012;23(1):238–244.
 450. Fleming GF, Filiaci VL, Hanjani P, et al. Hormone therapy plus temsirolimus for endometrial carcinoma (EC): gynecologic oncology group trial #248. *J Clin Oncol.* 2011;29(Suppl: abstr 5014).
 451. Colombo N, McMeekin, Schwartz J, et al. A phase II trial of the mTOR inhibitor AP23573 as a single agent in advanced endometrial cancer. *Proc Am Soc Clin Oncol.* 2007;25 [abstract 5516].
 452. Mackay H, Welch S, Tsao MS, et al. Phase II study of oral ridaforolimus in patients with metastatic and/or locally advanced recurrent endometrial cancer: NCIC CTG IND 192. *J Clin Oncol.* 2011;29(Suppl: abstr 5013).
 453. Oza AM, Poveda A, Clamp AR, et al. A randomized phase II (RP2) trial of ridaforolimus (R) compared with progestin (P) or chemotherapy (C) in female adult patients with advanced endometrial carcinoma. *J Clin Oncol.* 2011;29(Suppl: abstr 5009).
 454. Slomovitz BM, Lu KH, Johnston T, et al. A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. *Cancer.* 2010;116(23):5415–5419.
 455. Meyer PN, Slomovitz B, Djordjevic B, et al. The search continues: looking for predictive biomarkers for response mTOR inhibition in endometrial cancer. *J Clin Oncol.* 2011;29(Suppl: abstr 5016).
 456. Slomovitz BM, Brown J, Johnston TA, et al. A phase II study of everolimus and letrozole in patients with recurrent endometrial cancer. *J Clin Oncol.* 2011;29(Suppl: abstr 5012).
 457. Jiricny J. The multifaceted mismatch repair system. *Nat Rev Mol Cell Biol.* 2006;7:335–346.
 458. MacDonald ND, Salvesen HB, Ryan A, et al. Frequency and prognostic impact of microsatellite instability in a large population based study of endometrial carcinomas. *Cancer Res.* 2000; 60:1750–1752.
 459. Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet.* 1977;6:105–110.
 460. Black D, Soslow R, Levine D, et al. Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma. *J Clin Oncol.* 2006;24:1745–1753.
 461. Caduff RF, Johnston CM, Svoboda-Newman SM, et al. Clinical and pathological significance of microsatellite instability in sporadic endometrial carcinoma. *Am J Pathol.* 1996;148:1671–1678.
 462. Peltomäki P. Role of DNA mismatch repair defects in the pathogenesis of human cancer. *J Clin Oncol.* 2003;21:1174–1179.
 463. Gurin CC, Federici MG, Kang L, et al. Causes and consequences of microsatellite instability in endometrial carcinoma. *Cancer Res.* 1999; 59:462–466.
 464. Baylin SB, Herman JG, Graff JR, et al. Alterations in DNA methylation: a fundamental aspect of neoplasia. *Adv Cancer Res.* 1998;72:141–196.
 465. Resnick K, Frankel W, Morrison C, et al. Mismatch repair status and outcomes after adjuvant therapy in patients with surgically staged endometrial cancer. *Gynecol Oncol.* 2010;117:234–238.
 466. Moll UM, Chalas E, Auguste M, et al. Uterine papillary serous carcinoma evolves via a p53 driven pathway. *Hum Pathol.* 1996;27:1295–1300.
 467. Tashiro H, Isacson C, Levine R, et al. p53 mutations are common in uterine serous carcinoma and occur as an early event in their pathogenesis. *Am J Pathol.* 1997;150:177–185.
 468. Tashiro H, Isacson C, Levine R, et al. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. *Am J Pathol.* 1997;150:177–185.
 469. Lundgren C, Auer G, Frankendal B, et al. Nuclear DNA content, proliferative activity, and p53 expression related to clinical and histopathologic features in endometrial carcinoma. *Int J Gynecol Cancer.* 2002;12:110–118.
 470. Lax SF, Kendall B, Tashiro H, et al. The frequency of p53, K-ras mutation and microsatellite instability differs in uterine endometrioid and serous carcinoma. *Cancer.* 2000;88:814–824.
 471. De Luca A, Carotenuto A, Rachiglio A, et al. The role of the EGFR signaling in tumor microenvironment. *J Cell Physiol.* 2008;214(3): 559–567.
 472. Mendelsohn J. Targeting the epidermal growth factor receptor for cancer therapy. *J Clin Oncol.* 2002;20(suppl. 18):1S–13S.
 473. Khalifa MA, Mannel RS, Haraway SD, et al. Expression of EGFR, HER-2/neu, p53, and PCNA in endometrioid, serous papillary, and clear cell endometrial adenocarcinomas. *Gynecol Oncol.* 1994;53:84–92.
 474. Takahashi K, Saga Y, Mizukami H, et al. Cetuximab inhibits growth, peritoneal dissemination, and lymph node and lung metastasis of endometrial cancer, and prolongs host survival. *Int J Oncol.* 2009;35(4):725–729.
 475. Samarathai N, Hall K, Yeh IT. Molecular profiling of endometrial malignancies. *Obstet Gynecol Int.* 2010;2010:162363.
 476. Berchuck A, Rodriguez G, Kinney R, et al. Overexpression of HER-2/neu in endometrial cancer is associated with advanced stage disease. *Am J Obstet Gynecol.* 1991;164:15–21.
 477. Rolitsky C, Theil K, McGaughey V, et al. HER-2/neu amplification and overexpression in endometrial carcinoma. *Int J Gynecol Pathol.* 1999; 18:138–143.
 478. Santin A, Bellone S, Van Stedum S, et al. Determination of HER2/neu status in uterine serous papillary carcinoma: Comparative analysis of immunohistochemistry and fluorescence *in situ* hybridization. *Gynecol Oncol.* 2005;98:24–30.
 479. Slomovitz B, Broaddus RR, Burke TW, et al. Her-2/neu overexpression and amplification in uterine papillary serous carcinoma. *J Clin Oncol.* 2004;22:3126–3132.
 480. Kohler MF, Carney P, Dodge R, et al. p53 overexpression in advanced-stage endometrial adenocarcinoma. *Am J Obstet Gynecol.* 1996; 175:1246–1252.
 481. Backe J, Gassel AM, Krebs S, et al. Immunohistochemically detected HER-2/neu—expression and prognosis in endometrial carcinoma. *Arch Gynecol Obstet.* 1997;259:189–195.
 482. Morrison C, Zanagnolo V, Ramirez N, et al. HER-2 is an independent prognostic factor in endometrial cancer: association with outcome in a large cohort of surgically staged patients. *J Clin Oncol.* 2006;24:2376–2385.
 483. Fleming GF, Sill MW, Darcy KM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010;116(1):15–20.
 484. Oza AM, Eisenhauer EA, Elit L, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol.* 2008;26(26):4319–4325.
 485. Leslie KK, Sill M, Darcy KM, et al. Efficacy and safety of gefitinib and potential prognostic value of soluble EGFR, EGFR mutations, and tumor markers in Gynecologic Oncology Group phase II trial of persistent of recurrent endometrial cancer. *J Clin Oncol.* 2009;27(suppl. 15S):A-e16542.
 486. Caduff RF, Johnston CM, Frank TS. Mutations of the K-ras oncogene in carcinoma of the endometrium. *Am J Pathol.* 1995;146:182–188.
 487. Ito K, Watanabe K, Nasim S, et al. K-ras point mutations in endometrial carcinoma: effect on outcome is dependent on age of patient. *Gynecol Oncol.* 1996;63:238–246.

488. Courteny KD, Cocoran RB, Engleman JA. The PI3K pathway as a drug target in human cancer. *J Clin Oncol*. 2010;28:1075–1083.
489. Wang LE, Ma H, Hale KS, et al. Roles of genetic variants in the PI3K and RAS/RAF pathways in susceptibility to endometrial cancer and clinical outcomes. *J Cancer Res Clin Oncol*. 2012; 138(3):377–385.
490. Ramjaun AR, Downward J. Ras and phosphoinositide 3-kinase: partners in development and tumorigenesis. *Cell Cycle*. 2007;6(23): 2902–2905.
491. Stefansson IM, Salvesen HB, Akslen LA. Vascular proliferation is important for clinical progress of endometrial cancer. *Cancer Res*. 2006;66(6):3303–3309.
492. Kamat AA, Merritt WM, Coffey D, et al. Clinical and biological significance of vascular endothelial growth factor in endometrial cancer. *Clin Cancer Res*. 2007;13(24):7487–7495.
493. Gehrig PA, Bae-Jump VL. Promising novel therapies for the treatment of endometrial cancer. *Gynecol Oncol*. 2010;116(2):187–194.
494. Aghajanian C, Sill MW, Kathleen M, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2011; 29(16):2259–2265.
495. Nimeiri HS, Oza AM, Morgan RJ, et al. A phase II study of sorafenib in advanced uterine carcinoma/ carcinosarcoma: a trial of the Chicago, PMH, and California Phase II Consortia. *Gynecol Oncol*. 2010;117(1):37–40.
496. McMeekin DS, Sill MW, Benbrook D, et al. A phase II trial of thalidomide in patients with refractory endometrial cancer and correlation with angiogenesis biomarkers: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2007; 105(2):508–516.
497. Session DR, Kalli KR, Tummon IS, et al. Treatment of atypical endometrial hyperplasia with an insulin-sensitizing agent. *Gynecol Endocrinol*. 2003;17(5):405–407.
498. Soliman PT, Wu D, Tortolero-Luna G, et al. Association between adiponectin, insulin resistance, and endometrial cancer. *Cancer*. 2006; 106(11):2376–2381.
499. Chia VM, Newcomb PA, Trentham-dietz A, et al. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. *Int J Gynecol Cancer*. 2007;17(2):441–446.
500. Cantrell LA, Zhou C, Mendivil A, et al. Metformin is a potent inhibitor of endometrial cancer cell proliferation—implications for a novel treatment strategy. *Gynecol Oncol*. 2010;116(1):92–98.
501. Evans JM, Donnelly LA, Emslie-Smith AM, et al. Metformin and reduced risk of cancer in diabetic patients. *BMJ*. 2005;330(7503):1304–1305.
502. Tan BK, Adya R, Chen J, et al. Metformin treatment exerts anti invasive and antimetastatic effects in human endometrial carcinoma cells. *J Clin Endocrinol Metab*. 2011;96(3):808–816.
503. Zakikhani M, Dowling R, Fantus IG, et al. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. *Cancer Res*. 2006;66(21):10269–10273.
504. Zakikhani M, Dowling RJ, Sonenberg N, et al. The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. *Cancer Prev Res (Phila Pa)*. 2008;1(5):369–375.
505. Hanna RK, Zhou C, Malloy KM, et al. Metformin potentiates the effects of paclitaxel in endometrial cancer cells through inhibition of cell proliferation and modulation of the mTOR pathway. *Gynecol Oncol*. 2012.
506. Javle M, Curtin NJ. The role of PARP in DNA repair and its therapeutic exploitation. *Br J Cancer*. 2011;105(8):1114–1122.
507. Mendes-Pereira AM, et al. Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. *EMBO Mol Med*. 2009;1(6–7):315–322.
508. Dedes KJ, Wetterskog D, Mendes-Pereira AM, et al. PTEN deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors. *Sci Transl Med*. 2010;2(53):53ra75.
509. Forster MD, Wetterskog D, Mendes-Pereira AM, et al. Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer. *Nat Rev Clin Oncol*. 2011;8(5):302–306.
510. Zanolini KM, Belinson JL, Kennedy AW, et al. The use of paclitaxel and platinum-based chemotherapy in uterine papillary serous carcinoma. *Gynecol Oncol*. 1999;74:272–277.
511. Ramondetta L, Burke TW, Levenback C, et al. Treatment of uterine papillary serous carcinoma with paclitaxel. *Gynecol Oncol*. 2001;82: 156–161.
512. Gehrig PA. Uterine papillary serous carcinoma: a review. *Expert Opin Pharmacother*. 2007;8: 809–816.
513. Low JS, Wong EH, Tan HS, et al. Adjuvant sequential chemotherapy and radiotherapy in uterine papillary serous carcinoma. *Gynecol Oncol*. 2005;97:171–177.
514. Kelly MG, O'Malley DM, Hui P, et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. *Gynecol Oncol*. 2005;98(3):353–359.
515. Boruta DM, Gehrig PA, Nickles Fader A, et al. Management of women with uterine serous cancer: a Society of Gynecologic Oncology review. *Gynecol Oncol*. 2009;115:142–153.
516. Olawaiye AB, Boruta DM. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology review. *Gynecol Oncol*. 2009;113:277–283.
517. Thigpen JT, Blessing JA, DiSaia PJ et al. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 1994;12:1408.
518. Lee JW, Stone RL, Lee SJ et al. EphA2 targeted chemotherapy using an antibody drug conjugate in endometrial carcinoma. *Clin Cancer Res*. 2010;16(9):2562–2570.
519. Annunziata CM, Kohn EC, Lorusso P et al. Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors. *Invest New Drugs*. 2013;31(1):77–84.
520. Miller DS, Blessing JA, Drake RD et al. A phase II evaluation of pemetrexed (Alimta, LY231514, IND #40061) in the treatment of recurrent or persistent endometrial carcinoma: a phase II study of the Gynecologic Oncology. *Gynecol Oncol*. 2009;115(3):443–446.
521. Byron SA, Gartside MG, Wellens CL et al. Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation. *Cancer Res*. 2008;68(17):6902–6907.
522. Katoh M. FGFR2 abnormalities underlie a spectrum of bone, skin, and cancer pathologies. *J Invest Dermatol*. 2009;129(8):1861–1867.

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Mesenchymal tumors of the uterine corpus are rare, accounting for approximately 7% to 8% of all uterine cancers (1). The outcomes of many of these tumors seem to be less favorable than many of the more common uterine carcinomas. However, outcomes do vary significantly based on the specific histology. This is a group of tumors felt to arise from the mesenchymatous portion of the uterine corpus and often considered as uterine “sarcomas.” The World Health Organization (WHO) classification of mesenchymal uterine corpus tumors is summarized in Table 23.1 (2). Uterine carcinosarcomas are probably not best classified as a uterine sarcoma or mesenchymal tumor any longer, but rather should be classified as a metaplastic carcinoma of the uterus (3). However, uterine carcinosarcomas will be described in this chapter. A key concept of uterine sarcomas is that they are truly heterogeneous tumors with vastly different clinical presentations, responses to therapy, and outcomes. Much of the available literature, until more recently, is extremely limited by lumping all uterine sarcomas into one cohort.

EPIDEMIOLOGY AND RISK FACTORS

Histologic Distribution

Histopathologic criteria for uterine sarcomas have greatly evolved over the last few years and, therefore, histologic distribution may have shifted. Many series do not include or specify sarcoma subtypes and many are very small in number. Combining series with at least 100 cases including carcinosarcomas, the most common uterine sarcomas are leiomyosarcoma and carcinosarcoma (4–9) (Fig. 23.1A). Leiomyosarcomas account for over two-thirds of uterine sarcomas when excluding carcinosarcomas (4–10) (Fig. 23.1B). Endometrial stromal sarcomas (ESSs) account for approximately 25% of true uterine sarcomas with all of the other subtypes being exceedingly rare and accounting for <10% as a whole (4–10) (Fig. 23.1B). ESSs are by definition now considered all “low-grade.” Undifferentiated uterine sarcoma is now the preferred terminology for what was previously called “high-grade” ESSs. Therefore, endometrial stromal sarcoma information in this chapter primarily refers to these “low-grade” lesions. Abeler and colleagues have the most recent and largest series of uterine sarcomas ($n = 419$) from the Norwegian Cancer Registry, in which histologic subtype distribution was described (10). This series excluded carcinosarcomas altogether. Of these 419 sarcomas, 62% were leiomyosarcomas, 20% were ESSs, and 18% were various other subtypes that included undifferentiated sarcomas (6%), adenosarcomas (5.5%), sarcoma, not otherwise specified (NOS) (4.5%), rhabdomyosarcoma (<1%), giant-cell sarcoma (<1%), and perivascular epithelioid cell tumors (PEComa; <1%) (10).

Age Distribution

Patients with carcinosarcomas and adenosarcomas tend to be older at the time of diagnosis compared to those with leiomyosarcomas and ESSs. The mean/median ages reported among published series range from 42 to 51 years for ESSs (4,5,9,10–15), 48 to 57 years for leiomyosarcomas (4,5,9,10,16–18), 57 to 67 years for carcinosarcomas (4,5,9,19,20), 58 to 66 years for adenosarcomas (10,21), and 46 years for undifferentiated sarcomas (11). Subsequently, many patients with carcinosarcomas are postmenopausal at the time of diagnosis, whereas patients with leiomyosarcoma, endometrial stromal sarcoma, or undifferentiated sarcomas may be pre- or perimenopausal at the time of diagnosis. Additionally, the mean age for patients diagnosed with smooth muscle tumors of uncertain malignant potential (STUMP) is 43 years, and many patients are also likely to be premenopausal (22). This would have potential implications in terms of fertility in these patients. The other subtypes are so rare that it is difficult to discern a particular pattern of age distribution.

Racial Distribution

Zelmanowicz et al. (23) noted that women with carcinosarcomas are more likely to be of African American descent (among 453 patients and controls, 28% vs. 4%, $p = 0.001$) than those with endometrial adenocarcinomas. In the reviews of Mortel et al. and Norris et al. (24,25), 33% and 24% of patients with carcinosarcomas were non-White, respectively. Brooks et al. (26) reported that the age-adjusted incidence of uterine sarcomas in African American women was twice that of controls. The age-adjusted incidences of leiomyosarcomas for Black and White women, respectively, were 1.5 and 0.9 per 100,000. Those for carcinosarcomas in Black and White women, respectively, were 4.3 and 1.7 per 100,000.

Risk Factors

Prior Radiation Exposure

Prior exposure to pelvic radiotherapy is thought to increase the risk of developing a subsequent uterine sarcoma, primarily carcinosarcoma and undifferentiated sarcoma. Prior pelvic radiotherapy is not thought to increase the risk for uterine leiomyosarcoma or STUMP. In a large series from the Mayo Clinic, only 1 (0.6%) of 208 leiomyosarcoma cases had been exposed to prior pelvic radiotherapy (27). None of the 41 STUMP cases described by MD Anderson Cancer Center had a history of prior

Table 23.1 World Health Organization Classification of Mesenchymal Tumors of the Uterine Corpus

Mesenchymal Tumors

Endometrial stromal and related tumours

Endometrial stromal sarcoma, low grade

Endometrial stromal nodule

Undifferentiated endometrial sarcoma

Smooth muscle tumours

Leiomyosarcoma

Epithelioid variant

Myxoid variant

Smooth muscle tumour of uncertain malignant potential

Leiomyoma, not otherwise specified

Histological variants

Mitotically active variant

Cellular variant

Haemorrhagic cellular variant

Epithelioid variant

Myxoid

Atypical variant

Lipoleiomyoma variant

Growth pattern variants

Diffuse leiomyomatosis

Dissecting leiomyoma

Intravenous leiomyomatosis

Metastasizing leiomyoma

Miscellaneous mesenchymal tumours

Mixed endometrial stromal and smooth muscle tumour

Perivascular epithelioid cell tumour

Adenomatoid tumour

Other malignant mesenchymal tumours

Other benign mesenchymal tumours Mixed Epithelial and Mesenchymal Tumours

Carcinosarcoma (malignant mullerian mixed tumour; metaplastic carcinoma)

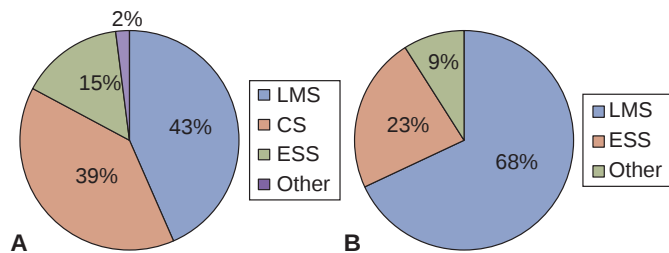
Adenosarcoma

Carcinofibroma

Adenofibroma

Adenomyoma

Atypical polypoid variant

**FIGURE 23.1** Histologic distribution of uterine sarcomas in series with at least 100 cases including carcinosarcomas (**A**) and excluding carcinosarcomas (**B**).

Source: From Park J, Kim D, Suh D, et al. Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989–2007. *J Cancer Res Clin Oncol*. 2008;134:1277–1287; Koivisto-Korander R, Butzow R, Koivisto A, et al. Clinical outcome and prognostic factors in 100 cases of uterine sarcoma: experience in Helsinki University Central Hospital 1990–2001. *Gynecol Oncol*. 2008;111:74–81; Kahanpää K, Wahlström T, Grohn P, et al. Sarcomas of the uterus: a clinicopathologic study of 119 patients. *Obstet Gynecol*. 1986;67:417–424; George M, Pejovic MH, Kramar A. Uterine sarcomas: prognostic factors and treatment modalities—study on 209 patients. *Gynecol Oncol*. 1986;24:58–67; Olah KS, Gee H, Blunt S, et al. Retrospective analysis of 318 cases of uterine sarcoma. *Eur J Cancer*. 1991;27:1095–1099; Pautier P, Genestie C, Rey A, et al. Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of grading score validated for soft tissue sarcoma. *Cancer*. 2000;88:1425–1431; Abeler VM, Royne O, Thorensen S, et al. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology*. 2009;54:355–364, with permission.

ESS, endometrial stromal sarcoma; CS, carcinosarcoma; LMS, leiomyosarcoma; AS, adenosarcoma.

pelvic radiotherapy (22). Christopherson et al. (28) described two cases among 33 patients with uterine leiomyosarcoma who had a history of radiotherapy.

In the series of carcinosarcomas reported by Norris et al. in 1966 (25), 9 of 31 patients (29%) had received pelvic radiotherapy from 7 to 26 years prior to diagnosis. Among 1,208 uterine malignancies in a report by Meredith et al. in 1986 (29), only 30 (2.4%) occurred in patients exposed to prior pelvic radiotherapy. Only 8 of these 30 patients had been irradiated for a gynecologic malignancy; others received pelvic radiation therapy for a benign diagnosis as this was done decades ago. Of irradiated patients, 5 (17%) developed carcinosarcomas, for a crude association of 11%. The risk of endometrial adenocarcinoma arising after radiation was much less at 2%. It has been suggested that postirradiation carcinosarcomas occur at a younger average age than those arising *de novo* (30). Latency to diagnosis of malignancy is generally shorter in older patients, however (29). Pothuri et al. compared the clinicopathologic characteristics of 23 cases of uterine cancers that occurred in patients with a prior history of cervical cancer treated with pelvic radiotherapy to 527 cases of uterine cancers that developed in patients without a history of pelvic radiotherapy (31). Carcinosarcomas and undifferentiated sarcomas accounted for 9 (39%) of the 23 radiation-associated malignancies compared to only 33 (8%) of the sporadic cases (31). It also seems that these radiation-associated malignancies tend to have a worse outcome, possibly due to lack of early symptomatology. The rarity of the other uterine sarcoma subtypes precludes the ability to make any definitive statements regarding this issue.

Hormone Exposure

There have been some suggestions that exposure to hormonal medications, including tamoxifen, may also increase the risk of uterine sarcomas. The association of estradiol-progestin therapy was recently assessed using data from the Finnish Cancer Registry, which captures nearly 100% of all cancers in Finland as well as the Reimbursement Registry of the Social Insurance Institution (32). Uterine sarcomas occurred in 76 out of the 243,857 women who were identified as having had used estradiol-progestin therapy for more than 6 months. Carcinosarcomas were not included in this analysis. The ever use of estradiol-progestin therapy was associated with a 60% elevation in the risk for

any uterine sarcoma (SIR, 1.6; 95% confidence interval [CI], 1.2–1.9). This association was mostly for leiomyosarcoma (standardized incidence ratio [SIR], 1.8; 95% CI, 1.3–2.4) and not statistically for endometrial stromal sarcoma (SIR, 1.4; 95% CI, 0.9–2.1). Also, this elevated risk was only noted in women who had used estradiol-progestin therapy for 5 years or more. Despite a possible increased relative risk, the overall absolute risk of uterine sarcomas is still exceedingly low, and these data should not dissuade the use of hormones in the appropriate case.

Tamoxifen Use

Tamoxifen use among breast cancer patients may also increase the risk of uterine malignancies, including possibly sarcomas. Lavie and colleagues, using data from 1,507 cases of women with breast cancer in the National Israeli Cancer Registry diagnosed from 1987 to 1988, noted that uterine cancers developed in 17/886 (1.9%) women treated with tamoxifen compared to only 4/621 (0.6%) of those who did not receive tamoxifen (odds ratio [OR], 3.1; 95% CI, 1–9.1) (33). The risk of uterine cancer was associated with increased duration of tamoxifen use (OR, 6.6; 95% CI, 2.0–21.1), whereas use of tamoxifen for 2 years or less was not associated with an increased risk of uterine cancer (OR, 2.1; 95% CI, 0.4–11.6). Uterine sarcomas developed in only 4 cases of the entire cohort. These included 2 carcinosarcomas and 2 rhabdomyosarcomas. All 4 occurred in patients who received tamoxifen, suggesting a possible association of tamoxifen use and uterine sarcoma risk. Hoogendoorn and colleagues reported that among patients diagnosed with uterine cancer, carcinosarcomas accounted for a much larger proportion of cases in those who had received prior tamoxifen therapy compared to those who had not (15% vs. 4%, respectively) (34).

Hereditary Predisposition

Hereditary predisposition to certain uterine sarcomas has also been suggested but still remains to be clearly elucidated. Among 164 Hereditary nonpolyposis colorectal cancer (HNPCC) families with disease-predisposing mutations, sarcomas of various sites represented 1% ($n = 14$) of the 1,570 malignant diagnoses using cases from the Danish HNPCC-register (35). Three of these 14 sarcomas were uterine: one was a carcinosarcoma in a 44-year-old with loss of MSH2 and MSH6 expression in the sarcoma, other was also a carcinosarcoma in a 55-year-old with loss of MSH6 expression, and the still other was a leiomyosarcoma in a 44-year-old with loss of MSH2 and MSH6 expression. Uterine leiomyosarcoma has also been recently suggested to be increased in women with hereditary retinoblastoma (36). The overall risk of uterine sarcoma is still low in these hereditary syndromes but of interest. Prophylactic hysterectomy is strongly recommended in women from HNPCC kindred once childbearing is complete due to the high risk of endometrial carcinoma, but no such recommendation exists for women with hereditary retinoblastoma since this is a recently described potential risk.

CLINICAL PRESENTATION AND DIAGNOSIS

Presenting Symptoms and Signs

The most common presenting symptom of uterine sarcomas is abnormal vaginal bleeding (4,11,13,21,26,36) (Table 23.2). Patients with leiomyosarcomas will also often note an abdominopelvic mass or one that is palpable on physical examination (4,26). A large number of leiomyosarcomas and ESSs are incidentally diagnosed after surgery for presumed uterine fibroids. The presence of endometrial stromal sarcoma was an incidental

Table 23.2 Common Presenting Symptoms in Patients with Uterine Sarcomas (% of Cases Describing that Symptom)

Symptom	ESS (4,11,13)	CS (4)	LMS (4,26)	AS (21,36)
Asymptomatic	14%	7%	11%	12%
Abnormal vaginal bleeding	68%	68%	53%	61%
Abdominopelvic mass	14%	16%	48%	—
Abdominopelvic pain	18%	9%	23%	20%
Uterine enlargement	64%	—	—	—
Uterine cavity lesion	21%	—	—	—
Vaginal discharge	4%	—	—	—
Abdominal distention	—	—	—	2%

ESS, endometrial stromal sarcoma; CS, carcinosarcoma; LMS, leiomyosarcoma; AS, adenosarcoma.

finding in 42% of cases reported by Memorial Sloan-Kettering Cancer Center (15). Therefore, it is quite likely that the vast majority of cases ultimately diagnosed with leiomyosarcoma or endometrial stromal sarcoma would have had some abnormal enlargement of the uterus discovered after presenting with abnormal vaginal bleeding. Vaginal bleeding in a postmenopausal female should be evaluated appropriately with endometrial sampling and possibly an intravaginal ultrasound. An enlarging pelvic mass in a postmenopausal female should also cause some concern for a malignant process. These symptoms and signs in premenopausal patients are a challenge and the diagnosis of malignancy is missed or often delayed since multiple benign conditions are more likely to be the cause of these symptoms. Carcinosarcoma often presents with vaginal bleeding in a postmenopausal female and often can be diagnosed with endometrial assessments, as it is a lesion that arises in the endometrium (unlike the true uterine sarcoma that often does not have an endometrial component or involve the endometrium).

There are no reliable serum tumor markers for uterine sarcoma. Serum CA-125 is elevated in 17% to 33% of leiomyosarcoma, ESSs, and carcinosarcomas (4). It should not be routinely used in the evaluation and diagnosis of these tumors. Preoperative endometrial assessments with either office pipelle or dilation and curettage (D&C) under anesthesia are limited in the evaluation and correct diagnosis of uterine sarcomas. However, endometrial assessments should be performed in women who present with abnormal vaginal bleeding, and uterine sarcoma may be discovered during this assessment. Bansal et al. reported that an invasive tumor was diagnosed in 86% of uterine sarcoma cases that had undergone a preoperative endometrial sampling (37). The correct histology for uterine sarcoma was only noted in 64% of the cases ultimately diagnosed with uterine sarcoma (37). However, the majority of the sarcomas in the series by Bansal and colleagues were carcinosarcomas on final pathology (32 [70%] of 46 sarcomas), with only 4 leiomyosarcomas, 2 endometrial sarcomas, and 8 other sarcomas diagnosed on final pathology (37).

Preoperative Imaging

Preoperative imaging is limited in differentiating benign from malignant uterine lesions, especially in the absence of obvious

extrauterine disease, but it is often available as part of the initial evaluation of these patients. Carcinosarcomas are often diagnosed using endometrial sampling; therefore, preoperative imaging is not important in the diagnosis for carcinosarcomas, but may be valuable in assessing for the presence of extrauterine disease. Small, single-institution, retrospective series have suggested that pelvic MRI may be of value in identifying uterine sarcomas and distinguishing them from benign uterine lesions. Namimto et al. reported a 100% sensitivity and specificity using diffusion-weighted imaging (DWI) and T2-weighted MR imaging in distinguishing between uterine sarcoma and benign lesions compared to DWI alone (38). This seems quite promising but not likely to be possible in clinical practice and not likely to be reproducible reliably. For example, Cornfeld and colleagues reported very poor accuracy for various objective MR imaging criteria in distinguishing leiomyomas with atypical imaging features from malignant uterine mesenchymal tumors (39). Using these various specific MR imaging criteria, the sensitivities for uterine sarcoma ranged from only 17% to 56% but the specificity was 80% to 100% (39).

Serum LDH and MR Imaging

Serum lactate dehydrogenase (LDH) may be an interesting additive to imaging in the evaluation of uterine lesions concerning for leiomyosarcomas (Table 23.3). Goto and colleagues reported an accuracy rate of 99.3% in predicting uterine leiomyosarcoma when combining serum LDH and dynamic MRI in a prospective trial (40). The positive predictive value was 91% using the combined assessment compared to 39% for LDH alone and 71% for MRI (dynamic or not). These results are impressive and would require further validation, but it is simple enough to obtain a serum LDH in patients with concerning lesions of the uterus. Another important point is that the series by Goto and colleagues, as well as other series, note a high specificity and nearly 100% negative predictive value for MRI with or without LDH. This can be useful in women who do not wish to undergo surgery and, especially, in women who are extremely desirous of fertility. It may also help when deciding upon the surgical approach in patients with presumed benign leiomyomas as well as much “concerning” lesions.

Table 23.3 Test Characteristics Using Dynamic MRI and Serum Lactate Dehydrogenase (LDH) in Predicting Uterine Leiomyosarcomas from Degenerating Leiomyomas

Test	Sensitivity	Specificity	Accuracy	PPV	NPV
Total serum LDH	100%	87.7%	86.6%	38.5%	100%
MRI	100%	96.9%	97.1%	71.4%	100%
Dynamic MRI	100%	87.5%	90.5%	71.4%	100%
LDH & dynamic MRI	100%	99.2%	99.3%	90.9%	100%

PPV, positive predictive value; NPV, negative predictive value.

Source: Adapted from Goto A, Takeuchi S, Sugimura K, et al. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. *Int J Gynecol Cancer*. 2002;12:354–361, with permission.

Uterine Morcellation

Laparoscopy has become a standard and preferred approach in the management of women with benign and malignant gynecologic conditions. Morcellation of the uterus, either for removal of the specimen during minimally invasive procedures, myomectomy for fertility preservation, or supracervical hysterectomy, is commonplace. Morcellation of the uterus is often not done in patients with carcinosarcomas since they are often older and the diagnosis of malignancy is known preoperatively. However, it is not unusual that a leiomyosarcoma or endometrial stromal sarcoma is incidentally diagnosed after some form of morcellation or less than total hysterectomy. Morcellation of a uterine leiomyosarcoma is associated with a worsened outcome. Perri et al. reported a significantly higher recurrence rate and lower overall survival (OS) in women who had undergone something less than a total hysterectomy and subsequently diagnosed with uterine leiomyosarcoma (41). The hazard ratios (HR) for recurrence and survival for TAH compared to other type of resection (myomectomy, morcellation, or supracervical hysterectomy) were 0.39 and 0.36, respectively. Park et al. reported a series in which the 5-year disease-free survival was 40% in women who underwent tumor morcellation and were subsequently diagnosed with leiomyosarcoma, compared to 65% in those with leiomyosarcoma who had not undergone morcellation ($p = 0.04$) (42). Similarly, the 5-year OS was 46% after morcellation compared to 73% in those not morcellated ($p = 0.04$) (42). Morcellation also appears to negatively impact on recurrence risks in cases diagnosed with ESSs, but has no adverse impact on OS (43).

Despite this potential adverse impact of morcellation on outcomes in patients ultimately diagnosed with leiomyosarcoma and endometrial stromal sarcoma, it cannot be stated that morcellation or myomectomy is not appropriate in the management of patients with presumed benign leiomyomas. The risk of leiomyosarcoma and endometrial stromal sarcoma in patients undergoing surgery for presumed benign leiomyoma is quite low. Combining 4 series that had a total of 4,981 patients, the risk of leiomyosarcoma after surgery for presumed benign leiomyoma was only 0.24%, and 0.06% for endometrial stromal sarcoma (44–47). This risk is not greater in those undergoing surgery for a stated indication of “rapidly” enlarging leiomyoma (45).

It is quite reasonable to obtain preoperative pelvic MRI in patients undergoing planned less than total hysterectomy for presumed benign leiomyoma, as it will help localize the tumors as well as provide an excellent negative predictive value. Serum LDH may also be quite useful in helping to determine when morcellation may not be best. However, a patient with a normal serum LDH and/or not suspicious MRI reasonably may be subjected to morcellation with little concern for uterine sarcoma. Morcellation may not be reasonable in patients with highly suspicious MR imaging and elevated serum LDH, as well as in postmenopausal patients with enlarging uterine masses, new uterine masses, or newly symptomatic uterine masses.

STAGING AND PROGNOSIS

Staging Systems

The American Joint Committee on Cancer (AJCC) has a staging system for soft-tissue sarcomas, but there are limitations in applying this to uterine sarcomas. The International Federation of Gynecology and Obstetrics (FIGO) did not have a sarcoma-specific system until recently. A modified system for endometrial carcinomas was most commonly used (18). Zivanovic and colleagues demonstrated that neither the modified FIGO system nor

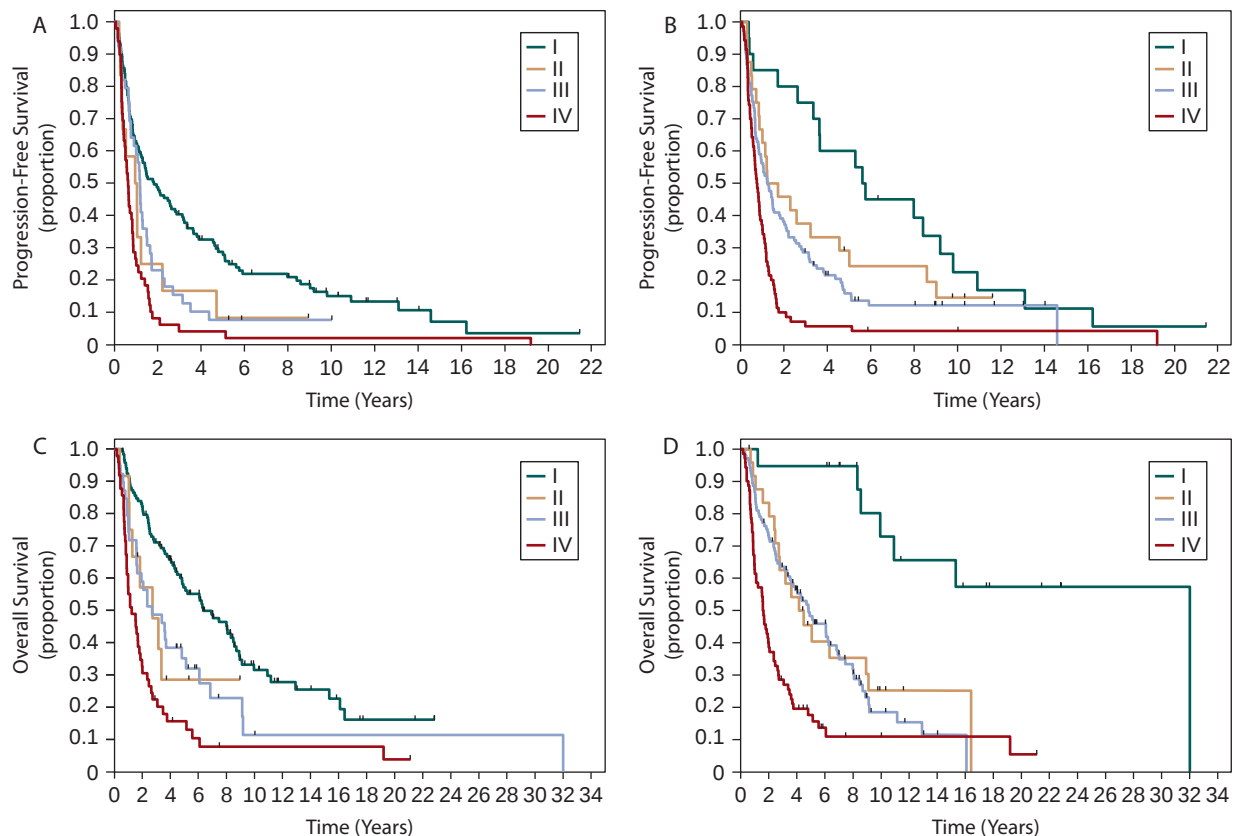


FIGURE 23.2. Progression-free survival by (A) International Federation of Gynecology and Obstetrics stage and (B) American Joint Committee on Cancer stage. Overall survival by (C) FIGO stage and (D) AJCC stage.
Source: From Zivanovic O, Leitao MM, Iasonos A, et al. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer staging systems. *J Clin Oncol.* 2009;27:2066–2072, with permission.

the AJCC staging system was adequate (18). Figure 23.2 depicts progression-free and OS based on staging using the modified FIGO and AJCC (18). The concordance indices for PFS using FIGO or AJCC systems were 0.600 and 0.596, respectively, and for OS were 0.620 and 0.633, respectively. These concordance indices are not ideal and are usually >0.700 in more accurate systems. The prognostic inadequacy for both the modified FIGO system and the AJCC system reported by Zivanovic and colleagues at Memorial Sloan-Kettering Cancer Center was further confirmed by investigators at Brigham and Women's Hospital (48).

FIGO devised a uterine sarcoma-specific staging system in 2009 for leiomyosarcoma, endometrial stromal sarcoma, and adenosarcoma (3) (Tables 23.4 and 23.5). Carcinosarcomas are to be staged using the system for endometrial carcinomas (3). There are no clear guidelines on how to stage the other much less common uterine sarcomas. These 2009 FIGO systems for the true uterine sarcomas have not yet been validated. Garg and colleagues reported that the 2009 FIGO system did not provide a more accurate prognostic capability compared to the 1988 system for endometrial carcinomas that was being used for sarcomas prior to 2009 (20). Figure 23.3 depicts the stage distribution for newly diagnosed uterine sarcomas using older staging criteria, which essentially stages any disease beyond the uterine corpus and/or cervix as stage III or IV. The majority of ESSs, leiomyosarcomas, and adenosarcomas present confined to the uterus and/or cervix. Carcinosarcomas and undifferentiated sarcomas have a much greater propensity for metastatic spread at the time of presentation. The value of preoperative imaging to assess for such extrauterine spread has been questioned (51). However, it is still quite reasonable to assess for extrauterine spread preoperatively in patients with newly diagnosed uterine

Table 23.4 2009 FIGO Staging System for Uterine Leiomyosarcomas and Endometrial Stromal Sarcomas

Stage	Definition
I	Tumor limited to uterus
IA	Less than or equal to 5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

Source: From D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol.* 2010;116:131–139, with permission.

Table 23.5 2009 FIGO Staging System for Uterine Adenosarcomas

Stage	Definition
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or paraaortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

Source: From D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol*. 2010;116:131–139, with permission.

sarcomas, since there is still at minimum approximately 25% or greater chance of extrauterine disease (as seen in Figure 23.3), except for adenosarcoma. The other much more rare subtypes tend to present confined to the uterus based on very small case reports and series.

Uterine sarcomas confined to the uterine body (typically stage I) tend to have a worse prognosis than the more common endometrial carcinomas, except for ESSs. The 5-year OS for patients with stage I endometrial stromal sarcoma is approximately 97% (52). The OS is actually excellent for patients with ESSs irrespective of stage. Including all stages of presentation, the OS is approximately 92% (14). This contrasts sharply with the outcomes seen for the other uterine sarcomas. The 5-year OS for adenosarcomas confined to the endometrium is 84%, which is reasonable (3). It drops to approximately 65% if there is any myoinvasion (5). The 5-year OS for leiomyosarcomas, carcinosarcomas, and undifferentiated sarcomas confined to the uterine corpus is 57%, 62%, and 52%, respectively (18,49,52). Patients diagnosed with STUMP previously were considered as low-grade leiomyosarcomas. These patients have an outstanding prognosis and this may have biased earlier publications regarding outcomes in “leiomyosarcoma.”

Nomogram

Improved prognostic systems and methods are needed for uterine sarcomas. Nomograms to provide prognostic and predictive information are being used more commonly in oncology. A nomogram to predict 5-year OS in patients with uterine leiomyosarcomas was developed by investigators at Memorial Sloan-Kettering Cancer Center (53) (Fig. 23.4). A total point score is obtained by adding up the various listed clinicopathologic criteria. This score is then plotted against the 5-year OS line at the bottom to come up with an estimated survival. This

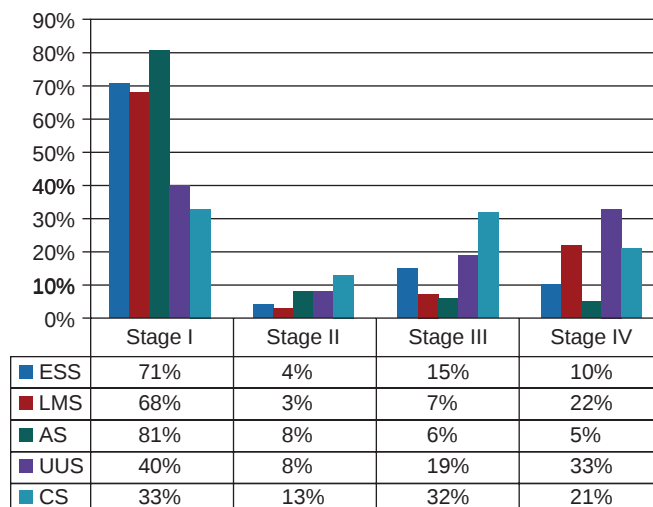


FIGURE 23.3. Stage distribution of the more common uterine sarcomas. ESS, endometrial stromal sarcoma; LMS, leiomyosarcoma; AS, adenosarcoma; UUS, undifferentiated uterine sarcoma; CS, carcinosarcoma.

Source: From Shah LP, Bryant CS, Kumar S, et al. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. *Obstet Gynecol*. 2008;112:1102–1108; Pradhan TA, Stevens EE, Ablavsky M, et al. FIGO staging for carcinosarcoma: can the revised staging system predict overall survival? *Gynecol Oncol*. 2011;123:221–224; Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. *Cancer*. 2008;112:820–830; Nugent EK, Zigelboim I, Case AS, et al. The value of perioperative imaging in patients with uterine sarcomas. *Gynecol Oncol*. 2009;115:37–40, with permission.

nomogram is freely available online at <http://www.mskcc.org/cancer-care/adult/endometrial-other-uterine/leiomyosarcoma/prediction-tools>. The bootstrap-validated concordance probability for this nomogram was 0.65. Although slightly better than current FIGO or AJCC systems, it is still not ideal, and will require further validation and development.

Molecular Prognostics

A possible reason for the limited prognostic capabilities of current staging systems and nomogram is that they rely on anatomic, clinical, and pathologic criteria that have not been consistently associated with outcome. A better molecular understanding of these tumors is urgently needed and may possibly provide greater prognostication. Estrogen (ER) and progesterone (PR) receptor expression in uterine leiomyosarcomas has been reported to be associated with outcome by Leitao and colleagues (54). In their cases presenting with extrauterine disease, including cervical extension alone, ER/PR expression was not prognostic. However, it was prognostic in those with disease confined to the uterine body. Most notably, of the 10 PR overexpressing cases, only one recurred and died compared to 9 of the 10 PR nonexpressing cases having recurred and 5 died (54). Ioffe and colleagues also reported a possible association with hormone receptor expression and outcome in uterine sarcomas (55). Subtyping hormone receptors may provide even further improved prognostication (56). Koivisto-Korander and colleagues assessed the association of immunohistochemical of various proteins (Ki-67, p53, CD10, CD44, desmin, SMA, ER α , and PR-A) with survival outcomes in patients with carcinosarcoma and leiomyosarcoma (57). None of the expression patterns of any of these proteins was associated with survival in patients with carcinosarcoma (57). However, in patients with leiomyosarcoma, only ER α and PR-A overexpression was associated with survival (57).

Expression patterns of other proteins have been reported to possibly be associated with outcome. β -catenin expression was

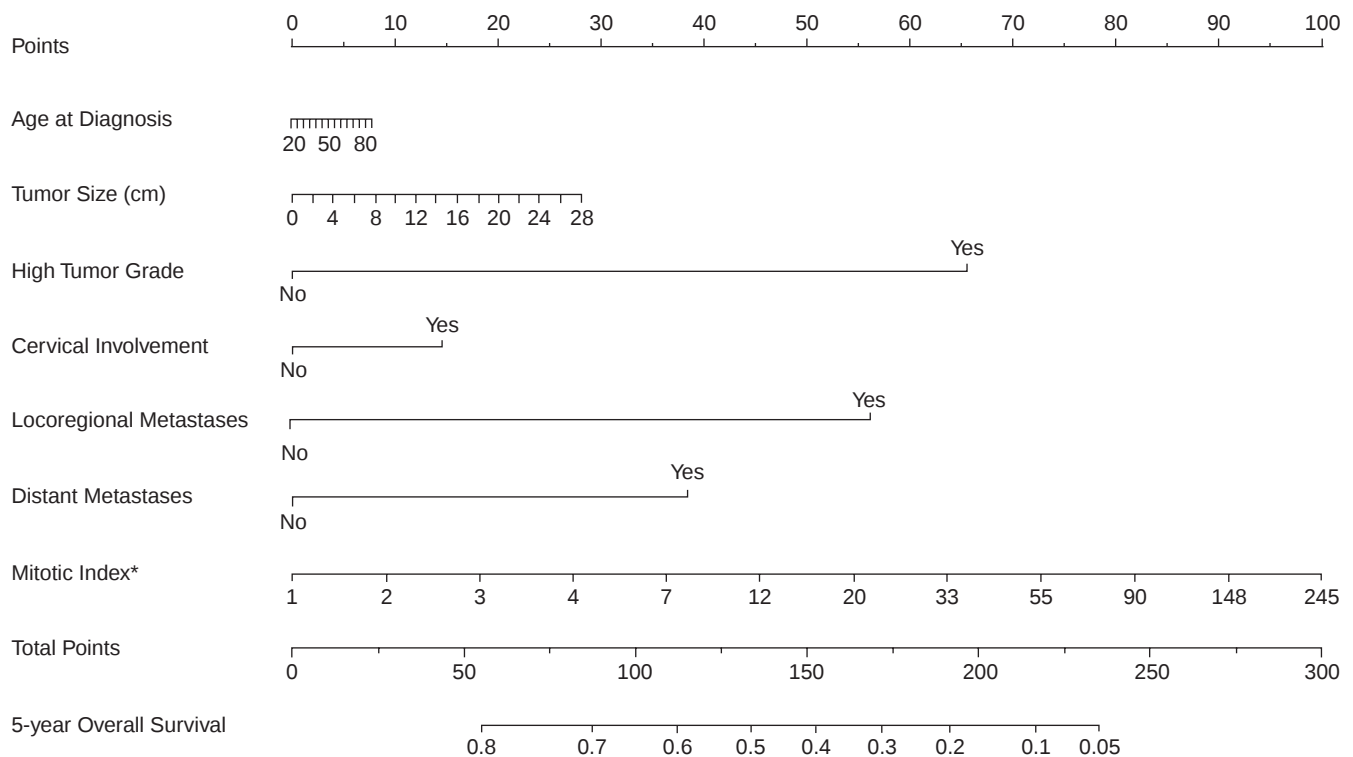


FIGURE 23.4. Nomogram for 5-year overall survival for uterine leiomyosarcoma. This is the uterine leiomyosarcoma nomogram for 5-year overall survival. The mitotic index (asterisk) was modeled using log transformation; for display purposes, values were converted back to original scale (exponential; concordance probability [CP], 0.671; bootstrap-validated CP, 0.651).

Source: Zivanovic O, Jacks LM, Iasonos A, et al. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. *Cancer*. 2012;118:660–669, with permission.

associated with crude survival in patients with leiomyosarcoma but not in those with endometrial stromal sarcoma, adenocarcinoma, or undifferentiated sarcoma (58). Cyclooxygenase-2 (COX-2) expression was reported to be independently associated with outcome in patients with leiomyosarcoma (59). Cox-2 was not prognostic in patients with uterine carcinosarcoma (60). P53, p16, Ki67, and bcl-2 expression patterns were all reported to be associated with outcome in patients with leiomyosarcomas, but only bcl-2 was prognostic in undifferentiated and ESSs in a series reported by D'Angelo and colleagues (61). CD10 and PTEN expression were not prognostic in this same report (61). These are all quite interesting hypothesis-generating reports as we begin to unravel the molecular biology of these rare tumors but all require further validation and investigation before we can start to incorporate them into clinically useful prognostic tools. However, improved prognostication will likely come from molecular-based analyses and possibly protein and/or gene expression profiling. Additional descriptions are also provided in the Pathology section of this chapter.

Patterns of Recurrence

The patterns of first recurrence are described in Table 23.6. The median progression-free survival (PFS) (i.e., time to recurrence) is over 100 months (8.3 years) in patients with endometrial stromal sarcoma based on current criteria for diagnosing this tumor (11,13,64,65). Prior studies reported median PFSs of 15 to 23 months for endometrial stromal sarcoma (5,9). However, this probably just reflects the inclusion of what is now considered to be undifferentiated sarcomas and not truly ESSs. Few data exist on patterns of recurrence for undifferentiated sarcomas but it is likely to reflect that seen with the other sarcomas

or what was previously reported for “endometrial stromal sarcomas.” The median time for adenocarcinomas is around 40 months (21). Leiomyosarcomas and carcinosarcomas have a very short median PFS: 12 to 19 months and 11 to 14 months, respectively (5,9,18,20,63,66,67). Extrapelvic recurrences are quite common with 82% of carcinosarcomas involving an extrapelvic site. The most common sites of extrapelvic recurrences are the lungs for ESSs and leiomyosarcomas. The abdomen is the most common extrapelvic site for adenocarcinomas and carcinosarcomas. STUMPS have an exceedingly low risk of recurrence and a nearly 100% OS. Only 3 of 41 STUMP cases treated at MD Anderson Cancer Center recurred (one each at 13, 47, and 68 months) (22). All 41 patients were alive and without evidence of disease at the time of publication (22). The rarity of other uterine sarcomas precludes definitive comments on patterns of recurrence but most tend to recur locally when they do.

MOLECULAR BIOLOGY AND GENETICS

The association with expression patterns of certain proteins and outcome was described above. These are limited and mostly nonvalidated data. The key to improved prognostic and predictive tools as well as therapeutics in patients with uterine sarcomas will only be achieved with a significant understanding of the inherent molecular biology of these tumors, which, in general, is very limited at this time. We will describe some recent molecular studies of particular interest but many more are in publication and we expect more to be forthcoming. Additional descriptions are also provided in the Pathology section of this chapter.

Table 23.6 Patterns of First Recurrence in Patients with Select Uterine Sarcomas

	ESS (11,13,65,66)	AS (21)	LMS (5,9,18,20,67,68)	CS (5,9,64,67)
Median PFS (months)	101–130	41	12–19	11–14
Pelvic only first recurrence ^a	43%	62%	41%	18%
Extrapelvic first recurrence ^b	57%	38%	59%	82%
Most common extrapelvic site	Lung	Abdomen	Lung	Abdomen

PFS, progression-free survival; ESS, endometrial stromal sarcoma (only includes true “low-grade” cases); AS, adenocarcinoma; LMS, leiomyosarcoma; CS, carcinosarcoma.

^a Includes vaginal ± other pelvic recurrence.

^b Some cases also with a concurrent pelvic recurrence.

Source: From Koivisto-Korander R, Butzow R, Koivisto A, et al. Clinical outcome and prognostic factors in 100 cases of uterine sarcoma: experience in Helsinki University Central Hospital 1990–2001. *Gynecol Oncol.* 2008;111:74–81; Pautier P, Genestie C, Rey A, et al. Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of grading score validated for soft tissue sarcoma. *Cancer.* 2000;88:1425–1431; Jin Y, Pan L, Wang X, et al. Clinical characteristics of endometrial stromal sarcoma from an academic medical hospital in China. *Int J Gynecol Cancer.* 2010;20:1535–1539; Cheng X, Yang G, Schmeler KM, et al. Recurrence patterns and prognosis of endometrial stromal sarcoma and the potential of tyrosine kinase-inhibiting therapy. *Gynecol Oncol.* 2011;121:323–327; Zivanovic O, Leitao MM, Iasonos A, et al. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer staging systems. *J Clin Oncol.* 2009;27:2066–2072; Pradhan TA, Stevens EE, Ablavsky M, et al. FIGO staging for carcinosarcoma: can the revised staging system predict overall survival? *Gynecol Oncol.* 2011;123:221–224; Clement PB, Scully RE. Mullerian adenocarcinoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. *Hum Pathol.* 1990;21:363–381; Beck TL, Singhal PK, Ehrenberg HM, et al. Endometrial stromal sarcoma: analysis of recurrence following adjuvant treatment. *Gynecol Oncol.* 2012;125:141–144; Kim WY, Lee JW, Choi CH, et al. Low-grade endometrial stromal sarcoma: a single center's experience with 22 cases. *Int J Cancer.* 2008;118:1084–1089; Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I–IV high grade uterine leiomyosarcoma: results of a prospective study. *Gynecol Oncol.* 2009;112:563–567; Leitao MM, Brennan MF, Hensley M, et al. Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. *Gynecol Oncol.* 2002;87:287–294; Chiang S, Ali R, Melnyk N, et al. Frequency of known gene rearrangements in endometrial stromal tumors. *Am J Surg Pathol.* 2011;35:1364–1372, with permission.

Gene rearrangements have been described and validated in patients with ESSs with at least 75% having a gene rearrangement (68). The t(7;17) translocation resulting in the *JAZF1-SUZ12* gene fusion is the most common translocation found in approximately 35% to 50% of ESSs (68). Other noted gene fusions are *JAZF1-PHF1*, *EPC1-PHF1*, *JAZF1* only, and *PHF1* only (68).

Undifferentiated endometrial sarcomas (previously referred to as high-grade ESSs) lack these *JAZF1* based rearrangements but instead appear to frequently harbor the *YWHAE-FAM22A/B* genetic fusion (69,70). The *YWHAE-FAM22A/B* fusion has been proposed as a potential oncogene in the development of undifferentiated (i.e., high-grade ESSs) due to the transforming properties of the *YWHAE-FAM22* protein that is expressed by this gene fusion (69,70). Additionally, the *YWHAE-FAM22A/B* fusion appears to be specific to these tumors since this rearrangement was not detected in 827 other cases representing 55 tumor types (70).

LMP2 is an important immuno-protease subunit that is induced by IFN- γ and suggested to be involved in various cell events, possibly including the suppression of tumor cell growth (71). Mice lacking LMP2 appear to spontaneously develop uterine leiomyosarcomas with an incidence of about 40% at 14 months of age (71). LMP2 expression appears to be absent in human leiomyosarcoma but is retained in human leiomyomata (71). LMP2 may be involved in the sarcomagenesis of uterine leiomyosarcomas and will require continued investigation. Leiomyosarcomas do not seem to harbor somatic mutations in *EGFR*, *CDKN2A*, *MET*, *KIT*, *RAS*, *BRAF*, *PI3KCA*, *HER-2*, or *PDGFR- α* , for which targeted therapies are available (72,73).

Growdon and colleagues analyzed uterine carcinosarcomas for the presence of somatic mutations (73). The rate of mutations identified for each gene analyzed was *PIK3CA* (56%), *KRAS* (44%), *TP53* (33%), *CTNNB1* (6%), and *NRAS* (6%). *TP53* mutation was the only mutational event that retained an independent association with survival. The Akt/ β -catenin pathway and alterations in Rb expression have been suggested to be involved in the development of carcinosarcomas of the uterus (74). This is felt to be modified through transactivation of the *Slug* gene. Cimbaluk et al. assessed immunohistochemical expression of potential therapeutic targets (75). Expression was low in both the epithelial and mesenchymal components

for HER-2 (6% and 0%, respectively) and c-Kit (0% in both). EGFR expression was 30% in the epithelial and 67% in the mesenchymal component. COX-2 was expressed in 70% of the epithelial component but in only 16% of the mesenchymal component. VEGF was highly expressed in both the epithelial (100%) and mesenchymal components (93%).

PATHOLOGY

Malignant mesenchymal tumors can be classified into pure mesenchymal tumors and tumors with a mixed epithelial and mesenchymal components. In the first group, the most common is leiomyosarcoma, followed by ESS, and rarely, others including rhabdomyosarcoma, liposarcoma, angiosarcoma, chondrosarcoma, osteosarcoma, and alveolar soft-part sarcoma. Mixed epithelial and mesenchymal tumors include carcinosarcoma and adenocarcinoma. In addition, there are 3 rare mesenchymal tumors occurring in the uterus that are usually benign but can cause problems in the differential diagnosis with malignant lesions: uterine tumors resembling ovarian sex-cord tumors (UTROSCTs), perivascular epithelioid cell tumors (PEComas), and inflammatory myofibroblastic tumor (76).

Leiomyosarcoma and Other Smooth Muscle Tumors

Leiomyosarcomas are malignant smooth muscle tumors that usually arise *de novo*. Recent studies have shown that some tumors have areas with benign morphology, suggesting some progression from leiomyoma to leiomyosarcoma (77,78), but clonality studies only support this progression in a small percentage of cellular or symplastic leiomyomas (78,79). Leiomyosarcoma is usually a solitary, poorly circumscribed mass with a soft and fleshy consistency. The cut surface is variegated with gray areas intermixed with yellow areas of necrosis and sometimes hemorrhagic areas. The epicenter of the tumor is the myometrium and most leiomyosarcomas are intramural. Occasionally, they can extend into the cervix or beyond the uterus through the serosa (Figs. 23.5–23.7).

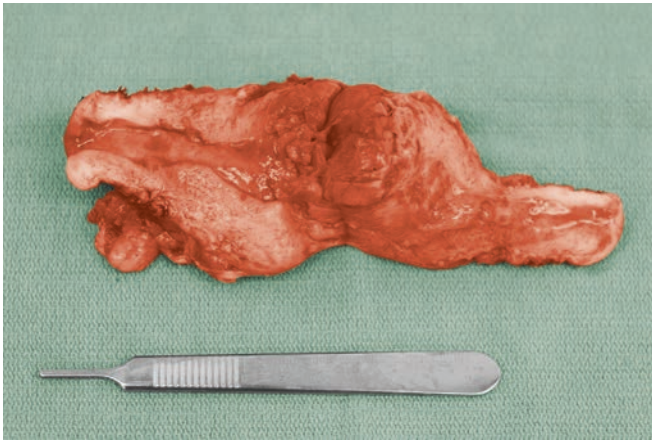


FIGURE 23.5. Leiomyosarcoma, gross.

Microscopically, most leiomyosarcomas are overtly malignant and have hypercellularity, coagulative tumor cell necrosis, abundant mitoses, atypical mitoses, marked cytologic atypia, and infiltrative borders (Fig. 23.8). Some cases lack some of these features, and occasionally the differential diagnosis between a benign and a malignant lesion can be controversial. The 3 most important criteria are coagulative tumor cell necrosis, high mitotic rate, and significant cytologic atypia. In conventional type of leiomyosarcomas (spindle cell type), the diagnosis of malignancy is rendered when any 2 of the following 3 criteria are present: tumor cell necrosis, diffuse moderate to severe cytologic atypia, and 10 or more mitoses per 10 high-power fields (HPF) (80). Tumor cell necrosis (TCN) has an abrupt transition from viable to necrotic tissue (Fig. 23.9). In contrast, hyaline necrosis seen in some leiomyomas has an area of hyalinized tissue between the necrotic and viable tumor. Some smooth-muscle tumors have histologic features that are not worrisome enough to render an unequivocal diagnosis of sarcoma. These tumors can be classified as atypical leiomyomas, smooth muscle tumors with low malignant potential (low probability of an unfavorable outcome), or STUMP depending on their histological features. Figure 23.10 summarizes the classification of uterine smooth muscle tumors based on their histologic characteristics. This classification is based in large part upon a large retrospective study from Stanford University published in 1994 (80), the largest to date. Tumors that clinically and pathologically appear to be leiomyomas but have up to 15 mitoses per 10 HPF behave in a benign fashion and are classified

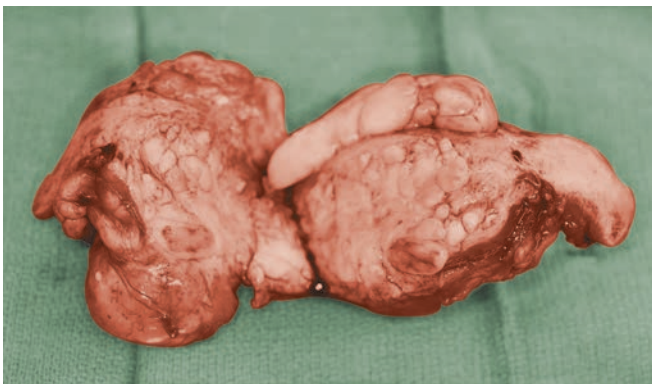


FIGURE 23.6. Leiomyosarcoma, gross, showing heterogenous appearance.

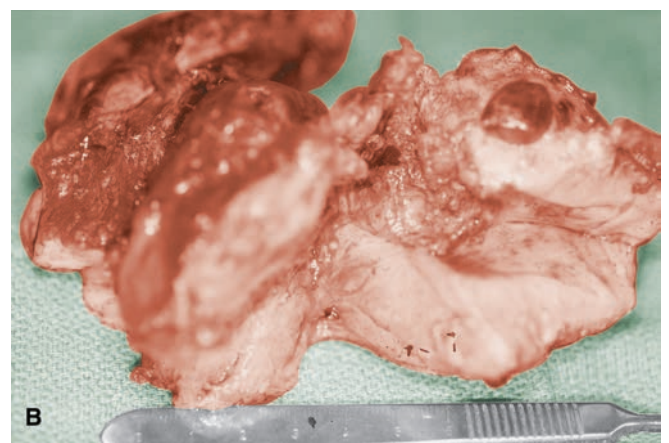
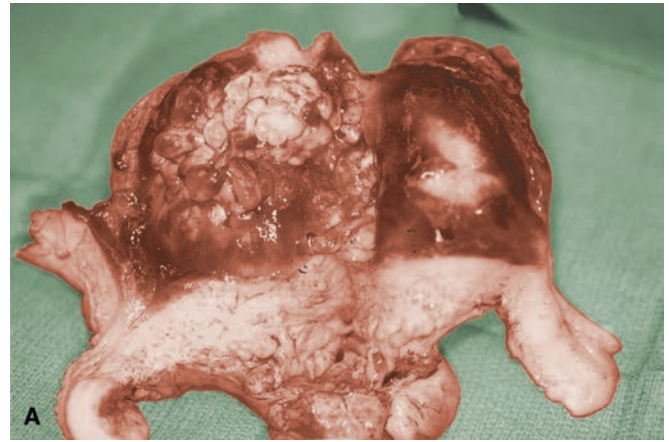


FIGURE 23.7. Leiomyosarcoma, gross, with extension beyond uterus.

as mitotically active leiomyomas (80,81). Leiomyomas are more likely to have a high mitotic count if they are excised during the secretory phase of the menstrual cycle, during pregnancy, or while patients are receiving exogenous progesterone therapy.

Five recent studies in the pathology literature have addressed the diagnosis and clinical behavior of borderline smooth muscle tumors classified as atypical leiomyomas, tumors with low malignant potential and tumors of uncertain malignant potential (22,82–85). The overall recurrence rate based on these 5

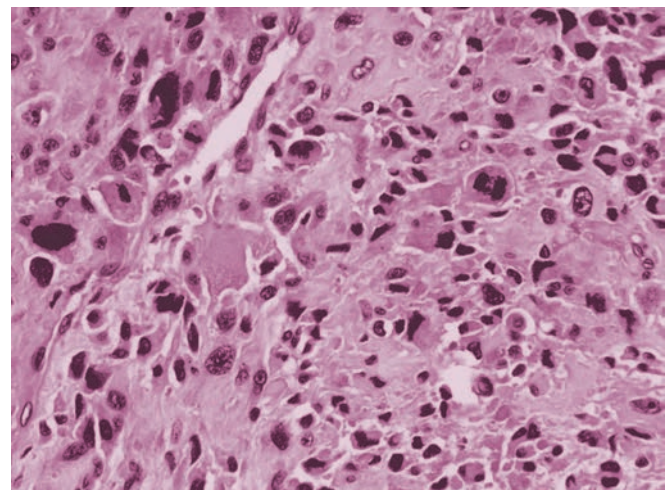


FIGURE 23.8. Leiomyosarcoma, microscopic.

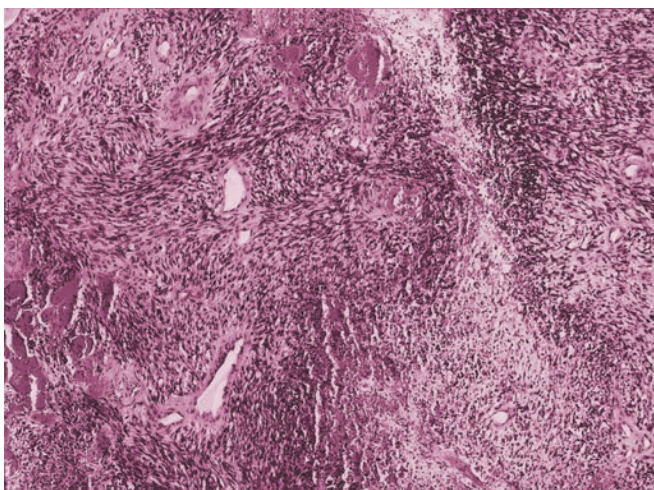


FIGURE 23.9. Leiomyosarcoma, microscopic, with abrupt transition from viable to necrotic tissue.

studies is 8.6%. Most tumors recurred as STUMPs, although 1 case recurred as leiomyosarcoma (22). Most patients were alive and free of disease at the time the studies were published, although 1 study reported 3 disease-specific deaths and all with more than 6 years after initial diagnosis (82). There are tumors that lack 1 of the 3 major diagnostic criteria (mitoses, atypia, necrosis) but have other worrisome features such as infiltrative borders, lymphovascular invasion, or atypical mitoses. Classification of such cases is always problematic. It is recommended that these unusual cases be reviewed by a gynecologic pathologist.

Infarcted necrosis of benign leiomyomas can be seen sometimes during pregnancy, after uterine artery embolization, thermal balloon endometrial ablation, therapy with tranexamic acid, or therapy with high-dose progestins. In addition, pedunculated submucosal leiomyomas can undergo spontaneous torsion, and infarction, even with protrusion through the cervix.

Infarcted leiomyomas should not be confused with leiomyosarcoma. The infarcted necrosis is not tumor cell necrosis, as mentioned before. In addition, infarcted leiomyomas are not associated with significant cytologic atypia, high mitotic rate, atypical mitoses, or invasive borders. An accurate clinical history can be very useful in many of these cases.

Several recent studies support the use of immunostains for p16, p53, and Ki67 (proliferative activity marker) in the differential diagnosis of problematic smooth-muscle tumors. p16 is overexpressed in uterine leiomyosarcomas compared with leiomyomas and STUMPs suggesting that p16 may be implicated in the pathogenesis of leiomyosarcomas. In addition, leiomyosarcomas have higher p53 expression and higher proliferative activity (Ki67) than other uterine smooth-muscle tumors. The combination of high p16, p53, and Ki67 expressions is supportive of the diagnosis of leiomyosarcoma if used in combination with H&E features, gross appearance of the tumor, and clinical features (86–89).

Classification criteria of smooth muscle tumors with either myxoid or epithelioid features differ from those used for spindle cell tumors. Epithelioid tumors have cells that are round rather than spindle shaped and have round nuclei mimicking epithelial cells (hence the term “epithelioid”) (Fig. 23.11). Epithelioid leiomyosarcomas have significant cytologic atypia, at least 3 mitoses per 10 HPF, and tumor cell necrosis in 50% of cases (90). At least one previous study suggests that epithelioid tumors may behave more aggressively than spindle-cell tumors and have a higher tendency to metastasize (91). Myxoid leiomyosarcomas are rare and may be histologically deceiving because of lack of tumor cell necrosis, minimal atypia, and a low mitotic rate. The most reliable histologic criteria of malignancy are infiltrative borders and lymphovascular invasion (92) (Fig. 23.12). Myxoid leiomyosarcomas have a similar long-term survival as other leiomyosarcomas, but at least one study reported better 5-year survival (73%) as compared with ordinary leiomyosarcomas (49%) (10).

Histologic parameters of leiomyosarcomas that have been suggested to correlate with a worst prognosis include mitotic rate (93,94), lymphovascular invasion (93), size (94), diffuse high-grade cytologic atypia (95), and negative ER and PR (54).

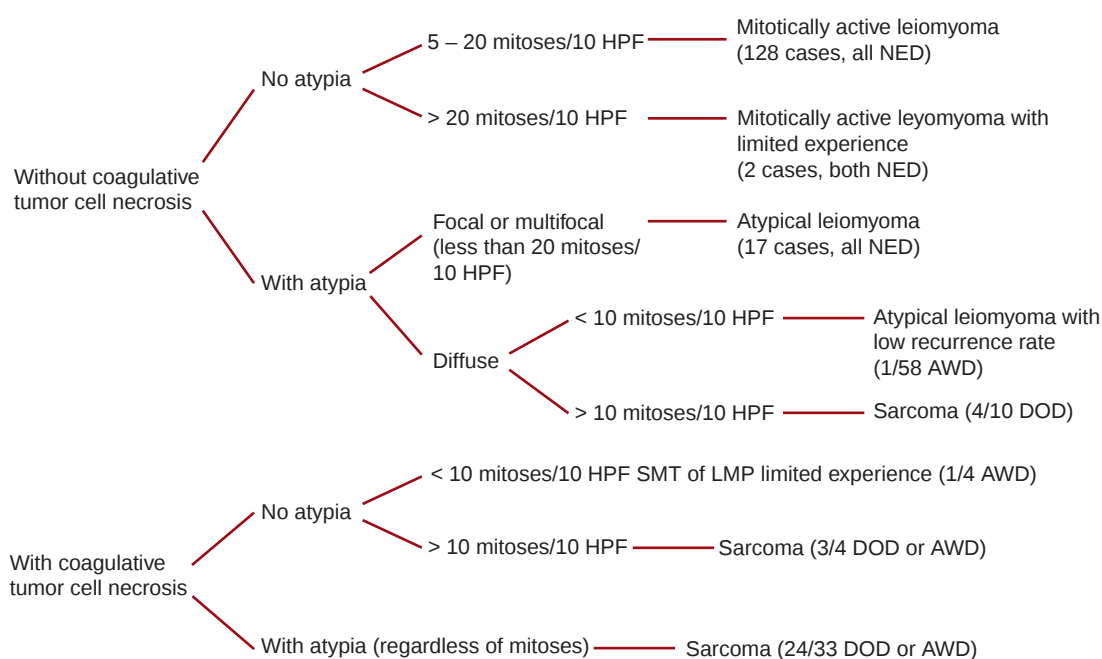


FIGURE 23.10. Uterine smooth muscle tumors (excluding epithelioid and myxoid types and cervical tumors). AWD, alive with disease; DOD, dead of disease; HPF, high power fields; LMP, low malignant potential; NED, no evidence of disease; SMT, smooth muscle tumor.

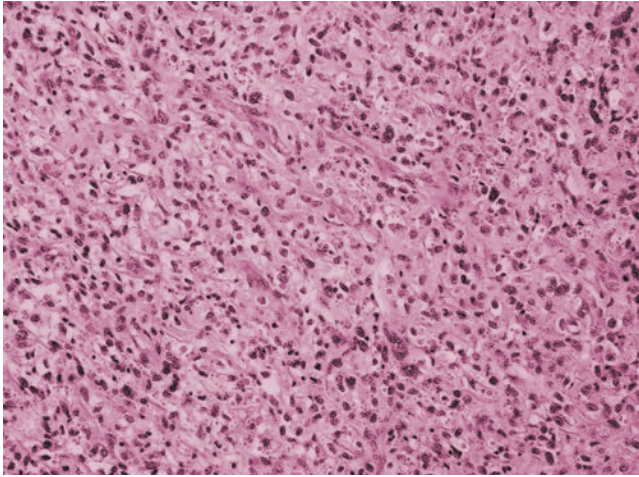


FIGURE 23.11. Epithelioid leiomyosarcoma, microscopic appearance.

However, many of these have not been found to be associated with outcome and, therefore, not entirely validated.

Benign metastasizing leiomyoma

Benign metastasizing leiomyoma (BML) is characterized by the presence of a uterine leiomyoma associated with one or more extrauterine smooth muscle tumors histologically benign. The most common site of "metastasis" is the lung, although "metastases" have also been described in the retroperitoneum, mediastinal lymph nodes, soft tissues, and bone. Before rendering the diagnosis of "benign metastasizing leiomyoma" pathologists need to sample the tumors extensively to rule out any aggressive components. The pathogenesis is unclear although some animal experiments suggest that BML may be secondary to lymphatic and hematological spread, coelomic metaplasia, and intraperitoneal seeding (pathogenesis similar to that of endometriosis) (96).

Carcinosarcoma

Uterine carcinosarcomas, also called malignant mixed müllerian tumors, are lesions containing carcinomatous and sarcomatous elements (Fig. 23.13). Numerous studies have shown

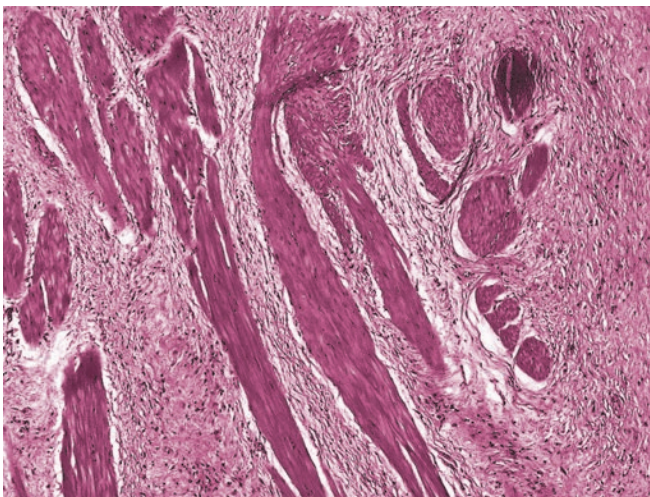


FIGURE 23.12. Myxoid leiomyosarcoma, microscopic appearance.

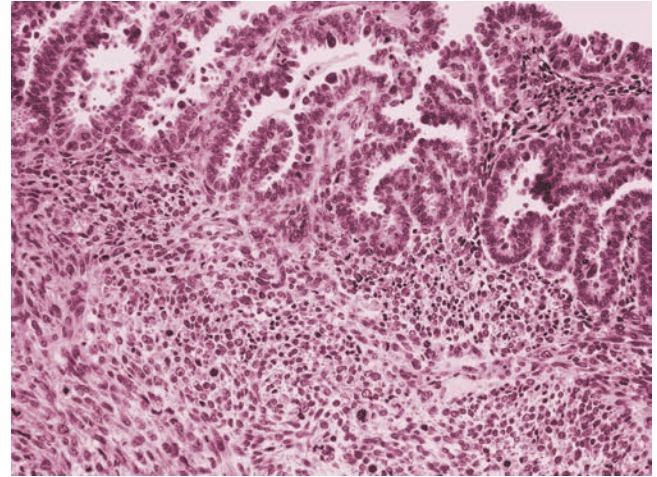


FIGURE 23.13. Carcinosarcoma, microscopic appearance.

that these tumors are clonal malignancies derived from a single stem cell and should be considered "metaplastic carcinomas" (97,98). One study has identified similar mutations signatures in *PIK3CA*, *KRAS* and *NRAS* in the carcinomatous and sarcomatous elements within a given tumor (73).

Most carcinosarcomas are polypoid tumors that fill the endometrial cavity and may protrude through the cervical os (Fig. 23.14). The tumors are soft and fleshy, with areas of necrosis and hemorrhage. Occasionally, they show gross myometrial invasion, and may extend into the cervix. The size of the tumor is quite variable and may range from less than 2 cm to over 20 cm in diameter. Microscopically, the tumors have a typical biphasic pattern with carcinomatous and sarcomatous elements. The carcinoma is usually high-grade and reminiscent of serous carcinoma, although some cases have undifferentiated, endometrioid, clear-cell, or even squamous carcinoma. The sarcomatous component is always high-grade and may be homologous or heterologous. In homologous tumors, the sarcomatous component is usually high-grade fibrosarcoma, although varieties such as leiomyosarcoma, malignant fibrous histiocytoma, or undifferentiated sarcoma may be found as well. Heterologous elements are seen in half of the cases. The most common heterologous sarcoma is rhabdomyosarcoma, followed by chondrosarcoma, and less often osteosarcoma and liposarcoma (99). Most carcinosarcomas have myometrial invasion, most commonly into less than half of the wall (99). Lymphovascular invasion is present in 60% and the carcinomatous element is usually the component invading myometrium and lymphovascular spaces (62,99).

Most studies suggest that the behavior of carcinosarcomas is predicted by the carcinomatous component. Tumors typically metastasize through lymphatic channels similar to endometrial carcinomas. Most metastases and recurrences are composed of pure carcinoma (27,28). Histopathologic adverse prognostic factors include heterologous elements (in stage I tumors), a high percentage of sarcomatous components in the main tumor and in the recurrences, and deep myometrial invasion (27–29).

Müllerian carcinosarcomas may arise in extrauterine-extraovarian sites. Most cases have been reported in the peritoneum, or retroperitoneum. Some cases occur at the site of previous radiotherapy, and some cases arise in areas of endometriosis (100–105).

Endometrial Stromal Neoplasms

In the current World Health Organization classification, endometrial stromal tumors are classified into endometrial stromal

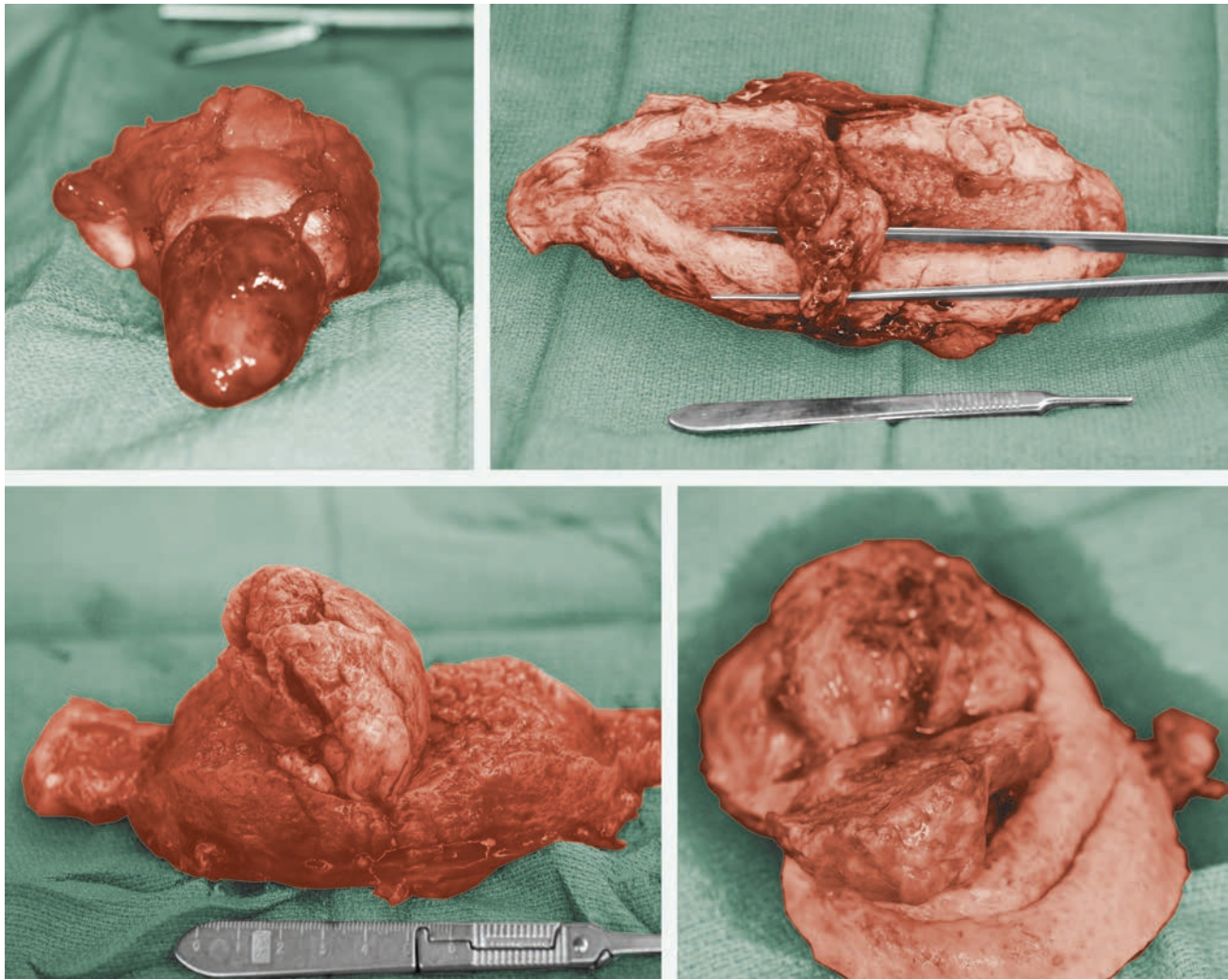


FIGURE 23.14. Carcinosarcomas, gross photographs of 4 cases demonstrating polypoid nature of lesions.

nodules, ESSs (by definition low-grade), and undifferentiated endometrial sarcoma. Both endometrial stromal nodules and ESSs are composed of cells identical to those found in the stroma of proliferative endometrium. Undifferentiated endometrial sarcomas, on the other hand, are high-grade sarcomas that do not resemble endometrial stroma and its diagnosis is made excluding other uterine sarcomas.

The differential diagnosis between an endometrial stromal nodule and an ESS is important since the nodules are always benign. Differential diagnosis is based upon the presence of infiltrating margins with or without angioinvasion in ESS. These 2 features are not seen in stromal nodules, which are always well circumscribed and have pushing margins (106).

Stromal Nodule

Stromal nodules are by far the least common of the pure endometrial stromal neoplasms. They are usually solitary masses with diameter varying from 1.2 to 22 cm with an average of 7.1 cm (107). On cut section, endometrial stromal nodules are fleshy and often tan-yellow. Microscopically, they are composed of uniformly bland, small cells resembling normal endometrial stromal cells with fusiform nuclei and scant cytoplasm. Abundant arterioles, reminiscent of the spiral arterioles of the normal

endometrium, are also present. The mitotic rate is low, with most tumors having fewer than 5 mitoses per 10 HPF. Most endometrial stromal nodules are cellular, and some have variable amounts of intercellular collagen, which occasionally forms dense collagen bands or nodules (Fig. 23.15). Another common finding is the presence of clusters of foamy histiocytes within the tumor. The borders between the tumor and the adjacent myometrium are microscopically well defined (pushing). Occasionally, they may have more irregular borders with minimal areas of tumor extending into adjacent myometrium, usually within 3 mm of the main tumor mass (106). Endometrial stromal nodules lack associated lymphovascular invasion. Other changes that can be seen in endometrial stromal nodules include smooth muscle metaplasia, cystic degeneration, sex-cord-like areas, and necrosis.

Endometrial stromal nodules may be confused with cellular leiomyomas. Since both tumors are benign, the misdiagnosis of one for the other is probably of no clinical consequence in a hysterectomy specimen. In a curettage specimen, the differential diagnosis is more important. There are some histologic features that favor a leiomyoma: blood vessels with thick muscular walls, cleft-like spaces, and merging with the adjacent myometrium. In addition, a battery of immunohistochemical stains may be of use. CD10 is usually present in endometrial stromal cells, and smooth muscle tumors stain positively for desmin and h-caldesmon.

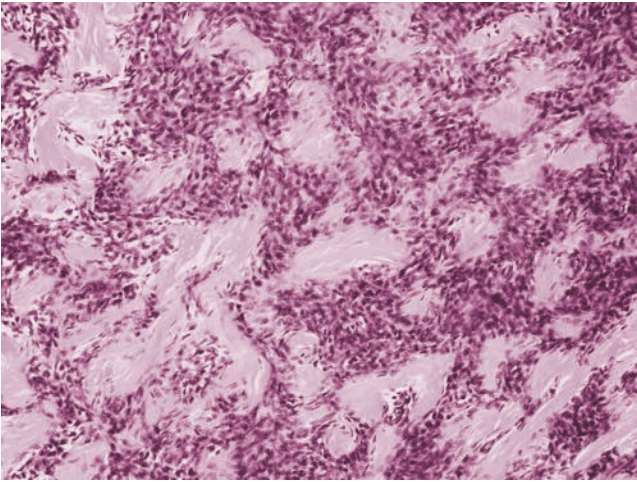


FIGURE 23.15. Endometrial stromal nodule, microscopic appearance.

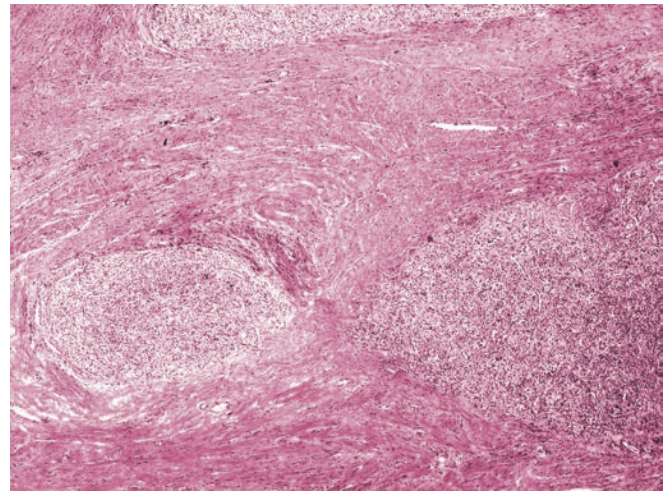


FIGURE 23.16. Endometrial stromal sarcoma, low-grade, microscopic appearance.

Endometrial Stromal Sarcoma

The last WHO classification divides endometrial sarcomas into 2 categories: ESSs (low-grade by definition), and undifferentiated endometrial sarcomas. However, recent studies have shown that not all ESS are low-grade and favor the subdivision of ESS into 2 categories: low-grade and high-grade, based on histological and molecular characteristics (90). This remains controversial.

The true low-grade ESSs have uniformly bland cells reminiscent of endometrial stromal cells. On gross examination, some are comprised of a single visible mass, and others have multiple masses or diffuse myometrial infiltration by worm-like masses (Fig. 23.16). Typically, these tumors show permeation of the myometrial wall, in some cases up to the serosa (Fig. 23.17). Most tumors have fewer than 10 mitoses per 10 HPF. Some ESSs have unusual histologic features that may confound the diagnosis. These features include myxoid changes, fibroblastic and/or smooth muscle differentiation, epithelioid changes, and extensive endometrioid glandular differentiation (108–111).

Low-grade ESSs are usually positive for ER, PR, and CD10, and approximately 50% have cytogenetic abnormalities involving rearrangements of chromosomes 6, 7, and 17. The most characteristic translocation of these tumors, t(T7;17) (Tp15;q21), generates a fusion of the *JAZF1* and *JJAZ1* genes. The presence of this chromosomal abnormality may be of use in the diagnosis of difficult cases or recurrent tumors (112).

The newly described entity of “high-grade ESS” is composed of tumors that display “either (1) a combination of low-grade and undifferentiated areas; (2) cytologic and immunohistochemical features that are intermediate between classic low-grade ESS and undifferentiated endometrial stroma (UES), or (3) cytologic features of UES but with the presence of finger-like infiltrative pattern of the surrounding myometrium or extension into lymphovascular spaces” (90). High-grade ESSs have been so far only described in the uterine corpus and they ranged in size from 3 to 9 cm (median, 7.5 cm). All tumors diffusely infiltrate myometrium, and have vascular invasion (90). These tumors have more nuclear atypia and mitoses than low-grade ESS, and can have necrosis, which is not seen in low-grade tumors. In addition, they have a characteristic gene *YWHAE-FAN22* rearrangement that is never present in true low-grade ESS. High-grade ESS can often be negative for ER and PR and have a worst prognosis than low-grade ESS, although they are not as aggressive as UES (90). Unlike low-grade ESS, high-grade ESS are often negative for ER, PR, and CD10 (90). This new distinct entity and whether

different from undifferentiated endometrial stromal sarcoma requires further validation.

Low-grade ESSs may occur in extrauterine sites including ovary, fallopian tube, cervix, vagina, vulva, pelvis, abdomen, retroperitoneum, placenta, sciatic nerve, or round ligament (113–118). Some of these cases are associated with endometriosis. Histologically, they are similar to uterine ESSs, and a uterine

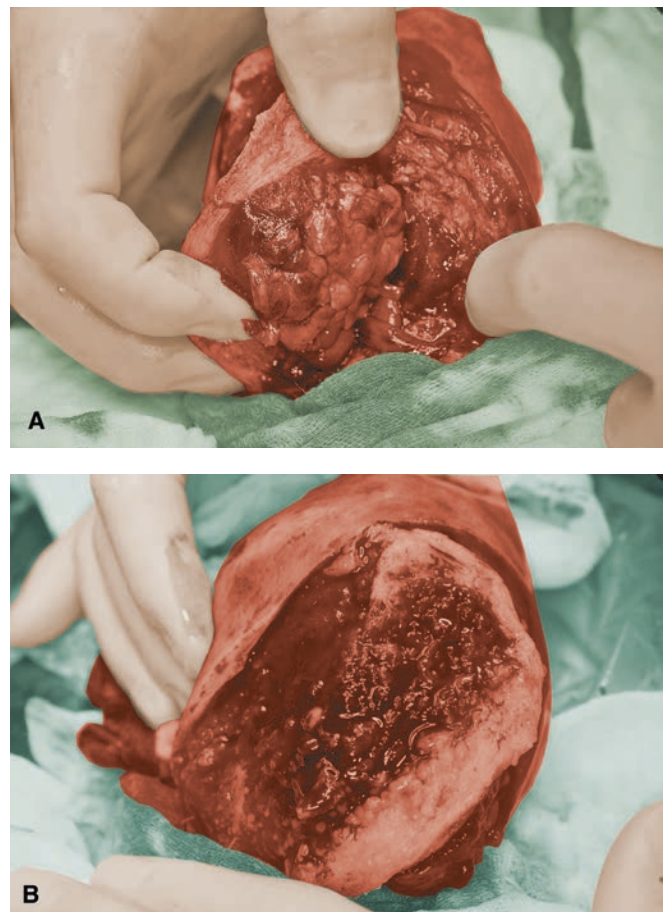


FIGURE 23.17. Endometrial stromal sarcoma, low-grade, gross appearance.

tumor needs to be excluded before accepting the lesion as a primary extrauterine ESS. The relapse rate for extrauterine ESS is 62%, which is similar to that of advanced low-grade uterine ESS.

Undifferentiated endometrial sarcomas are rare and account for only 6% of all uterine sarcomas (10). They have cytologic atypia to the extent that they cannot be recognized as arising from endometrial stroma. Morphologically, these high-grade lesions resemble undifferentiated mesenchymal tumors and behave as high-grade sarcomas (10,61,119). It is advisable to use a term such as “high-grade sarcoma,” “undifferentiated sarcoma,” or “poorly differentiated uterine sarcoma” (119) rather than “endometrial stromal sarcoma.” This last term may inaccurately suggest an indolent tumor. Undifferentiated uterine sarcomas are usually seen in patients older than 50 years, have a recurrence rate of over 85%, and are usually fatal (10,61,119).

Müllerian Adenosarcoma

Müllerian adenosarcomas are mixed müllerian tumors composed of malignant stroma and benign epithelium. Most adenosarcomas arise in the endometrium and, rarely, in the endocervix, lower uterine segment, and myometrium (21). Grossly, the majority are solitary polypoid masses with a spongy appearance secondary to the presence of small cysts. Occasional cases appear as multiple polyps or masses and can be multicentric. Their size is variable, being from 1 to 17 cm (mean, 5 cm).

Microscopically, the tumors have a benign epithelial component usually covering the surface of the polyps and in the form of benign glands uniformly distributed throughout the tumor. The mesenchymal component is usually a low-grade sarcoma that resembles endometrial stroma. The presence of hypercellular stroma around the glands is common, and some tumors have a leaf-like papillary growth pattern (Fig. 23.18). Sometimes the diagnosis of adenosarcoma may be difficult because of the very low-grade nature of the sarcoma. Minimal criteria were described by Clement and Scully in a review of 100 cases of adenosarcoma published in 1990 (21). They include at least one of the following: two or more stromal mitoses per 10 HPF, marked stromal hypercellularity, and significant stromal cell atypia. Even with these criteria, some cases are deceptively bland, and several cases have been seen in which the diagnosis was only possible after multiple “recurrences” of uterine polyps were reviewed (120). A minority of cases have “sarcomatous

overgrowth,” when more than 25% of the tumor is composed of pure sarcoma. In these cases, the sarcoma is typically high-grade and the lesions are aggressive (121) (Fig. 23.19).

Most adenosarcomas without stromal overgrowth express estrogen and progesterone receptors in the sarcomatous component and this may be used for therapeutic purposes. However, hormonal receptors are negative in adenosarcomas with stromal overgrowth (120,122). Besides stromal overgrowth, the only other histopathological feature associated with decreased survival is myometrial invasion (21,49,120,121). Müllerian adenosarcomas have been described in extrauterine sites including the ovary and areas of endometriosis in the vagina, rectovaginal septum, gastrointestinal tract, urinary bladder, pouch of Douglas, peritoneum, and liver (123–131).

Uterine Tumor Resembling Ovarian Sex-Cord Tumor

In 1976, Clement and Scully (132) coined the term uterine tumors resembling ovarian sex-cord tumors (UTROSCTs) to describe a series of uterine neoplasms with sex-cord-like pattern. Since then, sex-cord-like patterns have been demonstrated in endometrial stromal neoplasms, smooth-muscle neoplasms, and in cases lacking clear endometrial stroma and smooth-muscle differentiation. The term UTROSCT should be reserved for this last category. UTROSCT are tumors of uncertain histogenesis/lineage. Immunohistochemically these tumors co-express epithelial, myoid and sex-cord markers (133,134). This immunoprofile can also be seen in ESSs with sex-cord-like areas. However, UTROSCT lack the typical *JAZF1-JJAZ1* translocation frequently seen in endometrial stromal tumors (135). UTROSCTs are rare tumors, usually submucosal and well circumscribed, with a yellow cut surface. Histologically, they are composed of sertoliiform tubules with low mitotic activity and little nuclear atypia (132–134) (Fig. 23.20). Most of these tumors behave in a benign fashion, although there is at least one reported case with a small bowel metastasis (136).

Perivascular Epithelioid Cell Tumors

Perivascular epithelioid cell tumors (PEComas) are rare neoplasms presumably derived from perivascular epithelioid cells that coexpress melanocytic and smooth muscle markers. Other tumors that belong to the same family include angiomyolipoma

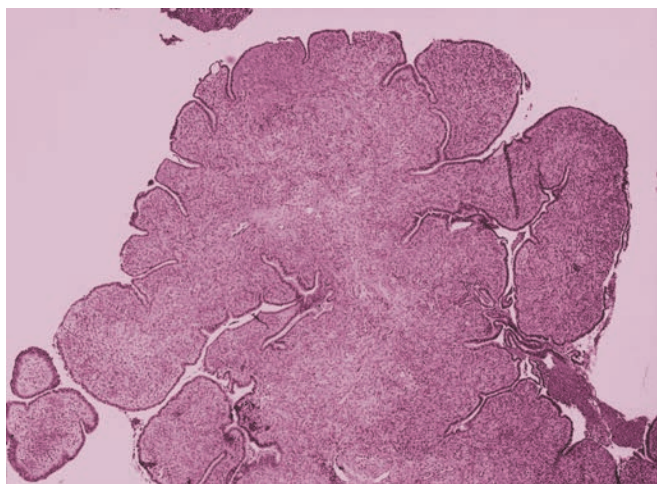


FIGURE 23.18. Müllerian adenosarcoma, microscopic appearance.

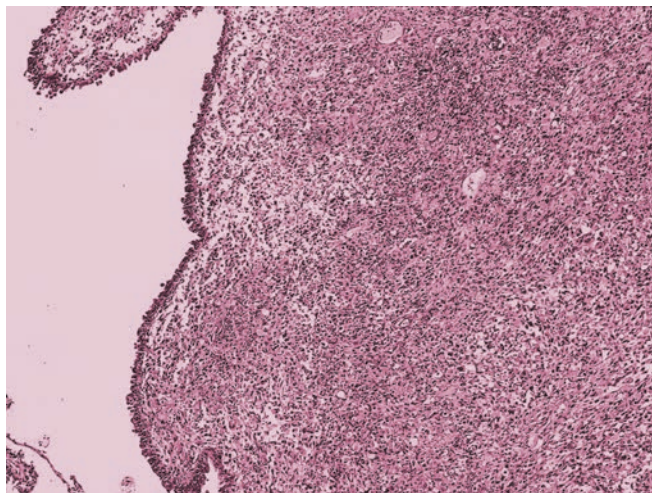


FIGURE 23.19. Müllerian adenosarcoma with sarcomatous overgrowth, microscopic appearance.

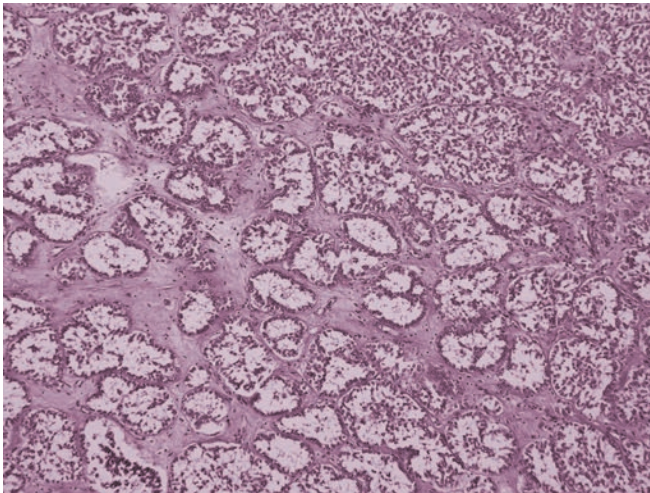


FIGURE 23.20. Uterine tumor resembling ovarian sex-cord tumor (UTROSCT), microscopic appearance.

(AML), clear-cell/sugar tumor of the lung, lymphangioleiomyomatosis (LLM), and myelomelanocytic tumor of ligamentum teres/falciform ligament. PEComas have been described in a variety of locations including visceral organs, soft tissues, skin, oral mucosa, orbit, and base of skull (137). Uterus and gastrointestinal tract are the most common locations for visceral PEComas. About 8% of PEComas occur in patients with the tuberous sclerosis complex. Most uterine PEComas are histologically and clinically benign. They can be either grossly well-circumscribed or focally infiltrative masses. Histologically, they are composed of epithelioid cells with clear or eosinophilic cytoplasm, sometimes associated with spindle cells, and a prominent vasculature (137,138). Approximately 25% of reported cases developed metastases and/or recurrences. Most malignant tumors have more than one of these three histologic features: necrosis, mitoses > 2 per 50 HPF, and lymphovascular invasion, but there is not a single reliable prognostic indicator other than the presence of lymphovascular invasion (137,138,139).

A distinct subset of PEComas, including some uterine, harbor *TFE3* gene fusions, and show immunoreactivity for TFE3 protein (140). In the past, *TFE3* gene fusions had only been described in alveolar soft-part sarcomas and some renal-cell carcinomas. PEComas with *TFE3* gene fusions appear to occur in younger people without tuberous sclerosis.

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumors (IMT) are indolent mesenchymal lesions that usually behave in a benign fashion or may recur locally. Most common sites include lung, mesentery, omentum, and retroperitoneum. Few cases have been reported in the uterus (141,142) where they present as polypoid masses in the lower uterine segment or bulky myometrial masses. They range in size from 1 to 12 cm. They are composed of bland spindle cells, with less than 2 mitoses per 10 HPF and no necrosis. Immunohistochemical expression of ALK is characteristic of all IMTs and can be used in the differential diagnosis with other uterine spindle-cell tumors that are negative (including smooth-muscle tumors, ESSs, and carcinosarcomas)(141).

Other Rare Uterine Sarcomas

Rarely other sarcomas can be found in the uterine corpus. Rhabdomyosarcomas, although more common in the cervix of

children, have also been encountered in the corpus in adults. They can be of embryonal or pleomorphic histology. They are aggressive tumors with a 5-year disease-specific survival of only 29%. Patients with pleomorphic rhabdomyosarcoma have a worse prognosis than those with embryonal histology (10,143,144). Uterine liposarcomas are rare tumors. Some of them arise in uterine lipoleiomyomas (145), and others are associated with smooth-muscle tumors and may represent leiomyosarcomas with cyst divergent differentiation (144,146). Other rare sarcomas described in the uterus include angiosarcoma, Ewing sarcoma, alveolar soft-part sarcoma, osteosarcoma, chondrosarcoma, fibrosarcoma, and malignant fibrous histiocytoma (144).

SURGERY

Surgery is a cornerstone in the treatment of the majority of soft-tissue sarcomas, including uterine sarcomas. Many women with uterine sarcomas will be premenopausal at the time of initial diagnosis and concerns about fertility and premature menopause need to be considered. Surgery to remove the primary tumor, myomectomy, or most often a hysterectomy, as well as to inspect the peritoneal cavity, is central in the initial management of these patients. The need to perform nodal evaluations, nodal dissections, and removal of the ovaries will be discussed. The role of cytoreductive procedures of extrauterine disease at the time of diagnosis and at recurrence will also be discussed. Fertility-preserving options are extremely limited, unfortunately, but they are possible in a few highly select cases of the less aggressive mesenchymal tumors.

Uterine Preservation

Myomectomy, or tumor resection, with preservation of the uterus is an option in younger women who wish to preserve fertility and are diagnosed with STUMP or other atypical leiomyomata of the uterus. Unfortunately, a total hysterectomy (never supracervical) must be performed in the majority of malignant mesenchymal tumors of the uterus. There is no clear option to preserve the uterus in patients diagnosed with leiomyosarcoma, undifferentiated (or high-grade) ESS, or carcinosarcoma. Uterine preservation has been described in 8 women diagnosed with “leiomyosarcoma,” and successful pregnancies were reported (147). However, it is unclear from this report whether these were all truly “high-grade” leiomyosarcomas or whether some, or all, were STUMPs or other less malignant histologies (147). A total hysterectomy must still be recommended until significant further investigation is conducted and reported.

Endometrial stromal tumors are a little challenging. A confirmed endometrial stromal nodule would not require completion hysterectomy since it is a benign lesion. However, it is difficult to confirm whether such a tumor is only an endometrial stromal nodule or an ESS without a significant amount of normal myometrium around it to confidently state that there are no infiltrating margins with or without angioinvasion (106). Therefore, a total hysterectomy should be recommended in postmenopausal women and in women who have completed childbearing. However, it may also still be necessary in women who may wish to have children. Uterine preservation for ESS has been reported in a very young 16-year-old girl (148) and in a 25-year-old who went on to carry a successful pregnancy (149).

Role of Nodal Evaluation or Lymphadenectomy

Two important questions to ask when deciding about whether to perform a procedure, in particular nodal dissections of

nonenlarged lymph nodes and removal of ovaries in premenopausal women, are (a) what is the risk of microscopic disease in those organs, and (b) is there a benefit to removing those organs. Lymph node metastasis in adult soft-tissue sarcomas is <3%, with some variation among histologic subtypes (150). Routine regional lymphadenectomy is not recommended for patients with adult soft-tissue sarcomas, but resection of bulky isolated metastases is considered (150).

The risk of lymph metastasis in leiomyosarcoma overall is approximately 7% (4,5,27,50,151,153) (Table 23.7). However, the rate of occult lymph node metastasis is less than 3% (151–154). There is no clear benefit to routine lymphadenectomy in patients who present with uterine leiomyosarcoma with disease confined to the uterus and/or clinically normal lymph nodes (4,16,27,50,151). Carcinosarcomas have a higher rate of both overall (27%) and occult (20%) lymph node metastasis (4,5,19,49,62,152) (Table 23.8). Undifferentiated endometrial sarcomas are also felt to behave similarly, but clear data are lacking. The role of lymphadenectomy beyond debulking of enlarged lymph nodes remains to be determined. Nemani and colleagues suggested that there is a benefit to lymphadenectomy irrespective of the use of radiotherapy (158). However, the current standard is that all patients, irrespective of stage, receive adjuvant systemic chemotherapy. It is quite possible that the therapeutic benefit of lymphadenectomy, if any, in patients with carcinosarcomas may be tempered by this. Nodal dissection in patients with carcinosarcoma is still reasonable and considered “standard.” The rate of overall and occult lymph node metastasis in ESS is 16% and 6% (4,5,13–15,154–157) (Table 23.9). Deep myometrial invasion and extensive lymph–vascular space invasion (LVSI) further increase the risk of occult metastasis (15). Both of these features are often not available at the time of hysterectomy. There is no clear known survival advantage to routine lymphadenectomy in these patients (14). It is reasonable to consider lymphadenectomy at the time of hysterectomy,

Table 23.7 Lymph Node and Ovarian Metastases in Uterine Leiomyosarcoma

Series	Lymph Node Metastasis		Ovarian Metastasis	
	All Cases	Occult Metastasis ^a	All Cases	Occult Metastasis ^a
Ayhan (151)	3/34 (8.8%)	1/27 (3.7%)	—	—
Major (152)	—	2/57 (3.5%)	—	2/59 (3.4%)
Leitao (153)	3/37 (8%)	1/27 (3.7%)	—	—
Goff (154)	—	0/9 (0%)	—	—
Gadducci (155)	—	0/4 (0%)	—	—
Giuntoli (27)	4/36 (11%)	—	—	—
Park (4)	0/11 (0%)	—	—	—
Koivisto (5)	0/15 (0%)	—	—	—
Kapp (50)	23/357 (6.4%)	—	—	—
Total	33/490 (6.7%)	3/124 (2.4%)	4/108 (3.7%)	4/130 (3.1%)

^aOccult metastasis means nodal metastasis in clinically normal lymph nodes and disease clinically confined to the uterine corpus and/or cervix.

Table 23.8 Lymph Node and Ovarian Metastases in Uterine Carcinosarcoma

Series	Lymph Node Metastasis		Ovarian Metastasis	
	All Cases	Occult Metastasis ^a	All Cases	Occult Metastasis ^a
Major (152)	—	51/287 (18%)	—	36/300 (12%)
Park (19)	—	13/41 (32%)	—	—
Park (4)	8/37 (22%)	—	—	—
Koivisto (5)	6/24 (25%)	—	—	—
Arend (49)	726/2709 (14%)	—	—	—
Galaal (62)	19/34 (56%)	—	—	—
Total	759/2804 (27.1%)	64/328 (19.5%)	—	36/300 (12%)

^aOccult metastasis means nodal metastasis in clinically normal lymph nodes and disease clinically confined to the uterine corpus and/or cervix.

recognizing the therapeutic, prognostic, or predictive value of this in ESS is unknown. Reoperation to complete a lymphadenectomy is not likely to be of any benefit in patients with ESSs that do not exhibit deep stromal invasion and extensive LVSI. The rate of lymph node metastasis in adenocarcinomas is approximately 3% (49). Based on very limited information, lymphadenectomy in patients with otherwise disease clinically confined to the uterus may not offer much benefit.

Role of Oophorectomy

The risk of ovarian metastasis is very low in leiomyosarcoma (152,153) (Table 23.7). Routine oophorectomy, especially in premenopausal patients, provides no benefit. A SEER analysis actually suggested a worse survival in cases that underwent a bilateral salpingo-oophorectomy (16). It is not entirely clear why removal of the ovaries would lead to a worse prognosis, but at least these data support retaining the ovaries in premenopausal women who are highly desirous of retaining ovarian function. Occult ovarian metastasis can be seen in approximately 12% of carcinosarcomas (152) (Table 23.8). Bilateral salpingo-oophorectomy should be recommended in these patients and fortunately, many will be postmenopausal. Occult ovarian metastasis in ESS is rare (15) (Table 23.9). However, ovarian preservation appears to be associated with a higher risk of recurrence but has no impact on OS since these patients do very well in general (11,14,52). Bilateral salpingo-oophorectomy is recommended because of this recurrence risk reduction but should be carefully discussed in young premenopausal women. The risk of ovarian metastasis and therapeutic benefit is difficult to discern due to a lack of large series addressing this in the other rare uterine sarcomas.

Cytoreductive Surgery for Patients with Extrauterine Disease at Initial Diagnosis

Cytoreductive surgery in patients with uterine sarcoma at the time of presentation has not been well described. The only information available is in patients presenting with uterine leiomyosarcoma and extrauterine metastasis (159). The median PFS in patients with a complete gross resection was 14.2 months,

Table 23.9 Lymph Node and Ovarian Metastases in Endometrial Stromal Sarcoma (Low Grade)

Series	Lymph Node Metastasis		Ovarian Metastasis	
	All Cases	Occult Metastasis ^a	All Cases	Occult Metastasis ^a
Park (4)	2/17 (12%)	—	—	—
Koivisto (5)	1/13 (8%)	—	—	—
Dos Santos (15)	7/36 (19%)	2/20 (10%)	11/87 (13%)	0/62 (0%)
Goff (154)	—	0/7 (0%)	—	—
Gadducci (155)	—	0/2 (0%)	—	—
Riopel (156)	3/8 (38%)	1/6 (17%)	—	—
Cheng (13)	4/18 (22%)	—	—	—
Shah (14)	7/100 (7%)	—	—	—
Signorelli (157)	3/19 (16%)	1/16 (6.3%)	—	—
Total	27/211 (12.8%)	4/51 (7.8%)	11/87 (13%)	0/62 (0%)

^aOccult metastasis means nodal metastasis in clinically normal lymph nodes and disease clinically confined to the uterine corpus and/or cervix.

compared to 6.8 months for those who underwent surgery and with visible residual disease ($p = 0.002$) (159). Similarly, OS was 31.9 months compared to 20.2 months, respectively ($p = 0.04$) (159). On multivariate analysis, complete surgical cytoreduction maintained an independent association with PFS but not with OS. However, the lack of independent statistical association with OS might be explained by the relatively small number of cases. Surgical cytoreduction may be a consideration in highly select cases in which complete resection of tumor is felt to be feasible without extensive procedures, such as exenteration. Any potential benefit of surgery should be weighed against the potential risks and these cases are to be individually managed.

Surgery for Recurrent Disease

Data are limited in regard to surgical cytoreduction of recurrent uterine sarcomas. Surgical cytoreduction is considered though in many of these cases especially if there has been a relatively long disease-free interval and sites of recurrence that seem amenable to a complete surgical resection. Surgery is often considered for recurrent ESSs due to their relative indolence, long disease-free intervals, and lack of other effective treatments. The approach to carcinosarcomas often is extrapolated from data for endometrial carcinomas currently. Resection of recurrent leiomyosarcoma has been described. Surgery for the other rare sarcomas is often a consideration, but there is no data for these other very rare uterine sarcomas.

Khoury-Collado et al. described a modern updated series of patients with uterine cancers that developed a recurrence in the pelvis after prior radiation therapy and underwent a pelvic exenteration from 1997 to 2011 (160). There were 6 uterine sarcomas among the 21 included cases: carcinosarcoma ($n = 2$), adenosarcoma ($n = 2$), leiomyosarcoma ($n = 1$), and ESS ($n = 1$). The 2 cases with carcinosarcomas had a short time from prior therapy to exenteration, and the median survival

after exenteration was only 6 months. The median survival after exenteration for the 4 other sarcomas was not reached and the 5-year OS was 66%. Pelvic exenteration seems to be a reasonable consideration in patients with isolated pelvic recurrences after prior radiotherapy. However, it must be recognized that pelvic exenterations are quite morbid and the outcomes reported are based on very small number of highly selected uterine sarcomas.

Resection of pulmonary metastases, both at the initial diagnosis and at the time of recurrence, is often considered in patients with soft tissue sarcomas and associated with a favorable survival benefit (161). Resection of pulmonary metastases specifically of recurrent uterine sarcomas without other extra-thoracic disease is associated with a survival benefit (162). Levenback and colleagues reported 5-year survival rate of 43% after pulmonary metastases resection among a group 45 uterine sarcomas including 38 leiomyosarcomas, 4 ESSs, and 3 carcinosarcomas (162). Unilateral pulmonary recurrences had a better survival after metastatectomy than patients with bilateral recurrences (mean survival 39 months vs. 27 months, respectively [$p = 0.02$]). Tumor size, use of adjuvant therapy after resection, histologic type, age, and time from hysterectomy to first pulmonary resection were not statistically associated with survival after metastatectomy.

Surgical cytoreduction of recurrent uterine leiomyosarcoma with or without pulmonary recurrences has also been reported to possibly provide a survival benefit. Leitao and colleagues reported a survival benefit with optimal (defined as largest residual tumor mass diameter ≤ 1 cm) resection of pulmonary and extrapulmonary first recurrences of uterine leiomyosarcoma (67). The median survival was 3.9 years after an optimal resection compared to only 0.7 years after suboptimal resection ($p = 0.002$). The only other prognostic factor was the time to first recurrence. The median survival was 5.1 years in cases with a time to first recurrence >12 months compared to 1.5 years for those with a time to recurrence of ≤ 12 months ($p = 0.005$). Tumor grade, thoracic versus nonthoracic procedures, sites of first recurrence, and use of adjuvant therapy after resection were not associated with survival. Secondary cytoreduction in these patients with recurrent uterine leiomyosarcoma was also reported to be associated with a survival benefit by Giuntoli et al. in a larger series (163). Secondary cytoreduction to no gross residual was independently associated with survival after adjusting for site of recurrence, use of chemotherapy, radiation therapy, combined surgery and chemotherapy, and recurrence time (163). Similar to Leitao et al., a longer time to recurrence was also prognostic of outcome but with 6 months used of the cutoff (163).

RADIATION THERAPY

Since the use of radiation therapy for patients with uterine sarcomas has been almost exclusively delivered in the postoperative setting (164), the role of preoperative, primary, or palliative radiotherapy will not be presented in this section. As they are more fully discussed in the chapter on epithelial tumors of the corpus, a detailed discussion of the techniques and complications of adjuvant radiation therapy will also not be presented in this chapter.

Uterine Sarcomas

There has been one published phase III randomized trial for all surgically staged patients with stage I and II uterine sarcomas. This study opened in July 1988 and closed to patient accrual in July 2001. Eligible patients underwent an initial

surgical resection that involved mandatory total abdominal hysterectomy and bilateral salpingo-oophorectomy. Retroperitoneal lymph node dissection was optional (only approximately 25% underwent lymph node sampling). Due to the time period of the inception of this trial, there were no recommendations regarding either collection of peritoneal washings or omentectomy. The study enrolled 224 patients for randomization from 36 institutions. Patient histologies included the following: 99 leiomyosarcomas (LMS), 92 carcinosarcomas (CS), 30 ESSs, 1 myxoid leiomyosarcomas, and 2 unclassified cell types. It must be noted that there was a central pathology review of tumor samples. Eligible study patients were randomized to undergo either observation or pelvic postoperative radiation therapy (PORT), which consisted of the delivery of approximately 50.4 Gy total dose in 28 daily 1.8 Gy fractions over 5 to 6 weeks. Conventional radiotherapy techniques using 2-dimensional (2-D) treatment planning techniques involving bony landmarks were employed to treat the whole pelvis as follows: (a) cranially, the superior aspect of the fifth lumbar vertebra; (b) caudally, the inferior aspect of the obturator foramen; (c) anteriorly, the upper margin of the symphysis pubis; and (d) posteriorly the level separating the second and third sacral vertebrae. Treatment field arrangements varied from 3 fields, 4-field “box” (55%), or parallel opposed pair (40%) beams. Chemotherapy was not administered to any study patients (165).

The primary objective of this European Organisation for Research and Treatment of Cancer (EORTC) trial was to determine whether adjuvant pelvic PORT could reduce the local (vaginal) and/or regional (pelvic) relapse rate of study patients versus those receiving no adjuvant therapy along with assessing if improvement in locoregional (LR) control translated in a significant reduction in distant metastases. Secondary objectives of EORTC 55874 focused on the impact of PORT on improving OS and PFS without significant increase in patient toxicity compared to the observational group (165).

EORTC 55874 was originally planned to accrue 75 patients per year for 3 years to obtain the projected 77 LR failures necessary to conduct the statistical analyses. However, due to slow accrual of patients, 2 unplanned interim analyses, the first in April 1995 and the second in December 2001, were required to assess the feasibility of completing study objectives. Thus, it required 13 years (median follow-up of 6.8 years) for patient accrual to record 68 out of the originally planned 77 LR relapses needed for adequate statistical evaluation. Of the 224 enrolled patients, 219 (2 in the observational cohort, 3 in the PORT group) had adequate follow-up data available for analysis (165).

Crude relapse rates for all cell types in EORTC 55874 were 47% (52 out of 110) in the PORT cohort and 50% (54 out of 109) in the observational arm. There was a significant reduction in overall LR relapse in the PORT group of 24 (21%) versus 44 (40%) in the no-adjuvant treatment arm ($p = 0.004$). Furthermore, there was a reduction in isolated LR relapse of 3% in the PORT group versus 18% in the nonirradiated arm. Distant metastases occurred as some component of failure in 49 (46%) of PORT patients versus 35 (32%) of observational patients. In addition, there was a higher isolated distant metastatic rate of 25.5% in the adjuvant group versus 10% in the nonirradiated cohort. The primary cause of death for study patients in EORTC 55874 was malignant disease in 81% (39 out of 48) of PORT patients and 93% (43 out of 46) for observational patients. There was no significant difference in OS or PFS as well as no difference in toxicity assessments between the PORT and observational groups (165) (Figs. 23.21 and 23.22).

Regarding patients with uterine CS, PORT did reduce LR failures from 47% (observational group) to 24% (PORT cohort) for patients with CS ($p < 0.05$), while not significantly increasing the overall distant metastatic rate (29% observational group vs. 35% PORT cohort). This improvement in LR control with adjuvant pelvic PORT was further noted when evaluating patients

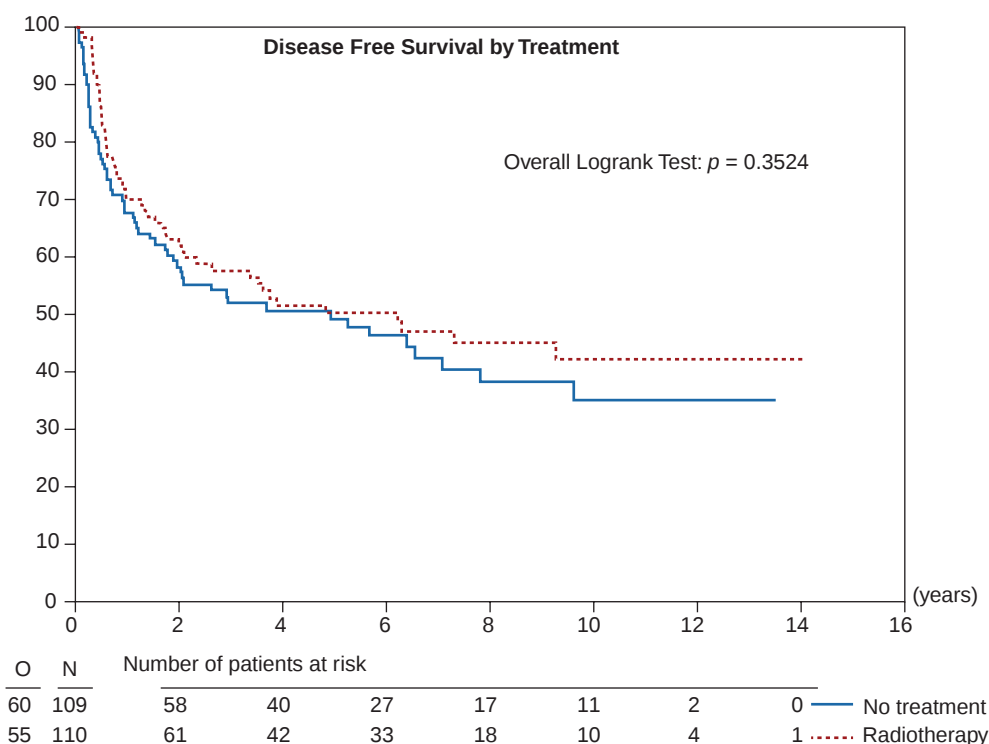


FIGURE 23.21. Disease-free survival from EORTC 55874 comparing postoperative radiation therapy versus observation in patients with uterine sarcoma.

Source: From Reed NS, Mangioni C, Malmstrom, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: An European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). *Eur J Cancer*. 2008;44:808–818, with permission.

having isolated LR failures (24% observational group versus 4% PORT cohort). However, there were more with isolated distant failures in the adjuvantly irradiated subset of patients with CS (7% observational group versus 15% PORT cohort) (165). This latter finding is similar to what has been shown for patients with endometrial carcinomas randomized to receiving adjuvant pelvic external beam radiation therapy versus the cohort not receiving any external beam irradiation (166). Nevertheless, EORTC 55874 seems to suggest that pelvic PORT should be considered as adjuvant therapy to improve the LR control in patients with stage I and II uterine CS. More importantly, PORT was beneficial to the OS of CS patients when compared to those receiving no adjuvant radiotherapy (HR, 1.58; 95% CI, 0.83, 3.01) (165).

Concerning patients with uterine LMS, the LR relapses in the observation group of 24% were comparable to the adjuvantly irradiated cohort of 20%. Yet, the overall distant failures rate of 33% in the observational group was less than the 54% rate found in the PORT cohort. However, isolated LR failures were 14% in the observational group versus 2% in the PORT cohort. Regarding isolated distant failures, there were 14% in the observational group versus 36% in the PORT cohort (165). Thus, EORTC 55874 may be used to defer adjuvant PORT for patients with stage I and II uterine LMS. Due to the observed

impact on improving isolated LR control in this patient subset population, one could make the argument for employing pelvic PORT as a salvage or palliative modality of therapy for selected patients with early-stage uterine LMS. Finally, EORTC 55874 showed a negative impact of PORT on OS in the LMS cohort (HR, 0.64; 95% CI, 0.36, 1.14) (165).

Most of the published papers on sarcomas of the uterus have been retrospective in nature, often requiring many years, if not decades, to accumulate enough patients to perform meaningful statistical analyses. Furthermore, these studies have often had to combine different cell types of sarcomas to attain numbers sufficient for evaluation (167–179). These retrospective studies have not achieved statistical power to reach definite conclusions.

However, the data from the nonrandomized review of the Surveillance, Epidemiology, and End Results (SEER) analyses of 2,677 cases of uterine sarcoma did demonstrate a statistically significant improvement in survival favoring adjuvant radiotherapy over observation for stage II, III, and IV (but not stage I) uterine sarcomas (26). The use of adjuvant PORT versus observation to significantly improve outcome, including OS, for advanced cases of uterine sarcoma (stages III and IVA) has been further supported in a retrospective single institutional study of 76 evaluable cases of uterine sarcomas (180). Yet, another SEER analysis of 1,819 patients with stage I/II uterine CS and

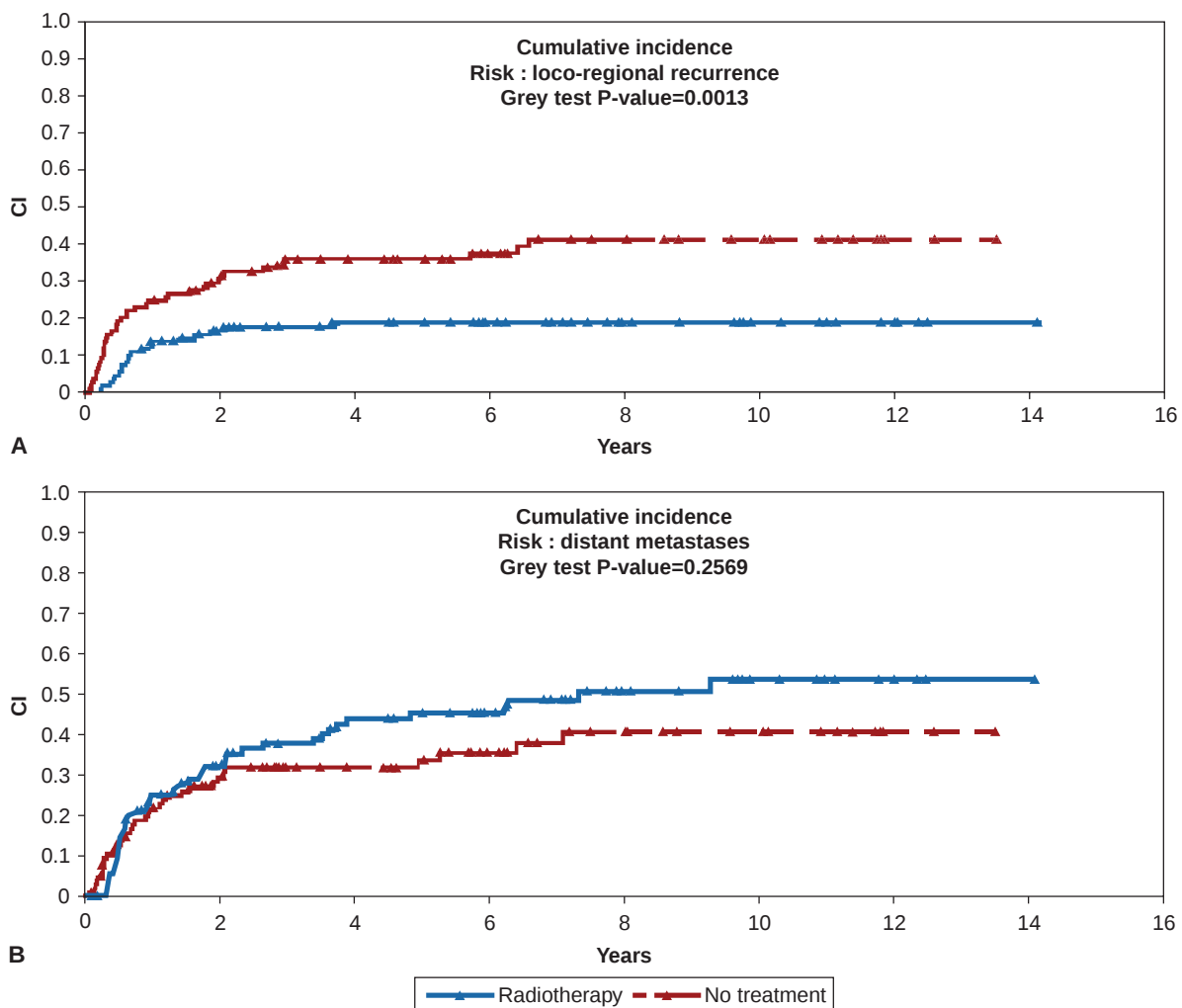


FIGURE 23.22. Cumulative incidence of locoregional recurrence (**A**) and distant metastases (**B**) of postoperative adjuvant radiation therapy vs. observation in patients with uterine sarcoma. Source: From Reed NS, Mangioni C, Malmstrom, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: An European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). *Eur J Cancer*. 2008;44:808–818, with permission.

1,088 with stage I/II uterine LMS revealed an improved survival for the subset of patients with CS who did not have any nodal sampling. However, there was no observed significant survival benefit for CS patient having a node dissection or for any subset of patients with LMS (181).

Recently, a retrospective review of the largest number to date of patients with uterine sarcoma was published (182). A query of the National Oncology Database (NODB) owned by Impac Medical Systems (Sunnyvale, CA) by these latter investigators yielded 3,650 evaluable patients with a diagnosis of uterine sarcomas. Of this initial group, 2,206 had definitive surgery; of these, 1,128 had CS, 529 LMS, and 361 EES comprising stages I through IV (and approximately one-third unknown stage). Statistical analyses showed no significant impact on OS for patients receiving predominantly pelvic PORT (with or without vaginal brachytherapy) versus those receiving no adjuvant therapy. However, it must be pointed out that there was again a noted significant reduction in LR relapse in the adjuvantly irradiated cohort versus the no treatment group of 53% at 5 years ($p < 0.001$). In addition, this LR control benefit of adjuvant radiation versus observation was preserved on subset analyses of patient with uterine CS ($p < 0.001$), LMS ($p < 0.01$) and ESS ($p < 0.05$) (182). Therefore, this latter study may be cited as evidence for future trials to prospectively incorporate adjuvant “volume-directed” radiation therapy into the discussion of potential therapeutic modalities to treat for patients with uterine sarcomas.

The GOG previously conducted 2 prospective clinical trials involving selected patients with uterine sarcomas. The earliest study reported on 156 evaluable patients with surgically staged I or II sarcomas of the uterus (183). Patients were enrolled from 1973 to 1982 and randomized (GOG protocol 20) to receive either at least one cycle of adjuvant doxorubicin or no adjuvant chemotherapy. Prior to study randomization, patients could receive *optional* adjuvant radiotherapy either preoperatively (external pelvic treatment of 40 Gy in 4 to 5 weeks with intracavitary vaginal brachytherapy of 20 Gy to point A) or postoperative pelvic external beam irradiation alone to 50 Gy in 5 to 6 weeks (184).

It should be noted that 11 of 48 (23%) patients with leiomyosarcomas in GOG 20 underwent adjunctive radiotherapy. Forty-nine of 109 patients (45%) with “nonleiomyosarcomas” (85.3% were carcinosarcomas) had adjuvant external beam therapy of the pelvis. Radiotherapy did not seem to affect recurrence in general. Table 23.10 shows that there was a notable decrease in vaginal recurrences in patients with early-stage uterine carcinosarcomas. Table 23.10 also demonstrates an increase in extravaginal failures in the group of patients with CS receiving radiotherapy (183). Table 23.11 depicts additional data from GOG 20 that demonstrate a significant reduction in pelvic relapses (10%) in treated patients compared with those

Table 23.10 Sites of First Recurrence for Uterine Carcinosarcomas^a Based on Use of Radiotherapy

	None	Vaginal	Extravaginal
No RT	28	11	10
RT	23	2	19

RT, radiation therapy.

^aPatients with stage I/II uterine carcinosarcomas.

Source: Modified from Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant Adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol*. 1985;3:1240–1245, with permission.

Table 23.11 Sites of First Recurrence for Uterine Carcinosarcomas^a Based on Use of Radiotherapy

	Pelvic	Extra-Pelvic
No RT	14/60 (23%)	12/60 (20%)
Pelvic RT	5/49 (10%)	17/49 (35%)

RT, radiation therapy.

^a85% of this group (93 patients) with nonleiomyosarcomas of the uterus were stage I/II uterine carcinosarcomas.

Source: Modified from Hornback NB, Omura G, Major FJ. Observations on the uterine sarcomas of adjuvant radiation therapy in patients with stage I and II uterine sarcoma. *Int J Radiat Oncol Biol Phys*. 1986;12:2127–2130, with permission.

untreated patients with predominantly uterine carcinosarcomas (23%) (184).

The second main GOG trial (GOG Protocol #40) for patients with uterine sarcomas involved a nonrandomized clinicopathologic evaluation of patients with clinical stage I and II disease uterine LMS and CS (152). This study opened in February 1979 and subsequently closed in October 1988. Of the 453 eligible patients, 430 (95%) had the mandated extrafascial hysterectomy, bilateral salpingo-oophorectomy, and selective retroperitoneal lymphadenectomy. Of this latter group, there were 301 (70%) patients with carcinosarcomas, of which 240 (80%) had surgical stage I/II disease. From this subset, Table 23.12 displays the locations of first sites of relapse(s). Although adjuvant pelvic external beam therapy was not mandated in this surgical trial, there again appears to be a possibility that postoperative pelvic PORT plays a role in reducing LR relapses in patients with early-stage uterine CS.

In a novel pilot study from France, 18 patients with uterine sarcomas with optimally debulked surgical stage I, II, and III sarcomas (13 of 18 with uterine LMS) received adjuvant doxorubicin, cisplatin, and ifosfamide (three cycles) followed by sequential pelvic external beam radiotherapy to a total dose of approximately 45 Gy in 5 weeks with or without vaginal brachytherapy (185). These investigators then performed a matched case-control study utilizing 18 patients of whom 16 underwent pelvic radiotherapy alone and 2 received no adjuvant treatment. With a median follow-up of 43 months (range, 23 to 56 months), this study found that only 5 patients (27.8%) had suffered recurrences. All failed solely in extrapelvic sites. Moreover, neither median survival nor disease-free survival had

Table 23.12 Sites of First Recurrence for Uterine Carcinosarcomas^a Based on Use of Radiotherapy

	No RT	Pelvic RT
Pelvis	43	20
Abdomen	43	19
Distant	38	31
None	83	59

^aFor patients with uterine carcinosarcomas who may have had more than one relapse.

Source: Modified from Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma: a Gynecology Oncology Group study. *Cancer*. 1993;71:1702–1709, with permission.

been reached for study patients at last follow-up. Thus, there is still much uncertainty regarding the role of pelvic external beam irradiation for patients with uterine LMS, especially reserving “volume directed” radiotherapy in combination with chemotherapy as adjunctive treatment or even as a part of salvage and/or palliative therapeutic intervention.

Uterine Carcinosarcomas

Regarding published reports on individual uterine sarcoma histologies, the most common type is currently being termed as metaplastic carcinomas (97), “mixed epithelial and stromal tumors of the uterus” (2), or historically known as uterine carcinosarcomas or some variant of mixed müllerian uterine tumors (169, 186–195). There has been one randomized phase III prospective trial of adjuvant radiotherapy in carcinosarcomas, (GOG 150). This study compared whole-abdominal irradiation to 3 cycles of cisplatin-ifosfamide chemotherapy with respect to recurrence rates, and DFS and OS. Also evaluated were therapeutic toxicities. Eligible were patients with carcinosarcomas confined to the abdomen who underwent optimal surgical debulking with no postsurgical residual disease greater than 1 cm. Patients randomized to receive radiotherapy were prescribed a total dose of 30 Gy to the whole abdomen using external beam therapy followed by a pelvic boost to an approximate cumulative pelvic dose of 50 Gy.

The first published report of the 2 treatment cohorts was based upon an analysis performed in December 2005 (196). There were 224 patients enrolled, of whom 206 were evaluable. In this latter group, 105 patients underwent adjuvant radiotherapy, while 101 were given chemotherapy. The estimated death rate for patients receiving chemotherapy was 32.8% lower than for those receiving radiotherapy ($p = 0.042$). A subsequently published update of GOG 150 based upon a May 2006 analysis demonstrated that this reduction in estimated death rate by chemotherapy was 31% relative to radiotherapy ($p = 0.046$) (197).

The most recent evaluation of the data of patients on GOG 150 occurred in November 2006 (198). At the time of this analysis, the median duration of follow-up for patients alive at last contact was 63 months. The breakdown of surgical stages for patients in the radiotherapy versus chemotherapy arms is as follows: stage I—35 out of 105 (33.3%) versus 29 out of 101 (28.7%); stage II—11 out of 105 (10.5%) versus 15 out of 101 (14.9%); stage III—45 out of 105 (42.9%) versus 47 out of 101 (46.5%); and stage IV—14 out of 105 (13.3%) versus 10 out of 101 (9.9%). The estimated crude probability of relapse within 5 years was a nonsignificant 58% versus 52% for the radio- and chemotherapy groups, respectively. The sites of first failure are presented in Table 23.13. Although not statistically significant, there were fewer vaginal but more abdominal relapses in the adjuvant radiotherapy group as compared to the chemotherapy arm. Table 23.14 demonstrates that the estimated 5-year survival was approximately 35% for those randomized to adjuvant radiotherapy versus 45% for those receiving chemotherapy. After adjusting for stage and age at diagnosis, there was a trend in death rate reduction of 29% for those receiving chemotherapy compared with radiotherapy (HR, 0.712; 95% CI, 0.484–1.048; $p = 0.085$; 2-tail test). Of interest, those patients who received adjuvant radiotherapy had more late complications, mainly gastrointestinal, than those having cytotoxic therapy ($p < 0.001$). In addition, 2 patients undergoing radiotherapy died as a direct result of radiation-induced hepatitis (198).

A recent retrospective single institutional study from a major academic medical center attempted to further verify the results of GOG 150 by evaluating 49 patients with optimally debulked stage I–IV uterine CS who received either adjuvant radiotherapy alone (pelvic or whole abdominal irradiation ± vaginal brachytherapy)

Table 23.13 Patterns of Failure for Uterine Carcinosarcomas

Sites of Recurrence ^a	WAI (n = 105), Number of Cases	Chemotherapy (n = 101), Number of Cases
Vagina	4	10
Pelvis	14	14
Abdomen	29	19
Distant	27	24

n, total number of cases in each arm; WAI, whole abdominal irradiation.

^aSome patients had multiple sites of relapse.

Modified from Wolfson AH, Brady MF, Rocereto T, et al. A Gynecologic Oncology Group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as postsurgical therapy in stage I–IV carcinosarcoma (CS) of the uterus. *Gynecol Oncol*. 2007;107:177–185, with permission.

or predominantly paclitaxel/carboplatin chemotherapy (± whole abdominal or pelvic irradiation ± vaginal brachytherapy). Although not statistically significant due to small sample size, this latter report did show a reduction in upper abdominal relapses (24% versus 35%) and extravaginal/pelvic failures (45% versus 91%) in the group receiving combined modality adjuvant therapy versus the cohort receiving adjuvant radiation therapy alone, respectively (199).

Results from other retrospective series that focused solely on uterine CS are inconsistent with respect to the impact of adjuvant therapy on outcome with some demonstrating no benefit for postoperative radiotherapy (169,189,191,192,194), while others have shown a significant impact of pelvic PORT on survival for patients with carcinosarcomas (186,188,193,195). One of these above studies involved a review of the nonrandomized SEER database of 2,461 women with carcinosarcomas from 1973 to 2003 (195). In this data set, 890 patients received adjuvant radiotherapy. The overall 5-year survivals of those receiving radiotherapy versus no irradiation were 41.5% and 33.2%, respectively ($p < 0.001$). Furthermore, a significant improvement in survival in this study was observed for all stages of disease, including stage IV.

Finally, there have been several published retrospective reports suggesting that combined adjuvant radiotherapy and chemotherapy may impart even longer survival, especially in stage I and II disease (187,190,200). Nevertheless, the role of adjuvant radiotherapy for the management of patients with uterine carcinosarcomas continues to remain inconclusive. Since there were more vaginal failures in the chemotherapy arm of GOG protocol 150 and other sites of relapse were similar or less common in frequency (abdominal recurrences) than those in the radiotherapy arm, then perhaps postoperative vaginal brachytherapy (either high- or low-dose rate) with chemotherapy (of greater than three cycles) should be considered for any patient having optimally debulked carcinosarcomas in future trials.

Uterine Leiomyosarcomas

There are no existing randomized phase III trials that demonstrate any impact of adjuvant radiation therapy on LR relapses or survival in this patient population. There still remains a paucity of information that specifies between upper abdominal and extra-abdominal distant sites of tumor involvement. The respective pelvic/extrapelvic percentages were 18.5% (22 out of 119)/41.2% (49 out of 119) for nonirradiated and 12.9%

Table 23.14 Chemotherapy in Leiomyosarcoma of the Uterus

Drug	n	Prior Therapy	Schedule	Overall Response (%)	Reference
<i>Single-Agent Chemotherapy</i>					
Primary Chemotherapy					
Liposomal doxorubicin	32	11 RT	50 mg/m ² q 4 wk	16	225
Topotecan	36	8 RT	1.5 mg/m ² × 5 d q 3 wk	11	226
Paclitaxel	33	8 RT	175 mg/m ² q 3 wk	9	227
Ifosfamide	35	15 RT	1.5 g/m ² × 5 d q 4 wk (1.2 g/m ² if prior RT)	17	228
Etoposide	28	7 RT	100 mg/m ² × 3 d q 3 wk	0	229
Cisplatin	33	8 RT	50 mg/m ² q 3 wk	3	230
Doxorubicin	28	N/A	60 mg/m ² q 3 wk	25	231
Piperazinedione	19	N/A	9 mg/m ² q 3 wk	5 ^a	232
Aminothiadiazole	20	N/A	125 mg/m ² q 1 wk	0	233
Diaziquone	24	N/A	22.5 mg/m ² q 3 wk	0	234
Trabectedin	20	7 RT	1.5 mg/m ² over 24 h q3 wk	10	250
Nonprimary Chemotherapy					
Gemcitabine	44	11 RT, 35 CT	1,000 mg/m ² weekly × 3 q 4 wk	21	236
	31	31 CT	1,250 mg/m ² weekly × 2 q 3 wk	3.2 ^b	236
	29	15 RT, 19 CT	1,250 mg/m ² weekly × 3 q 4 wk	3 ^b	237
	56	N/A	1,000 mg/m ² weekly × 3 q 4 wk	18 ^b	238
Paclitaxel	48	15 RT, 33 CT	175 mg/m ² q 3 wk (135 mg/m ² if prior RT)	8.4	239
Trabectedin	54	54 CT	1.5 mg/m ² q 3 wk	4 ^b	240
	49	49 CT	1–1.8 mg/m ² q 3 wk	4.1 ^b	241
	35	21 RT, 4 CT	1.5mg/m ² over 24 h q 3 wk	17 ^b	333
Trimetrexate	23	7 RT, 10 CT	5 mg/m ² orally × 5 days q 2 wk	4.3	242
Etoposide	29	6 RT, 27 CT	50 mg/m ² orally × 21 days q 4 wk	6.9	243
	28	7 RT, 27 CT	100 mg/m ² days 1, 3, 5 q 4 wk	11	244
Amonafide	26	8 RT, 25 CT	300 mg/m ² × 5 days q 3 wk	4	245
Mitoxantrone	12	12 CT	12 mg/m ² q 3 wk	0	246
Cisplatin	19	19 CT	50 mg/m ² q 3 wk	5	247
Temozolomide	11	N/A	180 mg/m ² orally × 5 days q 4 wk	18 ^c	249
Vinorelbine	16	16 CT	30 mg/m ² weekly × 8	6 ^c	248
Combination Chemotherapy					
Doxorubicin <i>plus</i>	20	N/A	60 mg/m ² q 3 wk	30	231
Dacarbazine			250 mg/m ² × 5 d q 3 wk		
Dacarbazine <i>plus</i>	18	7 RT	750 mg/m ² q 4 wk	28	253

(continued)

Table 23.14 Chemotherapy in Leiomyosarcoma of the Uterus (Continued)

Drug	n	Prior Therapy	Schedule	Overall Response (%)	Reference
Mitomycin			6 mg/m ² q 4 wk		
Doxorubicin			40 mg/m ² q 4 wk		
Cisplatin			60 mg/m ² q 4 wk		
Dacarbazine <i>plus</i>	10	10 No CT	750 mg/m ² q 4 wk	80	254
Mitomycin			6 mg/m ² q 4 wk		
Doxorubicin			40 mg/m ² q 4 wk		
Cisplatin			60 mg/m ² q 4 wk		
Mitomycin <i>plus</i>	35	8 RT	8 mg/m ² q 3 wk	23	255
Doxorubicin			40 mg/m ² q 3 wk		
Cisplatin			60 mg/m ² q 3 wk		
Hydroxyurea <i>plus</i>	38	11 RT	2 g orally × 1 day q 4 wk	18	256
Dacarbazine			700 mg/m ² q 4 wk		
Etoposide			300 mg/m ² × 2 days q 4 wk		
Ifosfamide <i>plus</i>	33	9 RT, 33 No CT	5 mg/m ² q 3 wk	30	257
Doxorubicin			50 mg/m ² q 3 wk		
Gemcitabine <i>plus</i>	34	14 RT, 16 CT	900 mg/m ² days 1, 8 q 3 wk	53 ^c	258
Docetaxel			100 mg/m ² day 8 q 3 wk (25% lower doses if prior RT)		
Gemcitabine <i>plus</i>	42	42 No CT	900 mg/m ² days 1, 8	36	215
Docetaxel			100 mg/m ² day 8 q 3 wk		
Gemcitabine <i>plus</i>	48	17 RT, 48 CT	900 mg/m ² days 1, 8	27	216
Docetaxel			100 mg/m ² day 8 q 3 wk		
Doxorubicin <i>plus</i>	38	38 No CT	60 mg/m ² q 3 wk	19 ^a	259
Cyclophosphamide			500 mg/m ² q 3 wk		
Gemcitabine <i>plus</i>	9	N/A	800 mg/m ² days 1, 8	22	260
Vinorelbine			25 mg/m ² days 1, 8 q 3 wk		
Temozolomide <i>plus</i>	11	10 CT	150 mg/m ² orally days 1–7 q 2 wk	9.1	262
Thalidomide			200 mg orally daily		
Biologic Agents					
Thalidomide	9	14 RT, 29 CT	200–1,000 mg orally daily	0	324
Sorafenib	37	N/A	400 mg orally twice daily	3 ^c	325
Sunitinib	23	23 CT	50 mg orally daily × 4 of 6 wk	8.7	321
Aflibercept	41	14 RT, 20 CT	4 mg/kg day 1 q2 wk	0	326
Ridarforolimus	57	57 CT	12.5 mg × 5 days q2 wk	0 ^c	331
Bevacizumab <i>plus</i> Doxorubicin	7	N/A	15 mg/kg q3 wk 75 mg/m ²	28	329

Note: All chemotherapy agents were given intravenously unless specified. CT, chemotherapy; N/A, not available; RT, radiation therapy.

^aUterine sarcoma.

^bAdult soft-tissue sarcoma.

^cAdult Leiomyosarcoma.

^dFemale genital tract leiomyosarcoma.

(8 out of 62)/43.5% (27 out of 62) for patients treated with postoperative radiotherapy (152,155,201). It does not appear that postoperative radiotherapy has any significant effect on reducing recurrences for patients with uterine leiomyosarcoma. However, 2 series combined to yield an 11.1% (4 out of 36) pelvic relapse rate with radiation versus 61.1% (22 out of 36) without the implementation of adjuvant radiation therapy (152,155). The major problem is that the majority of these patients have distant extra-abdominal metastases, such as the lung, despite having local control. There is an impending need in developing more effective systemic therapies to improve patient outcome (152,155).

A retrospective study from a single institution performed a case-control study of patients with uterine leiomyosarcomas; this study “showed a trend toward improved survival in the 31 cases with adjuvant pelvic irradiation compared with the controls who did not receive adjuvant radiation therapy” (27). Another more recent retrospective study of 143 patients with surgical stage I–IV uterine LMS from a consortium of institutions reported on 24 patients (17%) who received pelvic PORT and 63 (44%) who underwent adjuvant and/or palliative chemotherapy. This latter study found that the pelvic relapse rate was significantly reduced ($p = 0.02$) for patients undergoing radiotherapy (18%) versus those who did not have radiation therapy (49%). Although not maintained at 90 months of follow-up, this study also showed that the 5-year survival of the patients receiving adjuvant radiation (70%) was greater than those not having radiotherapy (35%) (202). The role of adjuvant radiotherapy in the management of patients with uterine LMS remains undefined.

Endometrial Stromal Sarcomas

There have been no randomized phase III trials that have been able to show any significant impact of adjuvant radiotherapy on outcome for patients with uterine EES. This class of endometrial sarcoma can be subdivided into either a low-grade category (ESS) or a high-grade sarcoma now termed undifferentiated uterine sarcoma. Gadducci and colleagues reported no abdominal or distant recurrences independent of the administration of adjuvant irradiation for all stages of low-grade ESS (203). Yet, there was a 33.3% (6 out of 18) pelvic recurrence rate, of which the majority did not undergo any radiation therapy. This latter finding suggests that postoperative external pelvis radiotherapy should at least be considered for the subset of patients with low-grade ESS.

One retrospective report reviewed 28 patients with ESSs of which 19 were low-grade and 9 were high-grade (204). Fifty percent of the patients in this series underwent adjuvant pelvic radiotherapy with no difference in the survival of the patients. In addition, almost 30% of those receiving adjuvant radiotherapy relapsed within the treatment field. Regarding undifferentiated endometrial sarcomas, another study documented multiple sites of recurrence, including abdominal (34.8% [11 out of 32]), distant (34.8% [11 out of 32]), and pelvic (40.6% [13 out of 32]) sites of relapse (205). However, a more recent small series of 13 patients with all stages of uterine EES showed that the 10 patient undergoing pelvic PORT (+/- vaginal boost) had an 89% LR control versus 50% LR control for the 3 not receiving any radiotherapy (206). Thus, the role of radiotherapy for patients with uterine EES remains uncertain.

CHEMOTHERAPY

Uterine sarcomas, although far less common than endometrial carcinomas, exhibit 2 features that would suggest a need

for systemic therapy: a recurrence rate of at least 50%, even in early-stage disease, and a high propensity for distant failure. The comparatively low incidence of uterine sarcomas has made randomized, controlled trials difficult. Despite this, cooperative group studies have provided data from phase II and III trials for the rational selection of systemic chemotherapy.

Crucial to the understanding of the use of chemotherapy in uterine sarcomas is the observation that these neoplasms are heterogeneous. Uterine carcinosarcomas (malignant mixed müllerian tumors) and leiomyosarcomas constitute 90% of cases entered into clinical trials. These 2 histologic subtypes are usually the only uterine sarcomas with sufficient numbers to permit meaningful phase III studies; however, as these 2 histologic subtypes appear to respond differently to chemotherapy, they should be studied separately.

Limited Disease

Uterine sarcoma has a high rate of distant metastases even in the absence of intraperitoneal or lymph node metastases. It has been concluded that this is due to the high rate of hematogenous and lymphatic dissemination (207). Therefore, the role of adjuvant systemic chemotherapy is under investigation in patients with apparently limited disease that has been fully surgically resected. A meta-analysis of almost 2,000 patients with localized resectable soft-tissue sarcomas (including uterine sarcomas) treated on small randomized trials of adjuvant anthracycline-based chemotherapy showed improved outcomes with chemotherapy compared to local treatment alone. There was an absolute risk reduction in recurrence of 12% and in death of 11% associated with doxorubicin-based chemotherapy combined with ifosfamide (208). Application of these data to uterine sarcoma is mired by the range of tumor sites included in the meta-analysis and the heterogeneity of sarcoma subtypes.

The largest randomized trial, to date, of adjuvant chemotherapy versus no further therapy in patients with uterine sarcoma did not segregate different histologic subtypes. Although the recurrence rate and median survival of patients treated with doxorubicin compared to no therapy were 41% versus 53% and 73 months versus 55 months, respectively, this phase III GOG trial of 156 evaluable patients concluded that there was no significant difference (183). Adjuvant pelvic radiotherapy was optional and not balanced between the arms. The fact that there was not a protocol-specified schedule of imaging for recurrence may have also affected the results. As with advanced disease, more recent trials have segregated the histologic subtypes. Previous studies reported that an effective adjuvant chemotherapy regimen was a combination of cyclophosphamide, vincristine, doxorubicin, and dacarbazine (DTIC); it yielded a 68% to 89% 5-year survival in stage I uterine sarcomas (209–212).

Uterine Carcinosarcoma

A nonrandomized study using adjuvant combination chemotherapy of etoposide, cisplatin, and doxorubicin demonstrated a 2-year survival of 92% in 23 patients with surgical stage I and stage II uterine carcinosarcoma. The fact that 7 patients also received radiation therapy makes interpretation of the results difficult (213). A pilot study concluded that multimodality treatment consisting of chemotherapy with epirubicin and cisplatin as well as radiation resulted in a 74% OS at a median follow-up of 55 months in 38 patients with surgical stages I and II uterine carcinosarcoma (200). However, the high dropout made the conclusion of multimodality treatment controversial. A phase III GOG study by Sutton et al. of 65 patients with completely resected stage I and II uterine carcinosarcoma who were treated with adjuvant ifosfamide and cisplatin reported 2- and 5-year survivals of 82% and 62%, respectively (214). Since more than

half of the recurrences involved the pelvis, the study suggested that a combined sequential approach with chemotherapy and radiotherapy might be beneficial for this group of patients. This would need to be verified in a randomized phase III study.

GOG 150, a phase III randomized study of patients with stage I–IV uterine carcinosarcoma (44% with stage I or II) who had undergone maximal resection of all gross disease compared whole abdominal radiation with three cycles of cisplatin and ifosfamide as adjuvant therapy. Although, not found to be statistically significant, there was a trend toward improved outcome in the chemotherapy group with recurrence and estimated death rates 21% and 29% lower, respectively, compared to the radiotherapy group (198).

Uterine Leiomyosarcoma

The role of adjuvant chemotherapy following complete resection of early stage uterine leiomyosarcoma is still under investigation but preliminary results of adjuvant systemic chemotherapy are promising. Two factors continue to limit the study of adjuvant therapy in patients with uterine leiomyosarcomas: the relatively low frequency of the disease, which makes it difficult to complete randomized trials in a reasonable period of time, and the lack of highly active agents.

The demonstrated activity of gemcitabine plus docetaxel in metastatic uterine leiomyosarcoma led to investigation of this combination in the adjuvant setting (215,216). A phase II, single-institution trial, of four cycles of fixed-dose-rate gemcitabine and docetaxel following complete resection of stage I–IV disease was performed (217). Among the 18 patients with early-stage disease, 59% remained disease-free at 2 years and the median OS had not been reached at the 5-year follow-up. The Sarcoma Alliance for Research through Collaboration (218) subsequently conducted a phase II, multicenter study of four cycles of adjuvant fixed-dose-rate gemcitabine docetaxel followed by 4 cycles of doxorubicin in 47 patients with uterus-limited leiomyosarcoma (219). Although 78% of the patients remained progression-free at 2 years, this dropped to 50% at the 3-year follow-up (220). Of note, in this study, age, menopausal status, hormone receptor status, grade, mitotic rate, or FIGO stage were not significantly associated with PFS. A proposed phase III multicenter randomized trial (GOG 277) will compare gemcitabine and docetaxel followed by doxorubicin to the current standard approach of observation, in order to determine if adjuvant chemotherapy improves outcomes for patients with uterus-limited high-grade leiomyosarcoma (221).

Low-Grade Endometrial Stromal Sarcomas

There are no data to support the use of adjuvant chemotherapy in patients who had complete resection of low-grade ESS confined to the uterus. The standard approach in this setting is observation alone. The role of adjuvant hormonal therapy in these patients has not been evaluated prospectively. Given the hormone-sensitive nature of these tumors, it is felt that estrogen replacement therapy may be detrimental in patients with low-grade ESS (222).

Adenosarcomas

Owing to the rarity of these tumors, there are no prospective data on the role of adjuvant systemic therapy for patients with completely resected adenosarcoma. Patients without “sarcomatous overgrowth” are often treated similarly to patients with ESS. The presence of “sarcomatous overgrowth” is associated with an increased propensity for disease spread and recurrence (144,223). Management for patients with “sarcomatous overgrowth” is often extrapolated from high-grade soft-tissue

sarcoma data. Patients should be encouraged to participate in clinical trials for soft-tissue sarcomas.

Advanced and Recurrent Disease

Neoadjuvant Chemotherapy

There have been no prospective studies evaluating the role of neoadjuvant chemotherapy in uterine sarcomas to date. The theoretical appeal of neoadjuvant therapy would be to not only potentially facilitate improved surgical outcomes through tumor shrinkage but also to permit an *in vivo* assessment of chemosensitivity to first-line drug therapy. The role of PET as an intermediate endpoint biomarker to assess treatment response early in patients with soft-tissue sarcomas undergoing neoadjuvant chemotherapy is under investigation (224).

Chemotherapy for Advanced/Recurrent Disease

Leiomyosarcomas

Numerous single agents have been, and continue to be, tested in patients with leiomyosarcomas (Table 23.14), but, unfortunately, results have been unimpressive (225–249). Doxorubicin and ifosfamide are the most active agents investigated as primary single-agent chemotherapy in recurrent and advanced uterine leiomyosarcomas. In 1983, the GOG demonstrated 7 responses among 28 patients (25%) treated with doxorubicin every 3 weeks as a single agent (231). This has been considered to be the most active single agent. The GOG has subsequently reported that treatment with liposomal doxorubicin yielded 1 complete (3.2%) and 4 partial (13%) responses and no advantage over historical results with doxorubicin (225). However, given the lower risk for cardiotoxicity, liposomal doxorubicin may remain a consideration for certain patients in whom doxorubicin therapy is precluded. The GOG demonstrated that ifosfamide had moderate activity, with 6 partial responses among 35 patients (17%) (228).

As in other types of soft-tissue sarcoma, gemcitabine has demonstrated activity with 1 (2.3%) complete response and 8 (18%) partial responses in persistent or recurrent uterine leiomyosarcomas (235). The median duration of response was only 4.8 months. In a small phase II study of temozolomide in advanced soft-tissue sarcoma, a partial response was seen in 2 (18%) of 11 patients with leiomyosarcoma (249). Limited activity was seen with single-agent paclitaxel, which was associated with a 9% overall response in 33 patients (227). Intravenous single-agent etoposide was shown to have an overall response of 11% in 28 patients (244), whereas prolonged oral etoposide had an overall response of 6.9% among 29 patients (243). However, no complete or partial responses were observed in another GOG phase II study with single-agent intravenous etoposide 100 mg/m² daily for 3 days every 3 weeks (229). Topotecan was tested in 36 patients with complete response in 1 (3%), partial response in 3 (8%), stable disease in 12 (33%), and increasing tumor in 20 (56%) (226).

A phase II study of trabectedin using a 24-hour infusion schedule in 20 chemotherapy naïve patients with advanced or recurrent uterine leiomyosarcoma demonstrated a 10% partial response rate with 50% of treated patients remaining progression-free for at least 6 months (250). Results of a randomized phase III study of trabectedin versus dacarbazine in patients with advanced leiomyosarcoma are awaited (NCT01343277). Trabectedin, although approved in Europe for the treatment of soft tissue sarcomas, is not approved in the U.S. thus far.

A small phase II trial of vinorelbine in patients who had failed prior doxorubicin-based chemotherapy demonstrated a

single partial response in 1 (6%) of 16 patients with leiomyosarcoma (248). Single-agent cisplatin also had a poor overall response of 3% to 5% in phase II trials (230,247). The antifolate compound trimetrexate was used in a small study reported in 2002, which was associated with an overall response of 4.3% in 28 patients who had received prior treatment (242). Mitoxantrone (246), diaziquone (234), amonafide (245), aminothiadiazo (233), and piperazinedione (232) were inactive as single agents. In a phase II trial comparing doxorubicin and docetaxel in advanced soft-tissue sarcoma, no objective responses were seen in the docetaxel group (251). Eribulin has also shown some promise in leiomyosarcoma (252). Newer agents such as the epothilone, ixabepilone, are currently being evaluated in phase II studies (NCT01220609).

Combination chemotherapy yields greater response rates (Table 23.14) (14,215,216,231,253-260). In 1983, the GOG demonstrated that the combination of doxorubicin and dacarbazine resulted in an overall response rate of 30%. Two years later, the same group demonstrated a 19% response rate using the combination of doxorubicin and cyclophosphamide (259). Both of the phase III trials were too small to make any definite conclusions. However, as mentioned, the trials did serve the purpose of allowing researchers to observe that leiomyosarcomas had a different chemotherapeutic response profile compared to uterine carcinosarcomas, resulting in the separation of the 2 different histologic entities in subsequent trials.

In 1996, the same group demonstrated an 18% overall response with a combination of dacarbazine, etoposide, and hydroxyurea (256). In the same year, using a combination of ifosfamide and doxorubicin, the GOG demonstrated an overall response of 30% in patients with advanced leiomyosarcoma with no history of prior treatment (257). A later study from the GOG showed that the use of mitomycin, doxorubicin, and cisplatin produced an overall response rate of 23% in 35 patients. Pulmonary toxicity was appreciable, however (255). Based on this study, the GOG conducted a phase II study with dacarbazine, doxorubicin, mitomycin, and cisplatin (DAMP), which produced a 28% response rate, but the complexity and toxicity of the regimen precluded further investigation, and the study was closed after the first stage of accrual (253).

Fixed dose-rate gemcitabine plus docetaxel was proven highly active and tolerable (40% overall response rate) in treated and untreated patients with uterine leiomyosarcomas (261). As initial therapy for metastatic uterine leiomyosarcoma this combination achieved a 36% response rate (2 complete and 13 partial responses) among 42 patients (216). The response rate for the doublet was 27% in the second-line setting, with a median PFS of greater than 5.6 months.

A phase II trial of fixed-dose rate gemcitabine and vinorelbine in patients with advanced soft-tissue sarcoma yielded a response rate of 22% in the nine uterine leiomyosarcoma patients but did not impart any advantage over historical results with single-agent gemcitabine (260). A combination of temozolomide and thalidomide in advanced leiomyosarcoma yielded a single (4%) response rate (262).

The effort in leiomyosarcomas continues to focus on the identification of active drugs and combinations in phase II trials. Given the paucity of survival data available from the randomized trials to compare various chemotherapy regimens, a pooled analysis of phase II studies was undertaken to compare the difference of response rate between single-agent and combination therapy. It showed that patients who received first- or second-line chemotherapy for the treatment of metastatic leiomyosarcoma had a higher response rate with combination chemotherapy than with single-agent chemotherapy (263). However, current phase III randomized clinical trials are only suggestive of the role of combination chemotherapy in advanced or recurrent uterine leiomyosarcomas.

Carcinosarcomas

Several drugs have been studied in this group of tumors as single agents (Table 23.15) (231,246,253,264-277). However, only 3 drugs have demonstrated clear-cut activity: ifosfamide, cisplatin, and paclitaxel (264-267,271,276,277). In a 5-day schedule, ifosfamide produced 25 complete and 12 partial responses (overall response of 36%) among 102 patients with no prior chemotherapy (185). In patients with prior chemotherapy, cisplatin produced an 18% response in 28 patients (276). A repeat trial in patients with no prior chemotherapy documented essentially the same response rate of 19% among a larger group of patients (264). Both trials used cisplatin at 50 mg/m² every 3 weeks. Investigators at the M. D. Anderson Cancer Center employed a higher dose ranging from 75 mg/m² to 100 mg/m² every 3 weeks. Only 12 patients with measurable disease were entered into the trial, but 1 complete and 4 partial responses were observed (overall responses, 42%) (277). The lack of randomization and the small number of cases in this trial preclude conclusions about the merits of the higher dose. Paclitaxel as a single agent was associated with a response rate of 21% in a group of 33 patients with uterine sarcoma who had prior chemotherapy, with an 8.2% response rate in patients who failed appropriate local therapy (271).

Doxorubicin, generally regarded as the most active agent in soft-tissue sarcomas, unfortunately demonstrated inconsistent activity in three trials of patients with uterine carcinosarcoma. The first 2 studies constituted 1 arm of each of 2 randomized trials. In the first, four responses among 41 patients (10%) with uterine carcinosarcomas (231) were observed. The second demonstrated a 19% response rate utilizing a dose of 60 mg/m² every 3 weeks in recurrent or advanced uterine sarcomas (259). The third, which employed a range of doses from 50 mg/m² to 90 mg/m² every 3 weeks, resulted in no response among the 9 patients with measurable disease (268). Topotecan 1.5 mg/m² daily for 5 days had unimpressive activity (10% response rate) in patients with advanced or recurrent uterine carcinosarcomas previously treated with chemotherapy (269). Demonstrating negligible activity in phase II studies were etoposide (275), mitoxantrone (246), piperazinedione (237), diaziquone (274), amonafide (272), trimetrexate (270), and aminothiadiazo (273).

In general, combination chemotherapy regimens usually result in a higher response rate than single-agent regimens. However, not all combination regimens have had an impact upon survival. This is clearly seen in the treatment of uterine carcinosarcomas. There have been numerous reports of combination chemotherapy for uterine carcinosarcomas (Table 23.15) (231,259,266,270,278-282). A combination of cyclophosphamide, vincristine, doxorubicin, and DTIC had a reported 23% overall response rate (281). A combination of etoposide, hydroxyurea, and DTIC resulted in a response of 15% in 32 patients (279). Subsequently, the EORTC reported a trial based upon 48 patients with unresectable or recurrent carcinosarcoma who were treated with a combination of cisplatin, doxorubicin, and ifosfamide. The overall response rate was an impressive 56%. Unfortunately, this regimen was also associated with a high incidence of nephrologic and hematologic toxicities (282). A phase II study of carboplatin and paclitaxel as first-line chemotherapy for women with advanced uterine carcinosarcoma reported an overall response rate of 54% with a favorable toxicity profile (283).

The first randomized study in 1983 by the GOG, which combined uterine carcinosarcoma with other sarcomas, resulted in patient numbers being too small for subset analysis (231). Nonetheless, combining doxorubicin and DTIC resulted in an overall response of 23% and a trend toward greater response as compared to single-agent doxorubicin (10%). A significant improvement in progression-free and OS could not be demonstrated, but

Table 23.15 Chemotherapy in Carcinosarcomas of the Uterus

Drug	n	Prior Therapy	Schedule	Overall Response (%)	Reference
<i>Single-Agent Chemotherapy</i>					
Primary Chemotherapy					
Cisplatin	63	28 RT	50 mg/m ² q 3 wk	19	230
Ifosfamide	91	34 RT	2 g/m ² × 3 days q 3 wk	29	265
	102	27 RT	1.5 g/m ² × 5 days q 3 wk	36	266
	28	8 RT	1.5 g/m ² × 5 days q 4 wk	32	267
Doxorubicin	21	21 No CT	60 mg/m ² q 3 wk	19 ^a	259
	9	6 No CT	50–90 mg/m ² q 3 wk	0	268
Piperazinedione	19	19 No CT	9 mg/m ² q 3 wk	5.3	232
Nonprimary Chemotherapy					
Doxorubicin	41	N/A	60 mg/m ² q 3 wk	10	231
Topotecan	48	16 RT, 44 CT	1.5 mg/m ² × 5 days q 3 wk	10	269
Trimetrexate	21	N/A	5 mg/m ² orally × 5 days q 2 wk	4.8	270
Paclitaxel	44	15 RT, 33 CT	170 mg/m ² q 3 wk	18	271
Amonafide	16	5 RT, 14 CT	300 mg/m ² × 5 days q 3 wk	6	272
Aminothiadiazone	22	10 RT, 18 CT	125 mg/m ² q 1 wk	5	273
Diaziquone	23	11 RT, 18 CT	22.5 mg/m ² q 3 wk	4	274
Mitoxantrone	17	17 CT	12 mg/m ² q 3 wk	0	246
Etoposide	31	14 RT, 29 CT	100 mg/m ² days 1, 3, 5 q 4 wk	6.5	275
Cisplatin	28	28 CT	50 mg/m ² q 3 wk	18	276
	12	7 CT	75–100 mg/m ² q 3 wk	42	276
Combination Chemotherapy					
Doxorubicin <i>plus</i>	31	N/A	60 mg/m ² q 3 wk	23	231
Dacarbazine			250 mg/m ² × 5 days q 3 wk		
Doxorubicin <i>plus</i>	30	30 No CT	60 mg/m ² q 3 wk	19 ^a	259
Cyclophosphamide			500 mg/m ² q 3 wk		
Ifosfamide <i>plus</i>	92	25 RT	1.5 g/m ² × 5 days q 3 wk	54	266
Cisplatin			20 mg/m ² × 5 days q 3 wk		
Ifosfamide <i>plus</i>	88	26 RT	1.6 g/m ² × 3 days q 3 wk	45	265
Paclitaxel			135 mg/m ² q 3 wk		
Ifosfamide <i>plus</i>	65	65 No CT	1.5 g/m ² × 5 days q 3 wk	N/A	278
Cisplatin			20 mg/m ² × 5 days q 3 wk		
Hydroxyurea <i>plus</i>	32	11 RT	2 g orally q 4 wk	15	279
Dacarbazine			700 mg/m ² q 4 wk		
Etoposide			100 mg/m ² × 3 days q 4 wk		
Etoposide <i>plus</i>	4	N/A	100 mg/m ² × 2 days q 4 wk	100	280
Cisplatin			50 mg/m ² q 4 wk		
Doxorubicin			50 mg/m ² q 4 wk		
Cyclophosphamide <i>plus</i>	26	14 CT	400 mg/m ² day 2 q 4 wk	23	281
Vincristine			1 mg/m ² days 1, 5 q 4 wk		

(continued)

Table 23.15 Chemotherapy in Carcinosarcomas of the Uterus (Continued)

Drug	n	Prior Therapy	Schedule	Overall Response (%)	Reference
Doxorubicin			40 mg/m ² day 2 q 4 wk		
Dacarbazine			200 mg/m ² × 5 days q 4 wk		
Cisplatin <i>plus</i>	32	32 No CT	50 mg/m ² q 3 wk	56 ^b	282
Doxorubicin			45 mg/m ² q 3 wk		
Ifosfamide			5 g/m ² q 3 wk		
Gemcitabine <i>plus</i>	24	9 RT, 24 CT	600 mg/m ² days 1, 8, 15	8	285
Docetaxel			35 mg/m ² days 1, 8, 15		
Paclitaxel <i>plus</i>	46	15 RT, 46 No CT	175 mg/m ² q 3 wk	54	283
Carboplatin			AUC 6 q 3 wk		
Biologic Therapy					
Imatinib	23	23	600 mg orally daily	0	320
Thalidomide	5	NA	200 mg orally daily	0	323
Aflibercept	19	19 CT	4 mg/kg day 1 q 2 wk	0	326

Note: All chemotherapy agents were given intravenously unless specified. CT, chemotherapy; N/A, not available; RT, radiation therapy.

^aUterine sarcoma.

^bFemale genital tract.

2 conclusions could be drawn from this trial. The first was the fact that a greater response to chemotherapy was significantly associated with an increase in OS and the disease-free survival. The second observation was that uterine carcinosarcomas had a different response profile compared to leiomyosarcomas. Two years later, the GOG compared cyclophosphamide plus doxorubicin to single-agent doxorubicin. A response of 25% was observed in carcinosarcomas; again, however, numbers were inadequate to show any significant benefit compared with single-agent doxorubicin. The trial was also closed early because of failure to reach statistical significance (259).

With the recognition of the difference in response to therapy between carcinosarcomas and leiomyosarcomas, randomized trials began to regard each of the 2 major histologic subtypes as separate patient populations. Unfortunately, this increased the time necessary to complete clinical trials. Nonetheless, a large randomized trial was performed and reported in 2000. The GOG evaluated the addition of cisplatin to ifosfamide in 194 eligible patients and found that this improved the overall response rate from 36% to 54% and prolonged the median progression-free interval by an absolute 2 months. However, this advantage was not associated with a significant OS gain and 6 treatment-related deaths occurred (266).

Based upon the finding of moderate activity (18% response rate) of paclitaxel for this disease (271), the GOG carried out a phase III trial of 3-day ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma. The group found that the addition of paclitaxel produced a 45% response rate compared with 29% in the ifosfamide single-agent arm with OS significantly improved. There was a significant decrease in the hazard of death and progression but more sensory neuropathy, as expected (265). A recent meta-analysis supports the use of combination chemotherapy in advanced or recurrent uterine carcinosarcomas with a reduction in the risk of death and disease progression compared to single-agent therapy (284). In order to determine the best first-line chemotherapy doublet, the

GOG are now conducting a noninferiority phase III trial, GOG 261, comparing paclitaxel with carboplatin and paclitaxel with ifosfamide in patients with uterine or ovarian carcinosarcoma (NCT00954174).

Data regarding second-line chemotherapy doublets is limited. A phase II trial of weekly gemcitabine and docetaxel in recurrent uterine carcinosarcoma was associated with an 8.3% overall response rate with a median PFS of only 1.8 months (285). Combination regimens that result in significant improvements in survival are still needed (Table 23.16).

Endometrial Stromal Sarcoma

In recurrent ESS, reports support hormonal therapy for patients with low-grade subgroup (13), and chemotherapy for high-grade tumors (286). Current definitions do not include high-grade lesions as a component of ESS. In a retrospective review of 74 patients with low-grade stromal sarcoma, none of the 10 patients who received chemotherapy had a response compared to 27% of patients who were treated with hormonal therapy (13). Randomized phase III trials with stromal sarcomas are limited due to the rarity of this disease. Two randomized trials compared single-agent and combination chemotherapy in advanced uterine sarcoma but did not report the response rate of stromal sarcomas separately. The GOG reported a phase II study of ifosfamide treatment in 21 cases with recurrent or metastatic ESSs. Three patients experienced complete response and four had partial responses, for an overall response of 33.3% (287). Another noncontrolled study observed a 50% response rate to doxorubicin therapy in ten patients with recurrent ESSs (288). Many other literatures are case reports and retrospective studies with a small number of cases. Published chemotherapy regimens include carboplatin and paclitaxel (289); doxorubicin, cisplatin, and ifosfamide (290); doxorubicin and ifosfamide (291); doxorubicin, vincristine, and cyclophosphamide (292); and prolonged oral etoposide (293).

Table 23.16 Phase III Clinical Trials in Uterine Sarcomas

Drug	n	Prior Therapy	Schedule	Overall Response (%)	Median PFS (months)	Median Overall Survival (months)	Leukopenia (%)	Neutropenia (%)	Thrombocytopenia (%)	Anemia (%)	GI (%)	Neuropathy (%)	Reference
Doxorubicin	41 CS/28 LMS	N/A	60 mg/m ² q 3 wk	10/25	3.5 ^a	7.7 ^a	16	N/A	4	N/A	2	N/A	158
Doxorubicin <i>plus</i>	31 CS/20 LMS	N/A	60 mg/m ² q 3 wk	23/30	5.5 ^a	7.3 ^a	35	N/A	13	N/A	9	N/A	
Dacarbazine			250 mg/m ² × 5 days q 3 wk										
Doxorubicin	21 CS/21 LMS	8 RT	60 mg/m ² q 3 wk	19 ^a	5.1 ^a	11.6 ^a	10	N/A	0	N/A	N/A	N/A	181
Doxorubicin <i>plus</i>	30 CS/17 LMS	9 RT	60 mg/m ² q 3 wk	19 ^a	4.9 ^a	10.9 ^a	35	N/A	0	N/A	N/A	N/A	
Cyclophosphamide			500 mg/m ² q 3 wk										
Ifosfamide	102 CS		1.5 g/m ² × 5 days q 3 wk	36	4	7.6	59	36	5	8	5	20	185
Ifosfamide <i>plus</i>	92 CS	25 RT	1.5 g/m ² × 5 days q 3 wk	54	6	9.4	97	67	64	19	18	29	
Cisplatin			20 mg/m ² × 5 days q 3 wk										
Ifosfamide	91 CS		2 g/m ² × 3 days q 3 wk	29	3.6	8.4	42	53	3	9	7	0	184
Ifosfamide	88 CS	26 RT	1.6 g/m ² × 3 days q 3 wk	45	5.8	13.5	36	44	3	15	8	3	
Paclitaxel			135 mg/m ² q 3 wk										

Note: All chemotherapy agents were given intravenously. GI, gastrointestinal; CS, carcinosarcoma; N/A, not available; LMS, leiomyosarcoma system; PFS, progression-free survival; RT, radiation therapy.

^aUterine sarcoma.

Table 23.17 Grade 3–4 Adverse Effects of Chemotherapy in Leiomyosarcoma (Adverse Rate > 5%)

Drug	n	Prior Therapy	Schedule	Overall Response (%)			Thrombo-			GI (%)	Others	Reference
				Response (%)	Leukopenia (%)	Neutropenia (%)	cytopenia (%)	Anemia (%)				
Liposomal doxorubicin	32	11 RT	50 mg/m ² q 4 wk	16.1	12.9	16.1	N/A	22.6	19.4	Dermatotoxicity 6.5%	225	
Topotecan	36	8 RT	1.5 mg/m ² × 5 days q 3 wk	11	33	90	13	16	16.7		226	
Paclitaxel	33	8 RT	175 mg/m ² q 3 wk	9	9.1	33.3	3	3	0	No neurotoxicity	227	
Ifosfamide	48	15 RT, 33 CT	175 mg/m ² q 3 wk	8.4	6.3	16.7	0	16.7	41.7		239	
	35	15 RT	1.5 g/m ² × 5 days q 4 wk	17	34	N/A	0	0	3	Neurotoxicity 3%, granulocytopenia 11%, dermatotoxicity 14%	228	
Doxorubicin	28	N/A	60 mg/m ² q 3 wk	25	16	N/A	4	N/A	2		231	
Gemcitabine	29	6 RT, 27 CT	50 mg/m ² orally × 21 days q 4 wk	6.9	24	35	18	12	6	Neurotoxicity 6%	233	
	44	11 RT, 35 CT	1,000 mg/m ² weekly × 3 q 4 wk	20.5	27.3	34.1	11.4	6.8	13.6		235	
Trabectedin	20	7RT	1.5 mg/m ² over 24 h q 3 wk	10	55	80	15	5	0	Hepatotoxicity 10%	250	
Temozolomide	11	N/A	180 mg/m ² orally × 5 days q 4 wk	18 ^c	0	0	0	4	4	Fatigue 4%	249	
Vinorelbine	16	16 CT	30 mg/m ² weekly × 8	6 ^c	N/A	N/A	N/A	N/A	N/A	Grade 3 toxicity 67%	248	
Doxorubicin <i>plus</i> Dacarbazine	20	N/A	60 mg/m ² q 3 wk	30	35	N/A	13	N/A	9		231	
Dacarbazine <i>plus</i> Mitomycin <i>plus</i> Doxorubicin <i>plus</i> Cisplatin			250 mg/m ² × 5 days q 3 wk									
	18	7 RT	750 mg/m ² q 4 wk	27.8	67	78	94	61.1	44.4		253	
			6 mg/m ² q 4 wk									
			40 mg/m ² q 4 wk									
Mitomycin <i>plus</i> Doxorubicin <i>plus</i> Cisplatin			60 mg/m ² q 4 wk									
	35	8 RT	8 mg/m ² q 3 wk	23	N/A	N/A	N/A	N/A	N/A	Pulmonary toxicity 8%	255	
			40 mg/m ² q 3 wk									
Hydroxyurea <i>plus</i> Dacarbazine <i>plus</i> Etoposide			60 mg/m ² q 3 wk									
	38	11 RT	2 g orally × 1 day q 4 wk	18	29	N/A	3	N/A	N/A		256	
			700 mg/m ² q 4 wk									
			300 mg/m ² × 2 days q 4 wk									

Ifosfamide <i>plus</i> Doxorubicin	33	9 RT	5 mg/m ² q 3 wk	30	0	49	0	0	0	Cardiac toxicity 3%	257
Gemcitabine <i>plus</i> Docetaxel	34	14 RT, 16 CT	50 mg/m ² q 3 wk 900 mg/m ² days 1, 8 q 3 wk	53	N/A	21	29	15	12	Dyspnea 21%, fatigue 21%	258
			100 mg/m ² day 8 q 3 wk								
	42	42 No CT	As above	36	17	14	14	24	14		215
	48	17 RT, 48 CT	As above	27	23	21	40	25	6.3	Fluid retention syndrome 19%	216
Gemcitabine <i>plus</i> Vinorelbine	9	N/A	800 mg/m ² days 1, 8	22	28	40	10	5	10		260
			25 mg/m ² days 1, 8 q3 wk								
Temozolomide <i>plus</i> Thalidomide	11	10 CT	150 mg/m ² orally × 7 q 2 wk	9.1	N/A	4	4	4	8	Neurotoxicity 12%	262
			200 mg orally daily								
Sunitinib	23	23 CT	50 mg orally daily × 4 of 6 wk	8.7	13	17	13	17	30		321
Bevacizumab <i>plus</i> Doxorubicin	7	N/A	15 mg/kg q 3 wk 75 mg/m ²	28	N/A	N/A	18	6	0	Alopecia 100% Cardiotoxicity gr ≥2 35%	329

Note: All chemotherapy agents were given intravenously unless specified. CT, chemotherapy; GI, gastrointestinal system; N/A, not available; RT, radiation therapy.

Etoposide <i>plus</i>	4	N/A	100 mg/m ² × 2 days q 4 wk	100	9.5	N/A	N/A	N/A	21.4	Alopecia 100%	280
Cisplatin <i>plus</i>			50 mg/m ² q 4 wk								
Doxorubicin			50 mg/m ² q 4 wk								
Cyclophosphamide <i>plus</i>	26	14 CT	400 mg/m ² day 2 q 4 wk	23	34.6	N/A	15.4	N/A	N/A	Septicemia 15.4%, neurotoxicity 7.7%	281
Vincristine <i>plus</i>			1 mg/m ² days 1, 5 q 4 wk								
Doxorubicin <i>plus</i>			40 mg/m ² day 2 q 4 wk								
Dacarbazine			200 mg/m ² × 5 days q 4 wk								
Cisplatin <i>plus</i>	32	32 No CT	50 mg/m ² q 3 wk	56 ^a	94.6	84.8	64.8	43.2	53.8	Neurotoxicity 15%, alopecia 64%	282
Doxorubicin <i>plus</i>			45 mg/m ² q 3 wk								
Ifosfamide			5 g/m ² q 3 wk								
Gemcitabine <i>plus</i> Docetaxel	24	9 RT, 24 CT	600 mg/m ² days 1,8,1535 mg/m ² days 1,8,15	8	50	46	13	13	13		285
Paclitaxel <i>plus</i> Carboplatin	46	15 RT, 46 No CT	175 mg/m ² q 3 wkAUC 6 q 3 wk	54	43	85	11	11	4.3	Neurotoxicity 11%	283

Note: All chemotherapy agents were given intravenously unless specified. CT, chemotherapy; N/A, not available; RT, radiation therapy.

^aUterine sarcoma.

^bFemale genital tract.

High-Grade Undifferentiated Endometrial Sarcoma

There are no prospective trials of chemotherapy specifically for high-grade undifferentiated endometrial sarcoma. Case reports of responses to ifosfamide and doxorubicin-based chemotherapy regimens have been documented in the literature (294,295). A phase II trial of first-line chemotherapy for recurrent of metastatic ESS reported a 33% response rate but did not segregate high-versus low-grade tumors (296). Participation in clinical trials for soft tissue sarcomas should be encouraged due to the paucity of data to guide systemic treatment.

PEComa

There are no prospective data on systemic chemotherapy for PEComa. A case report of a 9-year-old girl with uterine PEComa reported radiographic response following 2 cycles of neoadjuvant vincristine, ifosfamide, and doxorubicin, but analysis of the surgical specimen did not demonstrate any tumor response. Case reports of tamoxifen or anthracycline-based chemotherapy following surgical resection of gynecologic PEComas did not suggest any benefit from adjuvant therapy (176). In the metastatic or recurrent setting chemotherapy again did not appear to be effective (297). Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, which has activity in nonuterine PEComas, was not associated with responses in patients with uterine PEComas (298). Participation in clinical trials for soft-tissue sarcomas should be encouraged for these patients.

Rhabdomyosarcoma

Due to the rarity of uterine rhabdomyosarcoma, there are no prospective data to guide optimal therapy (177). Complete responses have been reported with neoadjuvant ifosfamide, vincristine, and actinomycin D combination chemotherapy in case series of pediatric patients with rhabdomyosarcoma of the genital tract (178).

Toxicity of Systemic Therapies

The most common toxicities of chemotherapy are hematologic and gastrointestinal toxicity. The grade 3–4 adverse effects of chemotherapy with overall response rate higher than 5% in leiomyosarcomas and carcinosarcomas are listed in Tables 23.17 and 23.18. Combination chemotherapy has a much higher incidence of grade 3–4 side effects compared with the single-agent regimen. The overall response rate of combination with ifosfamide plus cisplatin is 54%; however, the grade 3–4 of leukopenia is 97%, and 6 deaths occurred before the first dose reduction of ifosfamide (266). The more recent phase III trial with ifosfamide plus paclitaxel reported a 45% overall response rate with tolerable toxicities (265), which seems a relatively effective and safe regimen. Among other phase II trials of different chemotherapeutic regimens, liposomal doxorubicin, paclitaxel, doxorubicin, cisplatin, and etoposide plus cisplatin plus doxorubicin were reported to have less toxicity with moderate effect. Despite the routine use of growth factor support with gemcitabine and docetaxel, myelosuppression, in particular in previously treated patients, is still the predominant toxicity encountered with this combination (215,216). Lower limb edema is also more common in the second-line setting. Trabectedin is associated with fatigue, myelosuppression, transaminitis, and vomiting (299).

Newer agents such as palifosfamide-tris and eribulin may offer a more tolerable toxicity profile compared to the standard chemotherapy drugs. Palifosfamide-tris is a stabilized active metabolite of ifosfamide with less potential for bladder toxicity.

There is currently a phase III randomized study of doxorubicin plus palifosfamide/placebo as first-line chemotherapy for patients with metastatic soft-tissue sarcoma (NCT01168791). Another randomized ongoing phase III compares eribulin with dacarbazine in patients who have progressed within 6 months of standard chemotherapy (NCT01327885).

Hormonal Therapy

Although the role of hormonal therapy is clear in breast and endometrial cancers, it has not been extensively evaluated in mesenchymal uterine tumors. Few uterine sarcomas contain sufficient estrogen- or progesterone-receptor protein to influence therapy, the only exception being low-grade ESSs or stromal nodules. Estrogen and progesterone receptors were found in 55.5% and 55.8%, respectively, of samples from patients with various types of uterine sarcomas, but the median concentrations were substantially lower than those observed in breast or endometrial cancers. ESSs had higher receptor levels (300). Uniquely, low-grade ESSs are hormonally responsive in roughly two-thirds of cases, and long-term maintenance therapy should be beneficial. Several papers reported that long-term use of tamoxifen for the treatment of breast cancer was related to the development of uterine sarcoma (301,302). This is likely secondary to the stimulatory estrogenic effects of tamoxifen on the uterus. It is also, therefore, reasonable to avoid estrogen replacement therapy for these patients.

Endometrial Stromal Sarcoma

Progestins, gonadotropin-releasing hormone (GnRH) analogues (303), or aromatase inhibitors (286,304) have been used in the treatment of patients with advanced or recurrent ESSs, and they successfully gain long-term stability in case reports. A retrospective study of patients with low-grade ESS reported a response rate of 27% (5 complete and 3 partial responses), stable disease in 53% (16 patients), and a median time to progression of 24 months in the subgroup of patients who received hormonal therapy (13). The vast majority of these patients received megestrol acetate.

Lantta et al. (305) published 2 cases of extensive intraperitoneal low-grade ESS associated with high levels of progesterone receptors in complete remission with hormonal therapy. Three patients with high levels of progesterone receptors were reported by Baker et al. (306) to have partial responses or stabilization of disease on oral megestrol acetate. Piver et al. (307), in a collaborative survey of endolymphatic stromal myosis, recorded complete or partial responses to hormonal therapy in 6 of 13 patients (46%) treated with progestational agents. Scribner and Walker (308) reported a patient with an extensive ESS of the uterus whose tumor was reduced to resectable size by the administration of leuprolide acetate and megestrol acetate. Low-grade ESSs have also been reported to express *srp27*, an estrogen-induced 24-DK protein suggesting hormone responsiveness (309). Medroxyprogesterone acetate has induced major responses in pulmonary metastatic lesions from ESS (310,311). GnRH analogues were reported to control the progression of a recurrent low-grade ESS with moderate estrogen and progesterone receptor positivity (303). Medroxyprogesterone acetate and aromatase inhibitors, such as letrozole, were observed to be highly effective and have sustained progression control in 6 of 10 cases with low-grade stromal sarcoma (312). Spano et al. presented two cases of ESS with lung metastases treated with aminoglutethimide who achieved complete response and remained disease-free for 14 and 7 years, respectively (286). In a phase II trial of mifepristone, a selective progesterone receptor modulator, in recurrent, uterine cancer, no responses (0%) were seen in the 2 patients with low-grade ESS (313).

Other Uterine Sarcomas

There are anecdotal reports of responses to hormonal therapy in adenosarcomas and low-grade leiomyosarcomas (314). A retrospective study of an aromatase inhibitor in selected patients with advanced, predominantly low-volume disease, reported a partial response in 3 patients (9%). Patients whose tumors did not express estrogen or progesterone receptors did not derive any benefit from the aromatase inhibitor (315). The role of the aromatase inhibitor, letrozole, in advanced hormone receptor positive uterine leiomyosarcoma is being evaluated prospectively in an ongoing, open label phase II trial (NCT00856050). Another prospective study is comparing letrozole with observation for newly diagnosed uterine leiomyosarcoma (NCT00414076). One case of letrozole therapy in high-grade uterine carcinosarcoma with marked tumor control was reported, but the area has not been well studied (316).

Biologic Therapy

Since the high recurrence and poor response to radiotherapy and chemotherapy, biologic therapy may have more promise in the area of uterine sarcoma, as well as other types of soft-tissue sarcoma. The recent advances in the biology of uterine sarcoma related to probable treatment target have concentrated on tyrosine kinase receptors, vascular endothelial growth factor (VEGF), and the phosphatidyl 3-kinase (PI3K)/Akt pathway.

Since the discovery that high proto-oncogene *c-kit* expression in gastrointestinal stromal tumors (GISTs) may be amenable to control with tyrosine kinase inhibitors, such as imatinib mesylate and sunitinib, some interest has been focused upon uterine sarcomas (317). However, the expression of *c-kit* in the uterine sarcoma varies greatly in different studies (318–320). Given the great progress made in the GISTs with imatinib mesylate, a GOG phase II evaluation of this drug was conducted in previously treated patients with recurrent or persistent carcinosarcoma of the uterus (320). No activity was seen. The GOG investigated sunitinib maleate as a second- or third-line therapy for leiomyosarcoma of the uterus. The trial was reported as negative, with only 2 partial responses (9%) noted among the 23 patients (321).

Emoto et al. demonstrated inhibition of a VEGF-expressing malignant mixed tumor cell line by TNP-470, an angiogenesis inhibitor (322). Another angiogenesis inhibitor, thalidomide, did not demonstrate any activity in recurrent or persistent uterine carcinosarcoma (323) or uterine leiomyosarcoma (324). A phase II study of sorafenib, a small-molecule B-raf and VEGF receptor inhibitor, was also negative with only 1 (3%) partial response seen among the 37 patients with adult leiomyosarcoma (325). No responses were observed in a phase II trial of aflibercept in recurrent or metastatic gynecologic carcinosarcomas and uterine leiomyosarcoma (326).

A phase II study of pazopanib, an oral multitargeted kinase inhibitor, showed 1 partial response (2.4%) among the 41

patients in the leiomyosarcoma cohort (327). In the recently reported phase III trial of pazopanib versus placebo as second-line therapy for metastatic soft-tissue sarcoma (46% leiomyosarcoma), the response rate was 6% in the pazopanib group. There was a 3-month increase in PFS. Although this did not translate into a significant improvement in OS, pazopanib is now FDA-approved for patients with advanced soft-tissue sarcoma who have previously received chemotherapy (328). As there is a potential for life-threatening hepatotoxicity with this drug, patients should be carefully monitored for liver function. The results of a GOG phase II trial of pazopanib in previously treated uterine carcinosarcoma are awaited (NCT 01247571). There are also proposals to study this drug in combination with gemcitabine as second-line therapy for leiomyosarcoma (NCT01442662).

A phase II study of doxorubicin with bevacizumab in 17 chemotherapy-naïve patients with soft tissue sarcoma reported a lower than anticipated response rate of 12%, with significant cardiotoxicity ($\geq$ grade 2 in 35% of patients) (329). Among the 7 patients with uterine leiomyosarcoma, there were 2 (28%) partial responses. The GOG are currently conducting a phase III, placebo-controlled trial of gemcitabine and docetaxel with or without bevacizumab as first-line therapy for advanced or recurrent uterine leiomyosarcoma (NCT01012297).

Loss of PTEN function results in upregulation of the PI3K/Akt pathway and was shown to be associated with high-grade and recurrence of leiomyosarcoma (330). mTOR is a central regulator of this pathway. Ridaforolimus (formerly deforolimus), an mTOR inhibitor, did not show any responses in the 56 leiomyosarcomas patients but 36% had disease stabilization at 16 weeks (331). A phase III study of ridaforolimus as a maintenance strategy in metastatic sarcoma patients following benefit from chemotherapy reported a disappointing 3-week increase in PFS (332). Although there are published case reports of activity of sirolimus in nonuterine PEComas, this mTOR inhibitor does not appear to be active in uterine PEComas (298).

Advances in the understanding of the biology of uterine sarcomas may provide more treatment targets and make long-term control of the disease possible.

Systemic Therapy Summary

The current role of chemotherapy in the management of uterine sarcomas involves the treatment of patients with advanced or recurrent disease, and an emphasis on palliative intent. In leiomyosarcomas, the active drugs are doxorubicin, ifosfamide, gemcitabine, and docetaxel. For uterine carcinosarcomas, the drugs of choice are ifosfamide, cisplatin/carboplatin, and paclitaxel. Hormonal therapy, including progestational agents, GnRH analogues, and aromatase inhibitors, has a role in the treatment of advanced or recurrent low-grade ESSs. The use of hormonal agents in the treatment of other histologic subtypes has not been well studied. Efforts to identify additional active agents continue.

REFERENCES

- Kosary CL. Cancer of the corpus uteri. In: Ries LAG, Young JL, Keel GE, Eisner MP, et al., eds. *SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics*. National Cancer Institute, SEER Program, NIH pub. No. 07-6215, Bethesda, MD, 2007:123–132.
- Tumors of the uterine corpus. In: Tavassoli FA, Devilee P, eds. *World Health Organization Classification of Tumours. Pathology and genetics of Tumours of the Breast and Female Genital Organs*. Lyons, France: IARC Press; 2003:217–258.
- D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol*. 2010;116:131–139.
- Park J, Kim D, Suh D, et al. Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989–2007. *J Cancer Res Clin Oncol*. 2008;134:1277–1287.
- Koivisto-Korander R, Butzow R, Koivisto A, et al. Clinical outcome and prognostic factors in 100 cases of uterine sarcoma: experience in Helsinki University Central Hospital 1990–2001. *Gynecol Oncol*. 2008;111:74–81.
- Kahanpaa K, Wahlstrom T, Grohn P, et al. Sarcomas of the uterus: a clinicopathologic study of 119 patients. *Obstet Gynecol*. 1986;67:417–424.
- George M, Pejovic MH, Kramar A. Uterine sarcomas: prognostic factors and treatment modalities—study on 209 patients. *Gynecol Oncol*. 1986;24:58–67.

8. Olah KS, Gee H, Blunt S, et al. Retrospective analysis of 318 cases of uterine sarcoma. *Eur J Cancer*. 1991;27:1095–1099.
9. Pautier P, Genestie C, Rey A, et al. Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of grading score validated for soft tissue sarcoma. *Cancer*. 2000;88:1425–1431.
10. Abeler VM, Royne O, Thorensen S, et al. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology*. 2009;54:355–364.
11. Jin Y, Pan L, Wang X, et al. Clinical characteristics of endometrial stromal sarcoma from an academic medical hospital in China. *Int J Gynecol Cancer*. 2010;20:1535–1539.
12. Vera AAL, Guadarrama MBR. Endometrial stromal sarcoma: clinicopathologic and immunophenotype study of 18 cases. *Ann Diag Pathol*. 2011;15:312–317.
13. Cheng X, Yang G, Schmeler KM, et al. Recurrence patterns and prognosis of endometrial stromal sarcoma and the potential of tyrosine kinase-inhibiting therapy. *Gynecol Oncol*. 2011;121:323–327.
14. Shah LP, Bryant CS, Kumar S, et al. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. *Obstet Gynecol*. 2008;112:1102–1108.
15. dos Santos LA, Garg K, Diaz JP, et al. Incidence of lymph node and adnexal metastasis in endometrial stromal sarcoma. *Gynecol Oncol*. 2011;121:319–322.
16. Garg G, Shah JP, Liu R, et al. Validation of tumor size as staging variable in the revised International Federation of Gynecology and Obstetrics stage I leiomyosarcoma: a population-based study. *Int J Gynecol Cancer*. 2010;20:1201–1206.
17. Loizzi V, Cormio G, Nestola D, et al. Prognostic factors and outcomes in 28 cases of uterine leiomyosarcoma. *Oncology*. 2011;81:91–97.
18. Zivanovic O, Leitao MM, Iasonos A, et al. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer staging systems. *J Clin Oncol*. 2009;27:2066–2072.
19. Park J, Kim D, Kim J, et al. The role of pelvic and/or para-aortic lymphadenectomy in surgical management of apparently early carcinosarcoma of uterus. *Ann Surg Oncol*. 2010;17:861–868.
20. Pradhan TA, Stevens EE, Ablavsky M, et al. FIGO staging for carcinosarcoma: can the revised staging system predict overall survival? *Gynecol Oncol*. 2011;123:221–224.
21. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. *Hum Pathol*. 1990;21:363–381.
22. Guntupalli SR, Ramirez PT, Anderson ML, et al. Uterine smooth muscle tumor of uncertain malignant potential: a retrospective analysis. *Gynecol Oncol*. 2009;113:324–326.
23. Zelmanowicz A, Hildesheim A, Sherman MA, et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed müllerian tumors. *Gynecol Oncol*. 1998;69:253–257.
24. Mortel R, Nedwich A, Lewis GC, et al. Malignant mixed müllerian tumors of the uterine corpus. *Obstet Gynecol*. 1970;35:469–480.
25. Norris HJ, Roth E, Taylor HB. Mesenchymal tumors of the uterus. *Obstet Gynecol*. 1966;28:57–63.
26. Brooks SE, Zhan M, Cote T, et al. Survival epidemiology and end results analysis of 267 cases of uterine sarcomas, 1989–1999. *Gynecol Oncol*. 2004;93:204–208.
27. Giuntoli RL, Metzinger DS, DiMarco CS, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. *Gynecol Oncol*. 2003;89:460–469.
28. Christopherson WM, Williamson EO, Gray LA. Leiomyosarcoma of the uterus. *Cancer*. 1972;29:1512–1517.
29. Meredith RJ, Eisert DR, Kaka Z, et al. An excess of uterine sarcomas after pelvic irradiation. *Cancer*. 1986;58:2003–2007.
30. Varala-Duran J, Nochomovitz LE, Prem KA, et al. Post irradiation mixed müllerian tumors of the uterus. *Cancer*. 1980;45:1625–1631.
31. Pothuri B, Ramondetta L, Eifel P, et al. Radiation-associated endometrial cancers are prognostically unfavorable tumors: a clinicopathologic comparison with 527 sporadic endometrial cancers. *Gynecol Oncol*. 2006;103:948–951.
32. Jaakkola S, Lyytinen HK, Pukkala E, et al. Use of estradiol-progestin therapy associates with increased risk for uterine sarcomas. *Gynecol Oncol*. 2011;122:260–263.
33. Lavie O, Barnett-Griness O, Narod SA, et al. The risk of developing uterine sarcoma after tamoxifen use. *Int J Gynecol Cancer*. 2008;18:352–356.
34. Hoogendoorn WE, Hollema H, van Boven HH, et al. Prognosis of uterine corpus cancer after tamoxifen treatment for breast cancer. *Breast Cancer Res Treat*. 2008;112:99–108.
35. Nilbert M, Therkildsen C, Nissen A, et al. Sarcomas associated with hereditary nonpolyposis colorectal cancer: broad anatomical and morphological spectrum. *Familial Cancer*. 2009;8:209–213.
36. Francis JH, Kleinerman RA, Seddon J, et al. Increased risk of secondary uterine leiomyosarcoma in hereditary retinoblastoma. *Gynecol Oncol*. 2012;124:254–259.
37. Bansal N, Herzog TJ, Burke W, et al. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. *Gynecol Oncol*. 2008;110:43–48.
38. Namimoto T, Yamashita Y, Awai K, et al. Combined use of T2-weighted and diffusion-weighted 3-T MR imaging for differentiating uterine sarcomas from benign leiomyomas. *Eur Radiol*. 2009;19:2756–2764.
39. Cornfeld D, Israel G, Martel M, et al. MRI appearance of mesenchymal tumors of the uterus. *Eur J Radiol*. 2010;74:241–249.
40. Goto A, Takeuchi S, Sugimura K, et al. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. *Int J Gynecol Cancer*. 2002;12:354–361.
41. Perry T, Korach J, Sadetzki S, et al. Uterine leiomyosarcoma: does the primary surgical procedure matter? *Int J Gynecol Cancer*. 2009;19:257–260.
42. Park J, Park S, Kim D, et al. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. *Gynecol Oncol*. 2011;122:255–259.
43. Park J, Kim D, Kim J, et al. The impact of tumor morcellation during surgery on the outcomes of patients with apparently early low-grade endometrial stromal sarcoma of the uterus. *Ann Surg Oncol*. 2011;18:3453–3461.
44. Leibsohn S, D'Abbing G, Mishell DR Jr, et al. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. *Am J Obstet Gynecol*. 1990;162:968–976.
45. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. *Obstet Gynecol*. 1994;83:414–418.
46. Takamizawa S, Minakami H, Usui R, et al. Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas. *Gynecol Obstet Invest*. 1999;48:193–196.
47. Leung F, Terzibachian JJ, Gay C, et al. [Hysterectomies performed for presumed leiomyomas: should the fear of leiomyosarcoma make us apprehend non laparotomic surgical routes?]. *Gynecol Obstet Fertil*. 2009;37:109–114.
48. Raut CP, Nucci MR, Wang Q, et al. Predictive value of FIGO and AJCC staging systems in patients with uterine leiomyosarcoma. *Eur J Cancer*. 2009;45:2818–2824.
49. Arend R, Bagaria M, Lewin SN, et al. Long-term outcome and natural history of uterine adenosarcomas. *Gynecol Oncol*. 2010;119:305–308.
50. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. *Cancer*. 2008;112:820–830.
51. Nugent EK, Zigelboim I, Case AS, et al. The value of perioperative imaging in patients with uterine sarcomas. *Gynecol Oncol*. 2009;115:37–40.
52. Li N, Wu L, Zhang H, et al. Treatment options in stage I endometrial stromal sarcoma: a retrospective analysis of 53 cases. *Gynecol Oncol*. 2008;108:306–311.
53. Zivanovic O, Jacks LM, Iasonos A, et al. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. *Cancer*. 2012;118:660–669.
54. Leitao MM Jr, Hensley M, Barakat RR, et al. Immunohistochemical expression of estrogen and progesterone receptors and outcomes in patients with newly diagnosed uterine leiomyosarcoma. *Gynecol Oncol*. 2012;124:558–562.
55. Ioffe YJ, Li AJ, Walsh CS, et al. Hormone receptor expression in uterine sarcomas: prognostic and therapeutic roles. *Gynecol Oncol*. 2009;115:466–471.
56. Rodriguez Y, Baez D, de Oca FM, et al. Comparative analysis of the ER α /ER β ratio and neurotensin and its high-affinity receptor in the myometrium, uterine leiomyoma, atypical leiomyoma, and leiomyosarcoma. *Int J Gynecol Pathol*. 2011;30:354–363.
57. Koivisto-Korander R, Butzow R, Koivisto A, et al. Immunohistochemical studies on uterine carcinosarcoma, leiomyosarcoma, and endometrial stromal sarcoma: expression and prognostic importance of ten different markers. *Tumor Biol*. 2011;32:451–459.
58. Kildal W, Pradhan M, Abeler VM, et al. β -catenin expression in uterine sarcomas and its relation to clinicopathologic parameters. *Eur J Cancer*. 2009;45:2412–2417.
59. Lee CH, Roh J, Choi J, et al. Cyclooxygenase-2 is an independent predictor of poor prognosis in uterine leiomyosarcomas. *Int J Gynecol Cancer*. 2011;21:668–672.
60. Menczer J, Schreiber L, Sukmanov O, et al. COX-2 expression in uterine carcinosarcoma. *Acta Obstet Gynecol*. 2010;89:120–125.
61. D'Angelo E, Spagnoli LG, Prat J. Comparative clinicopathologic and immunohistochemical analysis of uterine sarcomas diagnosed using the World Health Organization classification system. *Hum Pathol*. 2009;40:1571–1585.
62. Galaal K, Kew FM, Tam KF, et al. Evaluation of prognostic factors and treatment outcomes in

- uterine carcinosarcoma. *Eur J Obstet Gynecol Reprod Biol.* 2009;143:88–92.
63. Leath CA 3rd, Numnum TM, Kendrick JE 4th, et al. Patterns of failure for conservatively managed surgical stage I uterine carcinosarcoma: implications for adjuvant therapy. *Int J Gynecol Cancer.* 2009;19:888–891.
 64. Beck TL, Singhal PK, Ehrenberg HM, et al. Endometrial stromal sarcoma: analysis of recurrence following adjuvant treatment. *Gynecol Oncol.* 2012;125:141–144.
 65. Kim WY, Lee JW, Choi CH, et al. Low-grade endometrial stromal sarcoma: a single center's experience with 22 cases. *Int J Cancer.* 2008;118:1084–1089.
 66. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: results of a prospective study. *Gynecol Oncol.* 2009;112:563–567.
 67. Leita MM, Brennan MF, Hensley M, et al. Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. *Gynecol Oncol.* 2002;87:287–294.
 68. Chiang S, Ali R, Melnyk N, et al. Frequency of known gene rearrangements in endometrial stromal tumors. *Am J Surg Pathol.* 2011;35:1364–1372.
 69. Lee C, Ou W, Marino-Enriquez A, et al. 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. *PNAS.* 2012;109:929–934.
 70. Lee C, Marino-Enriquez A, Ou W, et al. The clinicopathologic features of YWHA-FAM22 endometrial stromal sarcomas: a histologically high-grade and clinically aggressive tumor. *Am J Surg Pathol.* 2012;36:641–653.
 71. Hayashi T, Horiuchi A, Sano K, et al. Mice-lacking LMP2, immuno-proteasome subunit, as and animal model of spontaneous uterine leiomyosarcoma. *Protein Cell.* 2010;1:711–717.
 72. Murray S, Linardou H, Mountzios G, et al. Low frequency of somatic mutations in uterine sarcomas: a molecular analysis and review of the literature. *Mutation Res.* 2010;686:68–73.
 73. Growdon WB, Roussel BN, Scialabba VL, et al. Tissue-specific signatures of activating PIK3CA and RAS mutations in carcinosarcomas of gynecologic origin. *Gynecol Oncol.* 2011;121:212–217.
 74. Saegusa M, Hashimura M, Kuwata T, et al. Requirement of the Akt/ β -catenin pathway for uterine carcinosarcoma genesis, modulating E-cadherin expression through the transactivation of *Slug*. *Am J Pathol.* 2009;174:2107–2115.
 75. Cimbaluk D, Rotmensh J, Scudiere J, et al. Uterine carcinosarcoma: immunohistochemical studies on tissue microarrays with focus on potential therapeutic targets. *Gynecol Oncol.* 2007;105:138–144.
 76. Folpe AL, Kwiatkowski DJ. Perivascular epithelioid cell neoplasms: pathology and pathogenesis. *Hum Pathol.* 2010;41:1–15.
 77. Mittal K, Joutovsky A. Areas with benign morphologic and immunohistochemical features are associated with some uterine leiomyosarcomas. *Gynecol Oncol.* 2007;104:362–365.
 78. Mittal KR, Chan F, Wei JJ, et al. Molecular and immunohistochemical evidence for the origin of uterine leiomyosarcomas from associated leiomyoma and symplastic leiomyoma-like areas. *Modern Pathol.* 2009;22:1303–1311.
 79. Zhang P, Zhang C, Hao J, et al. Use of X chromosome inactivation pattern to determine clonal origins of uterine leiomyoma and leiomyosarcoma. *Hum Pathol.* 2006;37:1350–1356.
 80. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine isthmus muscle neoplasms. A clinicopathologic study of 213 cases. *Am J Surg Pathol.* 1994;18:535–558.
 81. Perrone T, Dehner LP. Prognostically favorable “mitotically active” the smooth muscle tumors of the uterus. A clinicopathologic study of 10 cases. *Am J Surg Pathol.* 1988;12:1–8.
 82. Giuntoli RL, Gostout BS, Di Marco CS, et al. Diagnostic criteria for uterine smooth muscle tumors: Leiomyoma variants associated with malignant behavior. *J Reprod Med.* 2007;52:1001–1010.
 83. Ip PP, Cheung AN, Clement PB. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): a clinicopathologic analysis of 16 cases. *Am J Surg Pathol.* 2009;33:992–1005.
 84. Ng JS, Chew SH, Low J. A clinicopathologic study of uterine smooth muscle tumors of uncertain malignant potential (STUMP). *Ann Acad Med Singapore.* 2010;39:625–628.
 85. Veras E, Zivanovic O, Jacks L, et al. “Low grade leiomyosarcoma” and late recurring smooth muscle tumors of the uterus: a heterogeneous collection of frequently misdiagnosed tumors associated with an overall favorable prognosis relative to conventional uterine leiomyosarcomas. *Am J Surg Pathol.* 2011;35:1626–1637.
 86. O'Neill CJ, McBride HA, Connolly LE, et al. Uterine leiomyosarcomas are characterized by high p16, p53, and MIB1 expression in comparison with usual leiomyomas, leiomyoma variants and smooth muscle tumors of uncertain malignant potential. *Histopathology.* 2007;50:851–858.
 87. Chen L, Yang B. Immunohistochemical analysis of p16, p53, and Ki67 expression in uterine smooth muscle tumors. *Int J Gynecol Pathol.* 2008;27:326–332.
 88. Atkins KA, Arronte N, Darus CJ, et al. The use of p16 in enhancing the histologic classification of uterine smooth muscle tumors. *Am J Surg Pathol.* 2008;32:98–102.
 89. Gannon BR, Manduch M, Childs TJ. Differential immunoreactivity of p16 in leiomyosarcomas and leiomyoma variants. *Int J Gynecol Pathol.* 2008;27:68–73.
 90. Prayson RA, Goldblum JR, Hart WR. Epithelioid smooth muscle tumors of the uterus: a clinicopathologic study of 18 patients. *Am J Surg Pathol.* 1997;21:383–391.
 91. Jones MW, Norris HJ. Clinicopathologic study of 28 uterine leiomyosarcomas with metastases. *Int J Gynecol Pathol.* 1995;14:243–249.
 92. Burch DM, Tavassoli FA. Myxoid leiomyosarcoma of the uterus. *Histopathology.* 2011;59:1144–1155.
 93. Pelmus M, Penault-Llorca F, Guillou L, et al. Prognostic factors in early stage leiomyosarcoma of the uterus. *Int J Gynecol Pathol.* 2009;19:385–390.
 94. D'Angelo E, Espinosa I, Ali R, et al. Uterine leiomyosarcomas: tumor size, mitotic index, and biomarkers Ki67, and Bcl-2 identify 2 groups with different prognosis. *Gynecol Oncol.* 2011;121:328–333.
 95. Wang WL, Soslow R, Hensley M, et al. Histopathologic prognostic factors in stage I leiomyosarcoma of the uterus: a detailed analysis of 27 cases. *Am J Surg Pathol.* 2011;35:522–529.
 96. Awonuga AO, Shavell VI, Imudia AN, et al. Pathogenesis of benign metastasizing leiomyoma: a review. *Obstet Gynecol Surv.* 2010;65:189–195.
 97. McCluggage WG. Malignant biphasic uterine tumors: carcinosarcomas or metaplastic carcinomas? *J Clin Pathol.* 2002;55:321–325.
 98. Taylor NP, Zigelboim I, Huettner PC, et al. DNA mismatch repair and TP53 defects are early events in uterine carcinosarcoma tumorigenesis. *Modern Pathol.* 2006;19:1333–1338.
 99. Ferguson SE, Tornos C, Hummer A, et al. Prognostic features of surgical stage I uterine carcinosarcoma. *Am J Surg Pathol.* 2007;31:1653–1661.
 100. Garamvoelgyi E, Guillou L, Gebhard S, et al. primary malignant mixed mullerian tumor of the female peritoneum. A clinical, pathologic, and immunohistochemical study of 3 pieces and review of the literature. *Cancer.* 1994;74:854–860.
 101. Rose PG, Rodriguez Please M, Abdul-Karim FW. Malignant mixed mullerian tumor of the female peritoneum: treatment and outcome of 3 cases. *Gynecol Oncol.* 1997;65:523–525.
 102. Sumathi VP, Murnaghan M, Dobbs SP, et al. Extragenital mullerian carcinosarcoma arising from the peritoneum: report of 2 cases. *Int J Gynecol Cancer.* 2002;12:764–767.
 103. Ko ML, Huang SH, Shen J, et al. Primary peritoneal carcinosarcoma report of a case with 5 year disease free survival after surgery and chemoradiation and review of the literature. *Acta Oncol.* 2005;44:756–760.
 104. Shintaku M, Matsumoto T. Primary mullerian carcinosarcoma of the retroperitoneum: report of a case. *Int J Gynecol Pathol.* 2001;20:191–195.
 105. Booth C, Zahn CM, McBroom J, et al. Retroperitoneal mullerian carcinosarcoma associated with endometriosis: a case report. *Gynecol Oncol.* 2004;93:546–549.
 106. Dionigi A, Oliva E, Clement PB, et al. Endometrial stromal nodules and endometrial stromal tumors with limited infiltration: a clinicopathologic study of 50 cases. *Am J Surg Pathol.* 2002;26:567–581.
 107. Chang KL, Crabtree GS, Kim Lim-Tan S, et al. Primary uterine endometrial stromal neoplasms: a clinicopathologic study of 117 cases. *Am J Surg Pathol.* 1990;14:415–438.
 108. Oliva E, Young RH, Clement PB. Myxoid and fibrous endometrial stromal tumors of the uterus: a report of 10 cases. *Int J Gynecol Pathol.* 1999;18:310–319.
 109. Yilmaz A, Rush DS, Soslow RA. Endometrial stromal sarcomas with unusual histologic features. A report of 24 primary and metastatic tumors emphasizing fibroblastic and smooth muscle differentiation. *Am J Surg Pathol.* 2002;26:1142–1150.
 110. Oliva E, Clement PB, Young RH. Epithelioid endometrial and endometrioid stromal tumors: a report of 4 pieces emphasizing their distinction from epithelioid smooth muscle tumors and other oxyphilic uterine and extrauterine tumors. *Int J Gynecol Pathol.* 2002;21:48–55.
 111. Clement PB, Scully RE. Endometrial stromal sarcomas of the uterus with extensive endometrioid glandular differentiation: a report of 3 cases that caused problems in the differential diagnosis. *Int J Gynecol Pathol.* 1992;11:163–173.
 112. Nucci MR, Harburger D, Koontz J, et al. molecular analyses of the JAZF1-JJAZ1 gene fusion by RT-PCR and fluorescence in situ hybridization in endometrial stromal neoplasms. *Am J Surg Pathol.* 2007;31:65–70.
 113. Chang KL, Crabtree GS, Soo Kim LT, et al. primary extrauterine endometrial stromal neoplasms: a clinicopathologic study of 20 cases and a review of the literature. *Int J Gynecol Pathol.* 1993;12:282–296.
 114. Irvin W, Pelkey T, Rice L, et al. Endometrial stromal sarcoma of the vulva arising in extraovarian endometriosis: a case report and literature review. *Gynecol Oncol.* 1998;71:313–316.

115. Kondi-Papthitis A, Smyrniotis B, Liapis A, et al. Stromal sarcoma arising in endometriosis. A clinicopathologic and immunohistochemical study of 4 cases. *Eur J Gynaecol Oncol.* 1998;19:588–590.
116. Lacroix-Triki M, Beyris L, Martel P, et al. Low grade endometrial stromal sarcoma arising from sciatic nerve endometriosis. *Obstet Gynecol.* 2004;104:1147–1149.
117. Androulaki A, Papathomas TG, Alexandrou P, et al. Metastatic low grade endometrial stromal sarcoma of clitoris: report of a case. *Int J Gynecol Cancer.* 2007;17:290–293.
118. Sato K, Ueda Y, Sugaya J, et al. Extrauterine endometrial stromal sarcoma with JAZF1/JJAZ1 fusion confirm with RT-PCR and interphase FISH presenting as an inguinal tumor. *Virchows Arch.* 2007;450:349–353.
119. Evans HL. Endometrial stromal sarcoma and poorly differentiated endometrial sarcoma. *Cancer.* 1982;50:2170–2182.
120. Gallardo A, Prat J. Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. *Am J Surg Pathol.* 2009;33:278–288.
121. Clement PB. Mullerian adenosarcoma of the uterus with sarcomatous overgrowth. A clinicopathologic analysis of 10 cases. *Am J Surg Pathol.* 1989;13:28–38.
122. Soslow RA, Ali A, Oliva E. Mullerian adenosarcomas: on immunophenotypic analysis of 35 cases. *Am J Surg Pathol.* 2008;32:1013–1021.
123. Anderson J, Behbakht K, De Geest K, et al. Adenosarcoma in a patient with vaginal endometriosis. *Obstet Gynecol.* 2001;98:964–966.
124. Liu L, Davidosmon S, Singh M. Mullerian adenosarcoma of vagina arising in persistent endometriosis: report of a case and review of the literature. *Gynecol Oncol.* 2003;90:486–490.
125. Raffaelli R, Piazzola E, Zanconato G, et al. A rare case of extrauterine adenosarcoma arising in endometriosis of the rectovaginal septum. *Fertil Steril.* 2004;81:1142–1144.
126. Yantiss RK, Clement PB, Young RH. Neoplastic and pre-neoplastic changes in gastrointestinal endometriosis: a study of 17 cases. *Am J Surg Pathol.* 2000;24:513–524.
127. Vata AR, Ruzis EP, Moussabeck O, et al. Endometrioid adenosarcoma of the bladder arising from endometriosis. *J Urol.* 1990;143:813–815.
128. Murugasu A, Miller J, Proietto A, et al. Extra-genital mullerian adenosarcoma with sarcomatous overgrowth arising in an endometriotic cyst in the pouch of Douglas. *Int J Gynecol Pathol.* 2003;13:371–375.
129. Dincer AD, Timmins P, Pietrocola D, et al. Primary peritoneal adenosarcoma with sarcomatous overgrowth associated with endometriosis. *Int J Gynecol Pathol.* 2002;21:65–68.
130. N'Senda P, Wendum D, Ballardur P, et al. Adenosarcoma arising in hepatic endometriosis. *Eur Radiol.* 2000;10:1287–1289.
131. Huang GS, arwnd RC, Sakaris A, et al. Extra-genital adenosarcoma: a case report, review of the literature and management discussion. *Gynecol Oncol.* 2009;115:472–475.
132. Clement PB, Scully RE. Uterine tumors resembling ovarian sex cord tumors. A clinicopathologic analysis of 14 cases. *Am J Clin Pathol.* 1976;66:512–525.
133. Hurrell DP, McCluggage WG. Uterine tumors resembling ovarian sex cord tumor is an immunohistochemically polyphenotypic neoplasm which exhibits coexpression of epithelial, myoid and sex cord markers. *J Clin Pathol.* 2007;60:1148–1154.
134. De leval L, Lim GS, Waltregny D, et al. Diverse phenotypic profile of uterine tumors resembling ovarian sex cord tumors: on immunohistochemical study of 12 cases. *Am J Surg Pathol.* 2010;34:1749–1761.
135. Staats PN, Garcia JJ, Dias-Santagata DC, et al. Uterine tumors resembling ovarian sex cord tumors (UTROSCT) lack the JAZF1-JJAZ1 translocation frequently seen in endometrial stromal tumors. *Am J Surg Pathol.* 2009;33:1206–1212.
136. Biermann K, Heukamp LC, Buttner R, et al. Uterine tumor resembling an ovarian sex cord tumor associated with metastasis. *Int J Gynecol Pathol.* 2008;27:58–60.
137. Folpe AL, Mentzel T, Lehr H, et al. Perivascular epithelioid neoplasms of soft tissue and gynecologic origin. *Am J Surg Pathol.* 2005;29:1558–1575.
138. Vang R, Kempson RL. Perivascular epithelioid cell tumor (PEComa) of the uterus. A subset of HMB45 epithelioid mesenchymal neoplasms with an uncertain relationship to pure smooth muscle tumors. *Am J Surg Pathol.* 2002;26:1–13.
139. Fadare O. Perivascular epithelioid cell tumor (PEComa) of the uterus: on outcome-based clinicopathologic analysis of 41 reported cases. *Adv Anat Pathol.* 2008;15:63–75.
140. Argani P, Aulmann S, Illei PB, et al. A distinct subset of PEComas harbor TFE3 fusions. *Am J Surg Pathol.* 2010;34:1395–1406.
141. Rabbani JT, Zaloudek CJ, Shekitka KM, et al. inflammatory myofibroblastic tumor of the uterus: a clinicopathologic study of 6 cases emphasizing distinction from aggressive mesenchymal tumors. *Am J Surg Pathol.* 2005;29:1348–1355.
142. Gupta N, Mittal S, Misra R. inflammatory pseudotumor of the uterus: an unusual pelvic mass. *Eur J Obstet Gynecol Reprod Biol.* 2011;156:118–119.
143. Ferguson SE, Gerald W, Barakat RR, et al. Clinicopathologic features of rhabdomyosarcoma of gynecologic origin in adults. *Am J Surg Pathol.* 2007;31:382–389.
144. Fadare O. Heterologous and rare homologous sarcomas of the uterine corpus: a clinicopathologic review. *Adv Anat Pathol.* 2011;18:60–74.
145. McDonald AG, Dal Chin P, Ganguly A, et al. Liposarcoma arising in uterine lipoleiomyoma: a report of the cases and review of the literature. *Am J Surg Pathol.* 2011;35:221–227.
146. Fadare O. Pleomorphic liposarcoma of the uterine corpus with focal the smooth muscle differentiation. *Int J Gynecol Pathol.* 2011;30:282–287.
147. Lissoni A, Cormio G, Bonazzi C, et al. Fertility-sparing surgery in uterine leiomyosarcoma. *Gynecol Oncol.* 1998;70:348–350.
148. Stadsvold JL, Molpus KL, Baker JJ, et al. Conservative management of a myxoid endometrial stromal sarcoma in a 16-year-old nulliparous woman. *Gynecol Oncol.* 2005;99:243–245.
149. Yan L, Tian Y, Fu Y, et al. Successful pregnancy after fertility-preserving surgery for endometrial stromal sarcoma. *Fertil Steril.* 2010;93:269.e1–e3.
150. Fong Y, Coit DG, Woodruff JM, et al. Lymph node metastasis from soft tissue sarcoma in adults: analysis of data from a prospective database of 1772 sarcoma patients. *Ann Surg.* 1993;217:72–77.
151. Ayhan A, Aksan G, Gultekin M, et al. Prognostic factors and the role of lymphadenectomy in uterine leiomyosarcomas. *Arch Gynecol Obstet.* 2009;280:79–85.
152. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma: a Gynecologic Oncology Group study. *Cancer.* 1993;71:1702–1709.
153. Leitaio MM, Sonoda Y, Brennan MF, et al. Incidence of lymph node and ovarian metastases in leiomyosarcoma of the uterus. *Gynecol Oncol.* 2003;91:209–212.
154. Goff BA, Rice LW, Fleischhacker D, et al. Uterine leiomyosarcoma and endometrial stromal sarcoma: lymph node metastases and sites of recurrence. *Gynecol Oncol.* 1993;50:105–109.
155. Gadducci A, Landoni F, Sartori E, et al. Uterine leiomyosarcoma: analysis of treatment failures and survival. *Gynecol Oncol.* 1996;62:25–32.
156. Riopel J, Plante M, Renaud MC, et al. Lymph node metastases in low-grade endometrial stromal sarcoma. *Gynecol Oncol.* 2005;96:402–406.
157. Signorelli M, Fruscio R, Dell'Anna T, et al. Lymphadenectomy in uterine low-grade endometrial stromal sarcoma: an analysis of 19 cases and a literature review. *Int J Gynecol Cancer.* 2010;20:1363–1366.
158. Nemani D, Mitra N, Guo M, et al. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. *Gynecol Oncol.* 2008;111:82–88.
159. Leitaio MM Jr, Zivanovic O, Chi DS, et al. Surgical cytoreduction in patients with metastatic uterine leiomyosarcoma at the time of initial diagnosis. *Gynecol Oncol.* 2012;125:409–413.
160. Khoury-Collado F, Einstein MH, Bochner BH, et al. Pelvic exenteration with curative intent for uterine malignancies. *Gynecol Oncol.* 2012;124:42–47.
161. Burt BM, Ocejio S, Mery CM, et al. Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extends survival. *Ann Thorac Surg.* 2011;92:1202–1207.
162. Levenback C, Rubin SC, McCormack PM, et al. Resection of pulmonary metastases from uterine sarcomas. *Gynecol Oncol.* 1992;45:202–205.
163. Giuntoli RL 2nd, Garrett-Mayer E, Bristow RE, et al. Secondary cytoreduction in the management of recurrent uterine leiomyosarcoma. *Gynecol Oncol.* 2007;106:82–88.
164. Sutton G, Kavanagh J, Wolfson A, et al. Corpus: mesenchymal tumors. In: Barakat RR, Markman M, Randall ME, eds. *Principles and Practice of Gynecologic Oncology*. 5th ed. Philadelphia, PA: Wolters-Kluwer/Lippincott, Williams & Wilkins; 2009:733–761.
165. Reed NS, Mangioni C, Malmstrom, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). *Eur J Cancer.* 2008;44:808–818.
166. Aalders J, Albelier V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol.* 1980;56:419–427.
167. Vongtama V, Karlen JR, Piver SM, et al. Treatment, results and prognostic factors in stage I and II sarcomas of the corpus uteri. *Am J Obstet Gynecol.* 1976;126:139–147.
168. Salazar OM, Bonfiglio TA, Patten SF, et al. Uterine sarcomas: natural history, treatment and prognosis. *Cancer.* 1978;42:1152–1160.
169. Perez CA, Askin F, Baglan RJ, et al. Effects of irradiation on mixed müllerian tumors of the uterine sarcomas. *Cancer.* 1979;43:1274–1284.
170. Hoffmann W, Schmandt S, Koradioterpymann RD, et al. Radiotherapy in the

- treatment of uterine sarcomas: a retrospective analysis of 54 cases. *Gynecol Obstet Invest.* 1996;42:49–57.
171. Knocke TH, Kucera H, Dorfler D, et al. Results of postoperative radiotherapy in the treatment of sarcomas of the corpus uteri. *Cancer.* 1998;83:1972–1979.
 172. Ferrer F, Sabater S, Farrutierne B, et al. Impact of radiotherapy on local control and survival in uterine sarcomas: a retrospective study from the GRUP Oncologic Catala-Occita. *Int J Radiat Oncol Biol Phys.* 1999;44:47–52.
 173. Chauveinc L, Deniaud E, Plancher C, et al. Uterine sarcomas: the Curie Institut experience. Prognostic factors and adjuvant treatments. *Gynecol Oncol.* 1999;72:232–237.
 174. Soumarova R, Horova H, Seneklova Z, et al. Treatment of uterine sarcoma: a survey of 49 patients. *Arch Gynecol Obstet.* 2002;266:92–95.
 175. Livi L, Paia F, Shah N, et al. Uterine sarcoma: twenty-seven years of experience. *Int J Radiat Oncol Biol Phys.* 2003;57:1366–1373.
 176. Dusenberry KE, Potish RA, Agent PA, et al. On the apparent failure of adjuvant pelvic radiotherapy to improve survival for women with uterine sarcomas confined to the uterus. *Am J Clin Oncol.* 2005;28:295–300.
 177. Dusenberry KE, Potish RA, Judson P. Limitations of adjuvant radiotherapy for uterine sarcomas spread beyond the uterus. *Gynecol Oncol.* 2004;94:191–196.
 178. Sorbe B, Johansson B. Prophylactic pelvic irradiation as part of primary therapy in uterine sarcomas. *Int J Oncol.* 2008;32:1111–1117.
 179. Sahinler I, Atalar B, Tecer GM, et al. Postoperative radiotherapy in the treatment of uterine sarcomas: long-term results and analysis of prognostic factors. *J BUON.* 2010;15:480–488.
 180. Rovirosa A, Ascaso C, Ordi J, et al. How to deal with prognostic factors and radiotherapy results in uterine neoplasms with a sarcomatous component? *Clin Transl Oncol.* 2009;11:681–687.
 181. Wright JD, Venkatraman ES, Shah M, et al. The role of radiation in improving survival for early-stage carcinosarcomas and leiomyosarcomas. *Am J Obstet Gynecol.* 2008;199:536e1–536e8.
 182. Sampath S, Schultheiss TE, Ryu JK, et al. The role of adjuvant radiation in uterine sarcomas. *Int J Radiat Oncol Biol Phys.* 2010;76:728–734.
 183. Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant Adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol.* 1985;3:1240–1245.
 184. Hornback NB, Omura G, Major FJ. Observations on the uterine sarcomas of adjuvant radiation therapy in patients with stage I and II uterine sarcoma. *Int J Radiat Oncol Biol Phys.* 1986;12:2127–2130.
 185. Pautier P, Rey A, Haie-Meder C, et al. Adjuvant chemotherapy with cisplatin, ifosfamide, and doxorubicin followed by radiotherapy in localized uterine sarcomas: results of a case-controlled study with radiotherapy alone. *Int J Gynecol Cancer.* 2004;14:1112–1117.
 186. Gerszten K, Faul C, Kounelis S, et al. The impact of adjuvant radiotherapy on carcinosarcoma of the uterus. *Gynecol Oncol.* 1998;68:8–13.
 187. Wong L, See HT, Khoo-Tan HS, et al. Combined adjuvant cisplatin and ifosfamide chemotherapy and radiotherapy for malignant mixed müllerian tumors of the uterine sarcomas. *Int J Gynecol Cancer.* 2006;16:1364–1369.
 188. Molpus KL, Redline-Frazier S, Reed G, et al. Postoperative pelvic irradiation in early stage uterine mixed müllerian tumors. *Eur J Gynaecol Oncol.* 1998;19:541–546.
 189. Le T. Adjuvant pelvic radiotherapy for uterine carcinosarcoma in a high risk population. *Eur J Surg Oncol.* 2001;27:282–285.
 190. Menczer J, Levy T, Piura B, et al. A comparison between different postoperative treatment modalities of uterine carcinosarcoma. *Gynecol Oncol.* 2005;97:166–170.
 191. Chi DS, Mychalczak B, Saigo PE, et al. The role of whole-pelvic irradiation in the treatment of early-stage uterine carcinosarcoma. *Gynecol Oncol.* 1997;65:493–498.
 192. Callister M, Ramondetta LM, Jhingran A, et al. Malignant mixed müllerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. *Int J Radiat Oncol Biol Phys.* 2004;58:786–796.
 193. Knocke TH, Weitmann HD, Kucera H, et al. Results of primary and adjuvant radiotherapy in the treatment of mixed müllerian tumors of the corpus uteri. *Gynecol Oncol.* 1999;73:389–395.
 194. Sartori E, Bazzurini L, Gadducci A, et al. Carcinosarcoma of the uterine sarcomas: a clinicopathological multicenter CTF study. *Gynecol Oncol.* 1997;67:70–75.
 195. Smith DC, MacDonald OK, Gaffney DK. The impact of adjuvant radiation therapy on survival in women with uterine carcinosarcoma. *Int J Gynecol Cancer.* 2008;18(2):255–261.
 196. Wolfson AH, Brady MF, Rocereto TF, et al. A Gynecologic Oncology Group randomized trial of whole abdominal irradiation (WWAI) vs. cisplatin-ifosfamide + mesna (WCIM) in optimally debulked stage I–IV carcinosarcoma (WCS) of the uterine sarcomas. *J Clin Oncol.* 2006;24:256.
 197. Wolfson AH, Brady MF, Rocereto TF, et al. A Gynecologic Oncology Group randomized trial of whole abdominal irradiation versus chemotherapy in optimally debulked carcinosarcomas of the uterus. *Int J Gynecol Cancer.* 2006;16:45.
 198. Wolfson AH, Brady MF, Rocereto T, et al. A Gynecologic Oncology Group randomized phase III trial of whole abdominal irradiation (WWAI) vs. cisplatin-ifosfamide and mesna (CIM) as postsurgical therapy in stage I–IV carcinosarcoma (CS) of the uterus. *Gynecol Oncol.* 2007;107:177–185.
 199. Makker V, Abu-Rustum NR, Alektiar KM, et al. A retrospective assessment of outcomes of chemotherapy-based versus radiation-only adjuvant treatment for completely resected stage I–IV uterine carcinosarcomas. *Gynecol Oncol.* 2008;11:249–254.
 200. Manolitsas T, Wain GV, Williams KE, et al. Multimodality therapy for patients with clinical stage I and II malignant mixed müllerian tumors of the uterus. *Cancer.* 2001;91:1437–1443.
 201. Gadducci A, Fabiani MG, Bonuccelli A, et al. Analysis of treatment failures in patients with early-stage uterine leiomyosarcoma. *Anticancer Res.* 1995;15:485–488.
 202. Mahdavi A, Monk BJ, Ragazzo J, et al. Pelvic radiation improves local control after hysterectomy for uterine leiomyosarcomas: a 20-year experience. *Int J Gynecol Cancer.* 2009;19:1080–1084.
 203. Gadducci A, Sartori E, Landoni F, et al. Endometrial stromal sarcoma: analysis of treatment failure and survival. *Gynecol Oncol.* 1996;63:247–253.
 204. Bodner K, Bodner-Adler B, Obermair A, et al. Prognostic parameters in endometrial stromal sarcoma: a clinicopathologic study in 31 patients. *Gynecol Oncol.* 2001;81(2):160–165.
 205. Geller MA, Argenta P, Bradley W, et al. Treatment and recurrence patterns in endometrial stromal sarcomas and the relation to c-kit. *Gynecol Oncol.* 2004;95:632–636.
 206. Valdivieco I, Rovirosa A, Colomo L, et al. Endometrial stromal sarcoma. Is there a place for radiotherapy? *Clin Transl Oncol.* 2010;12:226–230.
 207. Rose PG, Piver MS, Tsukada Y, et al. Patterns of metastasis in uterine sarcoma: an autopsy study. *Cancer.* 1989;63:935–938.
 208. Pervaiz N, Colterjohn N, Farrokhhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer.* 2008;113:573–581.
 209. Odunsi K, Moneke V, Tammela J, et al. Efficacy of adjuvant CYVADIC chemotherapy in early-stage uterine sarcomas: results of long-term follow-up. *Int J Gynecol Cancer.* 2004;14:659–664.
 210. Piver MS, Lele SB, Marchetti DL, et al. Effect of adjuvant chemotherapy on time to recurrence and survival of stage I uterine sarcomas. *J Surg Oncol.* 1988;38:233–239.
 211. Hempling RE, Piver MS, Baker TR. Impact on progression-free survival of adjuvant cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dacarbazine (CYVADIC) chemotherapy for stage I uterine sarcoma. A prospective trial. *Am J Clin Oncol.* 1995;18:282–286.
 212. Wong C, Lele SB, Natarajan N. Effect of adjuvant chemotherapy on long-term survival of stage I uterine sarcoma. *Proc Am Soc Clin Oncol.* 1999;18:386 (abstract 1492).
 213. Resnik E, Chambers SK, Carcangiu ML, et al. A phase II study of etoposide, cisplatin, and doxorubicin chemotherapy in mixed müllerian tumors (MMT) of the uterus. *Gynecol Oncol.* 1995;56:370–375.
 214. Sutton G, Kauderer J, Carson LF, et al. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2005;96:630–634.
 215. Hensley ML, Blessing JA, Degeest K, et al. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol Oncol.* 2008;109:323–328.
 216. Hensley ML, Blessing JA, Mannel R, et al. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol.* 2008;109:329–334.
 217. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I–IV high grade uterine leiomyosarcoma: results of a prospective study. *Gynecol Oncol.* 2009;112:563–567.
 218. Garcia del Muro X, Lopez-Pousa A, Martin J, et al. A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma. *Cancer.* 2005;104:1706–1712.
 219. Hensley ML, Wathen K, et al. Adjuvant treatment of high-risk primary uterine leiomyosarcoma with gemcitabine/docetaxel (GT), followed by doxorubicin (D): results of phase II multicenter trial SARC005. ASCO meeting abstracts. *J Clin Oncol.* 2010;28(suppl. 15):10021.
 220. Hensley ML, Maki RG, et al. 3- Year Follow-Up of SARC005: Adjuvant Treatment of High

- Risk Primary Uterine Leiomyosarcoma with Gemcitabine/docetaxel, Followed by Doxorubicin. Combined Meeting of the Connective Tissue Oncology Society and the Musculoskeletal Tumor Society, Chicago, IL; 2011.
221. Hensley ML. Phase III randomized study of adjuvant chemotherapy comprising gemcitabine hydrochloride and docetaxel followed by doxorubicin hydrochloride versus observation in patients with uterus-limited, high-grade uterine leiomyosarcoma. Retrieved March 1st 2012, from <http://cancer.gov/clinicaltrials/search/view?cdrid=724874&version=healthprofessional>.
 222. Chu MC, Mor G, Lim C, et al. Low-grade endometrial stromal sarcoma: hormonal aspects. *Gynecol Oncol*. 2003;90:170–176.
 223. Shi Y, Liu Z, Peng Z, et al. The diagnosis and treatment of Mullerian adenosarcoma of the uterus. *Aust N Z J Obstet Gynaecol*. 2008;48:596–600.
 224. Herrmann K. 18F-FDG-PET/CT Imaging as an early survival predictor in patients with primary high-grade soft tissue sarcomas undergoing neoadjuvant therapy. *Clin Cancer Res*. 2012;18(7):2024–2031.
 225. Sutton G, Blessing J, Hanjani P, et al. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2005;96:749–752.
 226. Miller DS, Blessing JA, Ball H, et al. Phase II trial of topotecan in patients with advanced, persistent, or recurrent uterine leiomyosarcomas: a Gynecologic Oncology Group study. *Am J Clin Oncol*. 2000;23:355–357.
 227. Sutton G, Blessing JA, Ball H. Phase II trial of paclitaxel in leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1999;74:346–349.
 228. Sutton G, Blessing JA, Barrett RJ, et al. Phase II trial of ifosfamide and mesna in leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Am J Obstet Gynecol*. 1992;166:556–559.
 229. Thigpen T, Blessing JA, Yordan E, et al. Phase II trial of etoposide in leiomyosarcoma of the uterus: a Gynecologic Oncology group study. *Gynecol Oncol*. 1996;63:120–122.
 230. Thigpen T, Blessing JA, Beecham J, et al. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol*. 1991;9:1962–1966.
 231. Omura GA, Major FJ, Blessing JA, et al. A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer*. 1983;52:626–632.
 232. Thigpen JT, Blessing JA, Homesley HD, et al. Phase II trial of piperazinedione in patients with advanced or recurrent uterine sarcoma. A Gynecologic Oncology Group study. *Am J Clin Oncol*. 1985;8:350–352.
 233. Asbury R, Blessing JA, Smith DM, et al. Aminothiadiazole in the treatment of advanced leiomyosarcoma of the uterine corpus. A Gynecologic Oncology Group study. *Am J Clin Oncol*. 1995;18:397–399.
 234. Slayton RE, Blessing JA, Look K, et al. A phase II clinical trial of diaziquone (AZQ) in the treatment of patients with recurrent leiomyosarcoma of the uterus, a Gynecologic Oncology Group study. *Invest New Drugs*. 1991;9:207–208.
 235. Look K, Sandler A, Blessing JA, et al. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;92:644–647.
 236. Svancarova L, Blay JY, Judson IR, et al. Gemcitabine in advanced adult soft-tissue sarcomas. A phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer*. 2002;38:556–559.
 237. Okuno S, Edmonson J, Mahoney M, et al. Phase II trial of gemcitabine in advanced sarcomas. *Cancer*. 2002;94:3225–3229.
 238. Patel SR, Gandhi V, Jenkins J, et al. Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. *J Clin Oncol*. 2001;19:3483–3489.
 239. Gallup DG, Blessing JA, Andersen W, et al. Evaluation of paclitaxel in previously treated leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2003;89:48–51.
 240. Yovine A, Rofrio M, Blay JY, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *J Clin Oncol*. 2004;22:890–899.
 241. Twelves C, Hoekman K, Bowman A, et al. Phase I and pharmacokinetic study of Yondelis™ (Ecteinascidin-743; ET-743) administered as an infusion over 1 h or 3 h every 21 days in patients with solid tumours. *Eur J Cancer*. 2003;39:1842–1851.
 242. Smith HO, Blessing JA, Vaccarello L. Trimetrexate in the treatment of recurrent or advanced leiomyosarcoma of the uterus: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol*. 2002;84:140–144.
 243. Rose PG, Blessing JA, Soper JT, et al. Prolonged oral etoposide in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1998;70:267–271.
 244. Slayton RE, Blessing JA, Angel C, et al. Phase II trial of etoposide in the management of advanced and recurrent leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Cancer Treat Rep*. 1987;71:1303–1304.
 245. Asbury R, Blessing JA, Buller R, et al. Amonafide in patients with leiomyosarcoma of the uterus: a phase II gynecologic oncology group study. *Am J Clin Oncol*. 1998;21:145–146.
 246. Muss HB, Bundy BN, Adcock L, et al. Mitoxantrone in the treatment of advanced uterine sarcoma. A phase II trial of the Gynecologic Oncology Group. *Am J Clin Oncol*. 1990;13:32–34.
 247. Thigpen JT, Blessing JA, Wilbanks GD. Cisplatin as second-line chemotherapy in the treatment of advanced or recurrent leiomyosarcoma of the uterus. A phase II trial of the Gynecologic Oncology Group. *Am J Clin Oncol*. 1986;9:18–20.
 248. Fidias P, Demetri G, et al. Navelbine shows activity in previously treated sarcoma patients: Phase II results from MGH/Dana Farber/Partner's CancerCare Study. *Proc Am Soc Clin Oncol*. 1998;abstract 1977.
 249. Talbot SM, Keohan ML, et al. A phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. *Cancer*. 2003;98:1942–1946.
 250. Monk BJ, Blessing JA, Street DG, et al. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;124:48–52.
 251. Verweij J, Lee SM, et al. Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcomas in adults: a study of the european organization for research and treatment of cancer soft tissue and bone sarcoma group. *J Clin Oncol*. 2000;18:2081–2086.
 252. Schoffski P, Ray-Coquard IL, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. *Lancet Oncol*. 2011;12:1045–1052.
 253. Long H 3rd, Blessing JA, Sorosky J. Phase II trial of dacarbazine, mitomycin, doxorubicin, and cisplatin with sargramostim in uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2005;99:339–342.
 254. Edmonson JH, Marks RS, Buckner JC, et al. Contrast of response to dacarbazine, mitomycin, doxorubicin, and cisplatin (DMAP) plus GM-CSF between patients with advanced malignant gastrointestinal stromal tumors and patients with other advanced leiomyosarcomas. *Cancer Invest*. 2002;20:605–612.
 255. Edmonson JH, Blessing JA, Cosin JA, et al. Phase II study of mitomycin, doxorubicin and cisplatin in the treatment of advanced uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2002;85:507–510.
 256. Currie J, Blessing JA, Muss HB, et al. Combination chemotherapy with hydroxyurea, dacarbazine (DTIC), and etoposide in the treatment of uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996;61:27–30.
 257. Sutton G, Blessing JA, Malfetano JH. Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996;62:226–229.
 258. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol*. 2002;20:2824–2831.
 259. Muss HB, Bundy B, DiSaia PJ, et al. Treatment of recurrent or advanced uterine sarcoma. A randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). *Cancer*. 1985;15:1648–1653.
 260. Dileo P, Morgan J, et al. Gemcitabine and vinorelbine combination chemotherapy for patients with advanced soft tissue sarcomas: results of a phase II trial. *Cancer*. 2007;109:1863–1869.
 261. Hensley ML, Anderson S, et al. Activity of gemcitabine plus docetaxel in leiomyosarcoma (LMS) and other histologies: report of an expanded phase II trial. *J Clin Oncol*. (Meeting Abstracts) 2004;22:9010.
 262. Boyar MS, Hesdorffer M, Keohan ML, et al. Phase II study of temozolomide and thalidomide in patients with unresectable or metastatic leiomyosarcoma. *Sarcoma*. 2008;2008:412503.
 263. Kanjeekal S, Chambers A, Fung MF, et al. Systemic therapy for advanced uterine sarcoma: a systemic review of the literature. *Gynecol Oncol*. 2005;97:624–637.
 264. Thigpen JT, Blessing JA, Beecham J, et al. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol*. 1991;9:1962–1966.
 265. Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcomas: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25:526–531.
 266. Sutton G, Brunetto VL, Kilgore L, et al. A phase III trial of ifosfamide with or without cisplatin

- in carcinosarcomas of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2000;79:147–153.
267. Sutton G, Blessing JA, Rosenshein N, et al. Phase II trial of ifosfamide and mesna in mixed mesodermal tumors of the uterus: a Gynecologic Oncology Group study. *Am J Obstet Gynecol.* 1989;161:309–312.
 268. Gershenson DM, Kavanagh JJ, Copeland LJ, et al. High-dose doxorubicin infusion therapy for disseminated mixed mesodermal sarcoma of the uterus. *Cancer.* 1987;59:1264–1267.
 269. Miller DS, Blessing JA, Schilder J, et al. Phase II evaluation of topotecan in carcinosarcomas of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2005;98:217–221.
 270. Fowler JM, Blessing JA, Soper JT, et al. Phase II evaluation of oral trimetrexate in mixed mesodermal tumors of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2002;85:311–314.
 271. Curtin JP, Blessing JA, Soper JT, et al. Paclitaxel in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2001;83:268–270.
 272. Asbury R, Blessing JA, Podczaski E, et al. A phase II trial of amonafide in patients with mixed mesodermal tumors of the uterus: a Gynecologic Oncology Group study. *Am J Clin Oncol.* 1998;21:306–307.
 273. Asbury R, Blessing JA, Moore D. A phase II trial of aminothiadiazoole in patients with mixed mesodermal tumors of the uterine corpus: a Gynecologic Oncology Group study. *Am J Clin Oncol.* 1996;19:400–402.
 274. Slayton RE, Blessing JA, Clarke-Pearson D. A phase II trial of diaziquone (AZQ) in mixed mesodermal sarcomas of the uterus. *Invest New Drugs.* 1991;9:93–94.
 275. Slayton RE, Blessing JA, DiSaia PJ, et al. Phase II trial of etoposide in the management of advanced or recurrent mixed mesodermal sarcomas of the uterus: a Gynecologic Oncology Group study. *Cancer Treat Rep.* 1987;71:661–662.
 276. Thigpen JT, Blessing JA, Orr JW Jr, et al. Phase II trial of cisplatin in the treatment of patients with advanced or recurrent mixed mesodermal sarcomas of the uterus: a Gynecologic Oncology Group study. *Cancer Treat Rep.* 1986;70:271–274.
 277. Gershenson DM, Kavanagh JJ, Copeland LJ, et al. Cisplatin therapy for disseminated mixed mesodermal sarcoma of the uterus. *J Clin Oncol.* 1987;5:618–621.
 278. Sutton G, Kauderer J, Carson LF, et al. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2005;96:630–634.
 279. Currie J, Blessing JA, McGehee R, et al. Phase II trial of hydroxyurea, dacarbazine (DTIC), and etoposide (VP-16) in mixed mesodermal tumors of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1996;61:94–96.
 280. Resnik E, Chambers SK, Carcangiu ML, et al. A phase II study of etoposide, cisplatin, and doxorubicin chemotherapy in mixed müllerian tumors (MMT) of the uterus. *Gynecol Oncol.* 1995;56:370–375.
 281. Piver MS, DeEulis TG, Lele SB, et al. Cyclophosphamide, vincristine, Adriamycin, and dimethyl-triazeno imidazole carboxamide (CYVADIC) for sarcomas of the female genital tract. *Gynecol Oncol.* 1982;14:319–323.
 282. van Rijswijk RE, Vermorken JB, Reed N, et al. Cisplatin, doxorubicin and ifosfamide in carcinosarcomas of the female genital tract. A phase II study of the European Organization for Research and Treatment of Cancer Gynecological Cancer Group (EORTC 55923). *Eur J Cancer.* 2003;39:481–487.
 283. Powell MA, Filiaci VL, et al. Phase II Evaluation of Paclitaxel and Carboplatin in the Treatment of Carcinosarcoma of the Uterus: A Gynecologic Oncology Group Study. *J Clin Oncol.* 2010;28:2727–2731.
 284. Galaal K, Godfrey K, et al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. *Cochrane Database Syst Rev.* 2001;(1): CD006812.
 285. Miller BE, Blessing JA, et al. A phase II evaluation of weekly gemcitabine and docetaxel for second-line treatment of recurrent carcinosarcoma of the uterus: a gynecologic oncology group study. *Gynecol Oncol.* 2010;118:139–144.
 286. Spano JP, Soria JC, Kambouchner M, et al. Long-term survival of patients given hormonal therapy for metastatic endometrial stromal sarcoma. *Med Oncol.* 2003;20:87–93.
 287. Sutton G, Blessing JA, Park R, et al. Ifosfamide treatment of recurrent or metastatic endometrial stromal sarcomas previously unexposed to chemotherapy: a study of the Gynecologic Oncology Group. *Obstet Gynecol.* 1996;87:747–750.
 288. Berchuck A, Rubin SC, Hoskins WJ, et al. Treatment of endometrial stromal tumors. *Gynecol Oncol.* 1990;36:60–65.
 289. Szlosarek PW, Lofts FJ, Pettengell R, et al. Effective treatment of a patient with a high-grade endometrial stromal sarcoma with an accelerated regimen of carboplatin and paclitaxel. *Anticancer Drugs.* 2000;11:275–278.
 290. Yamawaki T, Shimizu Y, Hasumi K. Treatment of stage IV “high-grade” endometrial stromal sarcoma with ifosfamide, Adriamycin, and cisplatin. *Gynecol Oncol.* 1997;64:265–269.
 291. Ihnen M, Mahner S, Janicke F, et al. Current treatment options in uterine endometrial stromal sarcoma: report of a case and review of the literature. *Int J Gynecol Cancer.* 2007;17(5):957–963.
 292. Lehner LM, Miles PA, Enck RE. Complete remission of widely metastatic endometrial stromal sarcoma following combination chemotherapy. *Cancer.* 1979;433:1189–1194.
 293. Lin YC, Kudelka AP, Tresukosol D, et al. Prolonged stabilization of progressive endometrial stromal sarcoma with prolonged oral etoposide therapy. *Gynecol Oncol.* 1995;58:262–265.
 294. Yamawaki T, Shimizu Y, et al. Treatment of stage IV “high-grade” endometrial stromal sarcoma with ifosfamide, adriamycin, and cisplatin. *Gynecol Oncol.* 1997;64:265–269.
 295. Thomas MB, Keeney GL, et al. Endometrial stromal sarcoma: treatment and patterns of recurrence. *Int J Gynecol Cancer.* 2009;19:253–256.
 296. Sutton G, Blessing JA, et al. Ifosfamide treatment of recurrent or metastatic endometrial stromal sarcomas previously unexposed to chemotherapy: a study of the Gynecologic Oncology Group. *Obstet Gynecol.* 1996;87:747–750.
 297. Bleeker JS, J. Quevedo JF, et al. “Malignant” perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. *Sarcoma.* 2012;2012:541626.
 298. Wagner AJ, Malinowska-Kolodziej I, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol.* 2010;28:835–840.
 299. Yovine A, Riofrio M, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *J Clin Oncol.* 2004;22:890–899.
 300. Sutton GP, Stehman FB, Michael H, et al. Estrogen and progesterone receptors in uterine sarcomas. *Obstet Gynecol.* 1986;68:709–714.
 301. McCluggage WG, Abdulkader M, Price JH, et al. Uterine carcinosarcomas in patients receiving tamoxifen. A report of 19 cases. *Int J Gynecol Cancer.* 2000;10:280–284.
 302. Kloos I, Delaloge S, Pautier P, et al. Tamoxifen-related carcinosarcomas occur under/after prolonged treatment: report of five cases and review of the literature. *Int J Gynecol Cancer.* 2002;12:496–500.
 303. Burke C, Hickey K. Treatment of endometrial stromal sarcoma with a gonadotropin-releasing hormone analogue. *Obstet Gynecol.* 2004;104:1182–1184.
 304. Maluf FC, Sabbatini P, Schwartz L, et al. Endometrial stromal sarcoma: objective response to letrozole. *Gynecol Oncol.* 2001;82:384–388.
 305. Lantta M, Kahanpää K, Karkkainen J, et al. Estradiol and progesterone receptors in two cases of endometrial stromal sarcoma. *Gynecol Oncol.* 1984;18:233–239.
 306. Baker TR, Piver MS, Lele SB, et al. Stage I uterine adenocarcinoma: a report of six cases. *J Surg Oncol.* 1988;37:128–132.
 307. Piver MS, Rutledge FN, Copeland L, et al. Uterine endolymphatic stromal myosis. *Obstet Gynecol.* 1984;63:725–745.
 308. Scribner DR Jr, Walker JL. Low-grade endometrial stromal sarcoma: preoperative treatment with depo-lupron and megace. *Gynecol Oncol.* 1998;71:458–460.
 309. Navarro D, Cabrera JJ, Leon L, et al. Endometrial stromal sarcoma expression of estrogen receptors, progesterone receptors and estrogen-induced srp27 (24K) suggests hormone responsiveness. *J Steroid Biochem Mol Biol.* 1992;41:589–596.
 310. Mansi JL, Ramachandra S, Wiltshaw E, et al. Endometrial stromal sarcomas. *Gynecol Oncol.* 1990;36:113–118.
 311. O'Brien AA, O'Brien DS, Daly PA. Aggressive endometrial stromal sarcoma responding to medroxyprogesterone following failure of tamoxifen and combination chemotherapy. Case report. *Br J Obstet Gynaecol.* 1985;92:862–866.
 312. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. *Gynecol Oncol.* 2006;101:464–469.
 313. Ramondetta LM, Johnson AJ, et al. Phase 2 trial of mifepristone (RU-486) in advanced or recurrent endometrial adenocarcinoma or low-grade endometrial stromal sarcoma. *Cancer.* 2009;115:1867–1874.
 314. Krumholz BA, Lobovsky FY, Halitsky V. Endolymphatic stromal myosis with pulmonary metastases. Remission with progestin therapy: report of a case. *J Reprod Med.* 1973;10:85–89.
 315. O'Ceirbhail R, Zhou Q, et al. Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors. *Gynecol Oncol.* 2010;116(3):424–429.
 316. Wang X, Tangjitgamol S, Liu J, et al. Response of recurrent uterine high-grade malignant mixed müllerian tumor to letrozole. *Int J Gynecol Cancer.* 2005;15:1243–1248.
 317. Maki RG. Recent advances in therapy for gastrointestinal stromal tumors. *Curr Oncol Rep.* 2007;9:165–169.
 318. Rushing RS, Shajahan S, Chendil D, et al. Uterine sarcomas express KIT protein but lack mutation(s) in exon 11 or 17 of c-KIT. *Gynecol Oncol.* 2003;91:9–14.

319. Winter WE 3rd, Seidman JD, Krivak TC, et al. Clinicopathological analysis of c-kit expression in carcinosarcomas and leiomyosarcomas of the uterine corpus. *Gynecol Oncol.* 2003;91:3–8.
320. Huh WK, Sill MW, et al. Efficacy and safety of imatinib mesylate (Gleevec) and immunohistochemical expression of c-Kit and PDGFR-beta in a Gynecologic Oncology Group Phase II Trial in women with recurrent or persistent carcinosarcomas of the uterus. *Gynecol Oncol.* 2010;117:248–254.
321. Hensley ML, Sill MW, et al. Sunitinib malate in the treatment of recurrent or persistent uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol Oncol.* 2009;115:460–465.
322. Emoto M, Ishiguro M, Iwasaki H, et al. Effect of angiogenesis inhibitor TNP-470 on the growth, blood flow, and microvessel density in xenografts of human uterine carcinosarcoma in nude mice. *Gynecol Oncol.* 2003;89:88–94.
323. Yi-Shin Kuo D, Timmins P, et al. Phase II trial of thalidomide for advanced and recurrent gynecologic sarcoma: a brief communication from the New York Phase II consortium. *Gynecol Oncol.* 2006;100:160–165.
324. McMeekin DS, Sill MW, et al. A phase II trial of thalidomide in patients with refractory leiomyosarcoma of the uterus and correlation with biomarkers of angiogenesis: a gynecologic oncology group study. *Gynecol Oncol.* 2007;106:596–603.
325. Maki RG, D'Adamo DR, et al. Phase II study of Sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol.* 2009;27:3133–3140.
326. Mackay HJ, Buckanovich RJ, et al. A phase II study single agent of aflibercept (VEGF Trap) in patients with recurrent or metastatic gynecologic carcinosarcomas and uterine leiomyosarcoma. A trial of the Princess Margaret Hospital, Chicago and California Cancer Phase II Consortia. *Gynecol Oncol.* 2012;125:136–140.
327. Sleijfer S, Ray-Coquard I, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol.* 2009;27:3126–3132.
328. van der Graaf WT, Blay JY, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012;379:1879–1886.
329. D'Adamo DR, Anderson SE, et al. Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. *J Clin Oncol.* 2005;23:7135–7142.
330. Hu J, Khanna V, et al. Genomic alterations in uterine leiomyosarcomas: potential markers for clinical diagnosis and prognosis. *Genes Chromosomes Cancer.* 2001;31:117–124.
331. Chawla SP, Staddon AP, et al. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. *J Clin Oncol.* 2012;30:78–84.
332. Blay J, Chawla SP, et al. Phase III, placebo-controlled trial (SUCCEED) evaluating ridaforolimus as maintenance therapy in advanced sarcoma patients following clinical benefit from prior standard cytotoxic chemotherapy: Long-term (≥ 24 months) overall survival results. ASCO meeting abstracts. *J Clin Oncol.* 2012;30(suppl. 15):10010.
333. Garcia-Carbonero R, Supko JG, et al. Ecteinascidin-743 (ET-743) for chemotherapy-naïve patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. *J Clin Oncol.* 2005;23:5484–5492.

EPIDEMIOLOGY AND RISK FACTORS

Established risk factors for ovarian cancer include a strong family history, early menarche, late menopause, increasing age, and nulliparity. The most important risk factor, after having a first-degree relative with the disease, is age. Women younger than 40 years without a positive family history rarely have ovarian cancer. Fifty percent of all cases of ovarian cancer in the United States occur in women over the age of 65. Older women have a much worse prognosis overall (Fig. 24.1) in part because they have an increased incidence of high-stage and high-grade disease at the time of diagnosis (Table 24.1) (1,2). However, in an analysis of the The Surveillance, Epidemiology, and End Results (SEER) database, age remained a poor prognostic factor even when results were adjusted for stage, grade, histologic cell type, race, and surgical treatment. The relative risks (RR) associated with endocrinologic factors are much smaller, though important, because they are potentially subject to modulation.

Epidemiology

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and Europe (excluding breast cancer). Data from the American Cancer Society suggested that 22,280 new cases of ovarian cancer and 15,500 deaths from ovarian cancer would be expected in the United States in 2012 (3). It has been estimated that, in the United States, 1 woman in 70 will develop ovarian cancer, and 1 woman in 100 will die of the disease. In Europe, the International Agency for Research on Cancer in Lyon estimated that in the 40 European reporting countries, there will be 66,734 new patients with ovarian cancer and 41,929 deaths (4). Both in the United States and in Europe, ovarian cancer is the fifth most common cause of cancer death. Estimates for global ovarian cancer burden, which include low malignant potential cancers (the U.S. and European numbers exclude it), are that 225,500 patients will develop epithelial ovarian cancer and about 140,200 will succumb to the disease.

Ovarian cancer rates vary between different countries and appear to be linked to socioeconomic status and reproductive patterns. North America and most of the industrialized countries of Europe have high incidence rates, while the disease is rare in Asia and Africa. The lowest rates of ovarian cancer are in Sub-Saharan Africa (Fig. 24.2). While the reason for this difference has not been elucidated, countries with a high incidence rate are generally characterized by smaller family sizes, high-fat diets, higher socioeconomic status, older age, and a predominantly Caucasian population. Once a woman moves from a country with a low incidence of ovarian cancer to one with a high incidence, her risk for the disease tends to approach that of the adopted country rather than the country of origin.

Weight/Body Mass Index

Many epidemiologic studies have reported that height and weight are relevant to a woman's risk of developing ovarian cancer, although the findings of these studies have been inconsistent. In a prospective cohort study that followed 495,477 women for 6 years, body mass index (BMI) and ovarian cancer mortality were significantly associated (Fig. 24.3). For women with a BMI of 35 to 39, the relative risk of developing ovarian cancer was 1.5 (CI, 1.1–2) while the relative risk of developing endometrial cancer was 6.3 (CI, 3.8–10.4). In 2012, a meta-analysis that summarized 47 studies involving 25,157 women with ovarian cancer and 81,311 women without the disease found a significant increase in relative risk (RR, 1.07) of ovarian cancer per 5-cm increase in height. The relative risk for ovarian cancer per 5 kg/m² increase in BMI was 1.1 in women who did not take hormone replacement therapy (HRT) but only 0.95 in women on HRT (6). The relationship between ovarian cancer risk and a high BMI at age 18 was stronger than the relationship between ovarian cancer risk and a high BMI occurring later in life (7). In summary, there is probably a small (1.3) but significant increase in the odds ratio for developing ovarian cancer if a woman's BMI is more than 30 (5,8). Given that the association of obesity and ovarian cancer is not strong, it is possible that it is caused by other confounding factors such as type 2 diabetes, high-fat diets, or factors that are currently unknown (9).

Reproductive Factors: Pregnancy and Breast Feeding

Early menarche and late menopause increase the risk of ovarian cancer, while increased parity, breastfeeding, and the use of oral contraceptives (OCP) reduce the risk. These findings suggest that the risk for ovarian cancer is linked to the number of ovulations that a woman experiences throughout her lifetime.

Several epidemiologic studies clearly show that pregnancy, breast-feeding, and OCP use are associated with a reduced risk of developing ovarian cancer (10–12). In addition, a number of case-control studies have shown that pregnancy lowers ovarian cancer risk and that the risk reduction is higher with each additional pregnancy. Interestingly, a pregnancy after age 35 is more protective against ovarian cancer than a pregnancy in a woman 25 years or younger (13).

In general, breast-feeding reduces the risk of ovarian cancer: Women who breast-feed for longer than 12 months have a substantial reduction in the risk of ovarian cancer, which is in addition to the risk reduction derived from childbirth (14). Breast-feeding probably reduces ovarian cancer incidence through several mechanisms, including suppression of ovulation, reduced serum concentrations of estradiol and LH, and elevated FSH levels.

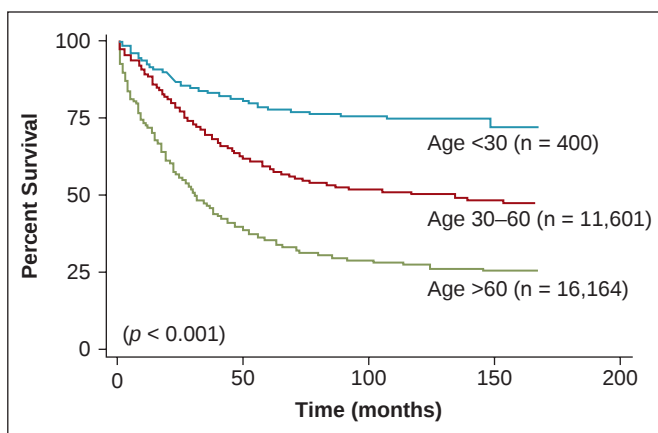


FIGURE 24.1. Disease-specific survival of patients based on age at diagnosis.

Source: Reprinted with Permission from Chan JK, Urban R, Cheung MK, et al. Ovarian cancer in younger vs. older women: a population-based analysis. *Br J Cancer*. 2006;95:1314–1320.

Table 24.1 Incidence of Stage and Grade by Age Grouping in SEER Data 1988–2001

n =	Total (n = 28,165) (%)	Age <30 (n = 400) (%)	Age 30–60 (n = 11,601) (%)	Age >60 (n = 16,164) (%)
Stage				
I	22	58	31	15
II	8	8	9	8
III	36	19	34	38
IV	34	16	26	40
Grade				
1	9	34	12	5
2	18	24	21	16
3	44	13	44	45
Unknown	29	29	23	34

Source: Adapted from Chan JK, Urban R, Cheung MK, et al. Ovarian cancer in younger vs. older women: a population-based analysis. *Br J Cancer*. 2006;95(10):1314–1320, with permission.

Oral contraceptives

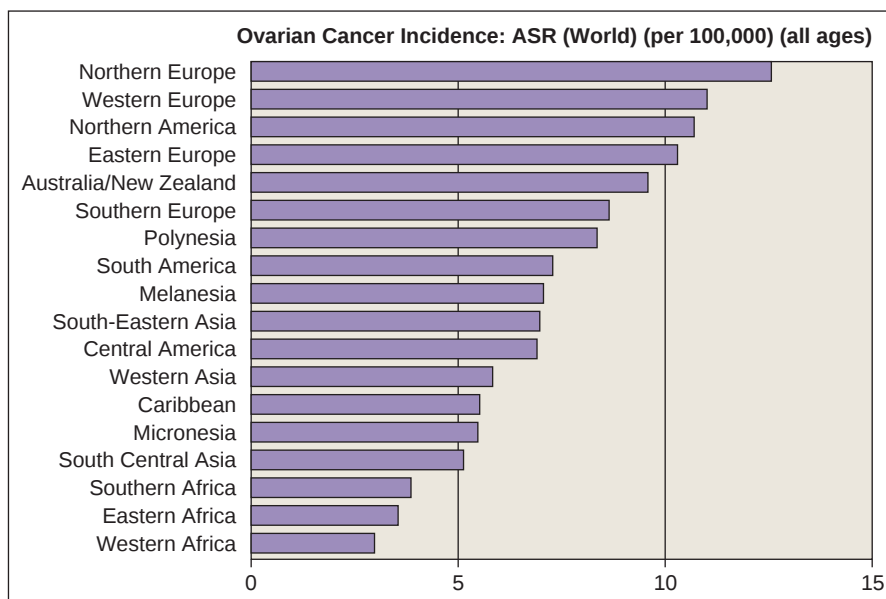
Women who use OCP for at least 5 years reduce their risk of ovarian cancer by an average of 50%, and the level of protection increases with duration of use (10) (Fig. 24.4). Therefore, protection against ovarian cancer is probably the most important noncontraceptive benefit of OCPs. A meta-analysis reanalyzing data from 45 epidemiologic studies, which included 23,257 women with ovarian cancer and 87,303 controls, showed that in high-income countries, the use of OCP reduced ovarian cancer incidence from 1.2 to 0.8 per 100 users and mortality from 0.7 to 0.5 (15). These data confirmed not only that women who use OCP are at reduced risk of ovarian cancer, but also that the protection continues for decades after OCPs are discontinued. Furthermore, the reduction in risk is greater with more prolonged use. However, OCP had little effect on risk for

mucinous tumors, which is consistent with a different biology of these tumors (16) and the current understanding that most are metastatic from the gastrointestinal tract.

The mechanisms underlying the profound and long-lasting protection against ovarian cancer provided by the OCPs are not well understood. The protective effects may be mediated by suppression of ovulation, reduction of gonadotropin levels, and/or induction of apoptosis (10). In view of the protective effects of parity and breast-feeding, however, the mechanism of protection might involve the reduced number of lifetime ovulatory cycles and its associated injury to the epithelial cells on the surface of the ovary. According to an older hypothesis (the “incessant ovulation” hypothesis) (17), ovarian cancer develops from an aberration in the repair process of the surface epithelium, which is ruptured and repaired during each ovulatory cycle. In support of this theory, it is well known that domestic

FIGURE 24.2. Age-standardized incidence rates (ASR) of ovarian cancer in the world.

Source: From Ferlay J, Bray F, Pisani P, et al. *GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0*. IARC Cancer Base No. 5. Lyon: IARC, 2001, with permission.



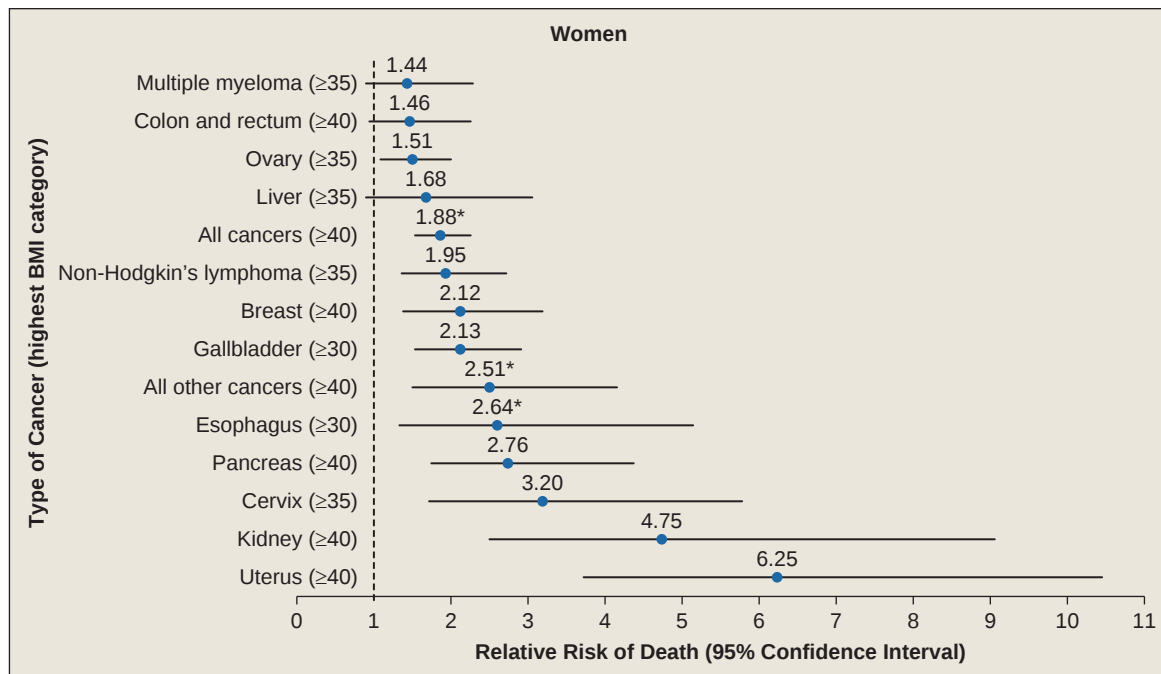


FIGURE 24.3 Summary of mortality from cancer according to body-mass index for U.S. Women in the Cancer Prevention Study II, 1982 to 1998. For each relative risk, the comparison was between women in the highest body-mass-index category (indicated in parentheses) and women in the reference category (body-mass-index, 18.5 to 24.9). Asterisks indicate relative risks for women who never smoked. Results of the linear test for trend were significant ($p \leq 0.05$) for all cancer sites. Printed with permission from: Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348:1625–1638.

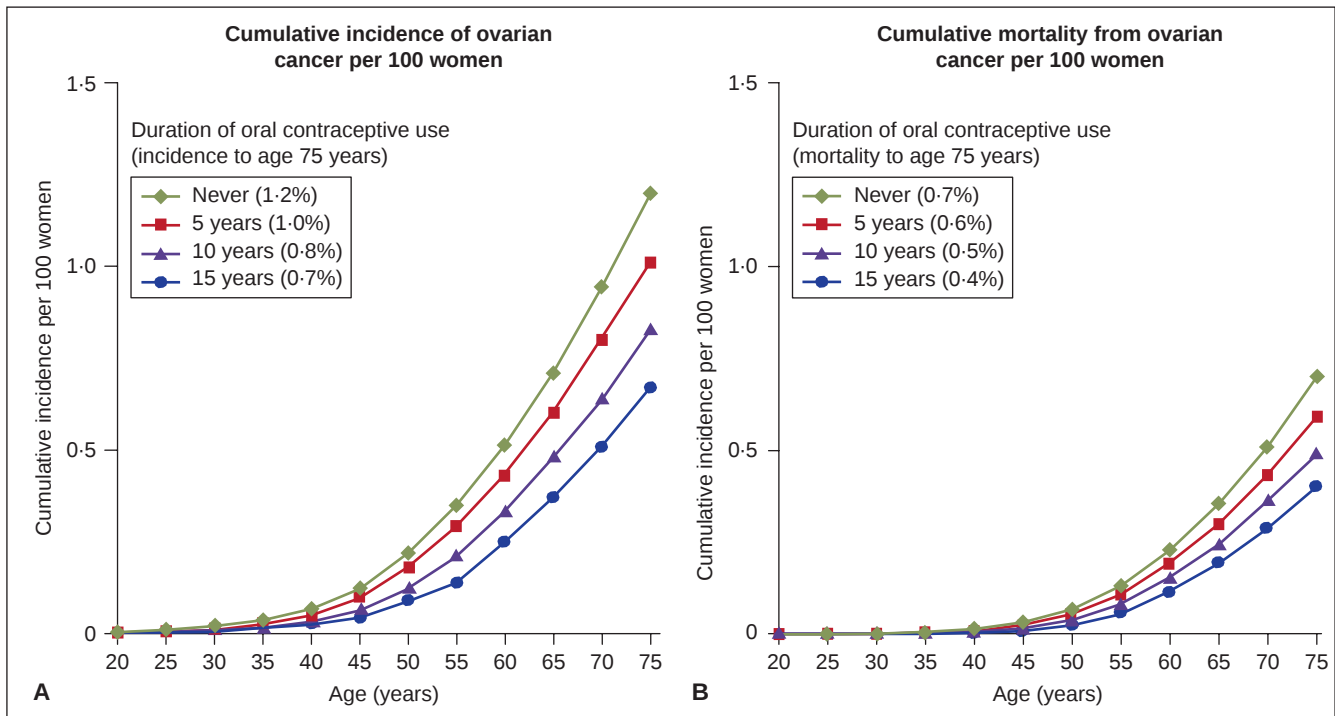


FIGURE 24.4 Absolute risk of ovarian cancer for women in high income countries, by duration of use of oral contraceptives. (A) Cumulative incidence of ovarian cancer per 100 women. (B) Cumulative mortality from ovarian cancer per 100 women.

Source: From Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: Collaborative reanalysis of data from 45 epidemiological studies including 23257 women with ovarian cancer and 87303 controls. *Lancet*. 2008;371:303–314.

egg-laying hens, which are forced to ovulate incessantly, have a high incidence of lesions believed to be ovarian-derived tumors with peritoneal carcinomatosis (18, 19). Alternative hypotheses addressing how OCPs may reduce ovarian cancer incidence center around their ability to treat endometriosis and reduce the risk of acquiring pelvic inflammatory disease (PID) (20), 2 conditions known to be associated with ovarian cancer (see below). However, these hypothesis are at odds with an origin of ovarian cancer in the fallopian tube (21; see Pathology section).

A case-control study has shown that progestin-only contraceptive users have a reduced risk (0.39) for developing ovarian cancer (22, 23). Moreover, the increase in progestin levels seen during pregnancy suggests that the protective effect of pregnancy may involve progestins as well as the reduction in the number of lifetime ovulations. Recent studies in primates indicate that the progestin component of OCPs has a chemopreventive effect by inducing apoptosis of ovarian surface cells that have undergone genetic damage (24). This is supported by the finding that women who use a long acting progestin-only contraceptives (Depo-Medroxyprogesterone Acetate—Depo Provera), which does not completely suppress ovulation, experience a protective effect similar to that observed with OCPs, which completely suppress ovulation (10).

Hormone Replacement Therapy

Currently, the primary indications for the prescription of HRT are severe postmenopausal symptoms and osteoporosis. Several prospective cohort studies (12, 25–28) examined how postmenopausal estrogen or estrogen/progestin HRT relates to the risk of developing ovarian cancer. Using data from the Breast Cancer Detection Demonstration Project, which is a cohort study of over 44,000 postmenopausal women, Lacey and colleagues found that use of estrogen-only HRT increased ovarian cancer RR by 1.6 (CI, 1.2–2), while the RR for women using an estrogen/progestin combination was not significantly increased (RR, 1.1; 0.64–1.7) (11). In a prospective, double-blind study, the Women's Health Initiative (WHI), over 8,000 women who had not had a hysterectomy were randomized to either placebo or 0.625 mg conjugated equine estrogen with 2.5 mg medroxyprogesterone acetate (25). After an average of 5.6 years of follow-up, 20 women in the estrogen/progestin group were diagnosed with an invasive ovarian cancer versus 12 in the placebo group, which is not a significant difference (HR: 1.64; 0.78–3.45). There was no difference in the histologic subtype of ovarian cancers between the 2 groups. While the authors found the increase worrisome, they also pointed out that, because the absolute number of women who developed ovarian cancer was small, the trial had limited precision in this regard, and risk of ovarian cancer should therefore “not have an appreciable influence on most women's decision making when seeking relief for moderate to severe vasomotor symptoms” (25). The observational “Million Women Study” (26), confirmed an increased risk with estrogen-only HRT (RR, 1.49; 1.2–1.81) and showed a lower risk with estrogen/progestin combination therapy (RR, 1.15; 1–1.33). This study also reviewed the cumulative incidence of gynecologic cancers, including ovarian, endometrial, and breast cancer in women taking HRT. The gynecologic cancer incidence per 1,000 women increased from 19 per 1000 in “never-users” to 26 per 1000 in current users of estrogen only, and to 35 per 1000 in current users of estrogen/progestin combinations (Fig. 24.5). The strength of this study, which followed nearly 1 million women, was that the results were adjusted for age at menopause, OCP use, BMI, smoking, and physical activity. HRT was found to be unrelated to the risk of mucinous ovarian cancer.

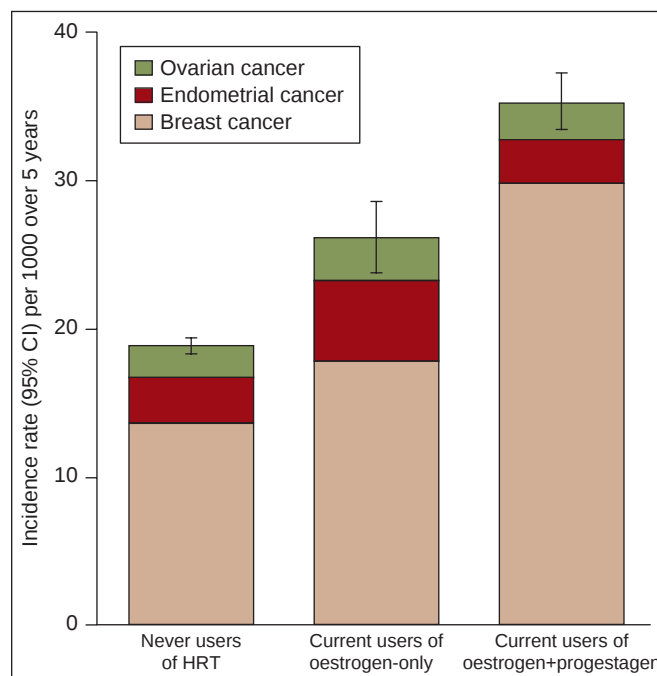


FIGURE 24.5. Standardized incidence rates (95% CI) for ovarian, endometrial and breast cancer per 1000 women in the study cohort over a 5-year period, for current users of various types of HRT and for never users*

*Incidence rates are standardized by age, region of residence, socioeconomic status, time since menopause, parity, use of oral contraceptives, BMI and alcohol consumption. Rates apply to women with a uterus and ovaries.

Source: Reprinted with permission from Beral V, Million Women Study Collaborators, Bull D, et al. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet*. 2007;369(9574):1703–1710.

In conclusion, a review of the major studies suggests a 30% to 58% increase in ovarian cancer risk in women who take HRT (12, 25–28). The risk is certainly increased in women taking estrogen-only HRT independent of whether they had a previous hysterectomy (11). Regular use of vaginal and transdermal estrogen also carries a slightly increased risk of ovarian cancer (26, 28). Most of the studies found that estrogen-progestin HRT and estrogen-only HRT are associated with essentially equal risk, calling a possible protective effect of progestins into question (12, 26, 28). However, one large study found no evidence that estrogen/progestin combinations increase the incidence of ovarian cancer (11). The risk of ovarian cancer was found to increase with duration of HRT exposure, and the largest risk was seen among women who used HRT for over 20 years. Most studies show that a treatment duration of less than 5 years carries no statistically increased ovarian cancer risk (26, 27), although one study did find that even a short duration of use increases risk (28). The negative impact of HRT on ovarian cancer risk is reversible after 2 years, when it approaches the risk observed in never-users (26, 28). This suggests that HRT has a direct growth-promoting effect on steroid receptors expressed on ovarian cancer cells (16,22). In contrast, the positive, risk-reducing effect of OCPs is maintained even 2 decades after the pill is discontinued.

The risk of excess ovarian cancer with HRT is relatively small, and could be represented as one extraovarian cancer for every 8,300 women who take HRT (28). This should not be the deciding factor in clinical decisions regarding HRT use. Current clinical practice is to prescribe HRT to patients with severe postmenopausal symptoms and to administer it at the lowest effective dose for a limited period of time (less than 5 years) (26, 27). Short-duration, low-dose use of HRT for menopausal symptom management seems to have an acceptable risk-benefit ratio for some women.

Surgery: Tubal Interruption and Hysterectomy

In general, studies have confirmed that both tubal interruption and hysterectomy at least partially protect against the development of ovarian cancer. The four most common surgical sterilization methods, tubal ligation, thermal injury, rings, and clips are probably equally effective in reducing risk. A large prospective cohort study, the Nurses Health study (29), confirmed smaller case-control studies and showed a RR of 0.33 (CI, 0.16–0.64) of developing ovarian cancer in women who had a tubal ligation compared to those who did not. The same study reported a weak inverse relationship between hysterectomy and ovarian cancer (RR, 0.67; CI, 0.45–1). The effect of hysterectomy was greater when the surgery was performed at an earlier age.

Since tubal ligation could serve as a form of secondary prevention of ovarian cancer for women at risk, a retrospective case-control study evaluated the effect of tubal ligation in patients with *BRCA1* mutations (30). In this high-risk group, women who had undergone a tubal ligation had a considerably reduced risk of developing ovarian cancer when compared to women who had not (OR, 0.39; CI, 0.22–0.7). Women who both had a tubal ligation and had used OCP in the past had an even lower odds ratio of developing ovarian cancer (OR, 0.28; CI, 0.15–0.52). Possible explanations for the protective effect of tubal interruption against ovarian cancer include an impaired blood supply to the ovaries/distal tubes through the superior branch of the uterine artery leading in most women to earlier menopause (and fewer lifetime ovulations) and the possibility that occluding the tube blocks the upward flow of carcinogens from the uterus and reduces pelvic infection rates.

Inflammation: Pelvic Inflammatory Disease and Endometriosis

Pelvic Inflammatory Disease (PID) is a generalized infection of the female genital tract. Several small case-control studies had suggested that PID is associated with ovarian cancer. However, this association only gained wide acceptance with the publication of a large study (31) comparing the ovarian cancer incidence of 68,000 women who had experienced PID versus 136,000 who had not. In this well-designed study, the hazard ratio for ovarian cancer in patients with a history of PID (adjusted appropriately for confounding factors) was twice as high (HR 1.92) as that of controls, and was even higher (HR 2.46) in women who had at least 5 episodes of PID. Such indications of a dose-response effect always add credibility to epidemiologic findings (32).

Endometriosis, characterized by the ectopic growth of endometrial glands in the ovary and the abdominal cavity, affects 10% of women of reproductive age. In smaller case-control studies, a history of endometriosis has been consistently shown to be associated with clear cell and endometrioid ovarian carcinoma with an odds ratio of approximately 2. In many endometrioid and clear cell ovarian cancers, endometriosis is detected histologically adjacent to the carcinoma. Combining data from 13 ovarian cancer case-control studies (7,900 patients with ovarian cancer), the Ovarian Cancer Association Consortium (OCAC) published a definitive report that self-reported endometriosis increased the risk of clear cell (OR, 3.05; CI, 2.4–3.8) and endometrioid ovarian cancer (OR, 2.04; CI, 1.7–2.5) (33). In this report endometriosis was also associated, for the first time, with low-grade serous cancers (OR, 2.11; CI, 1.4–3.2), suggesting that these cancers, which are generally believed to arise from serous borderline tumors, can also arise from endometriotic implants.

There are 2 pathologic subtypes of endometriosis: displaced benign ectopic endometrial glands and atypical endometriosis. Given the high prevalence of endometriosis, it is likely that “benign” endometriosis acts through the creation of a

microenvironment of chronic inflammation and is only one of several factors that can spur the development of clear cell and endometrioid cancers. In contrast, the endometriosis with cytological atypia and complex hyperplasia (“atypical endometriosis”) present in 2% to 3% of all patients who undergo surgery for endometriosis is most likely a direct precursor for type I/low-grade ovarian cancers (34,35). This hypothesis was supported by a recent study in which *ARID1A* gene mutations were detected in 30% of endometrioid and 46% of clear cell cancers, as well as in areas of atypical endometriosis that were adjacent to the cancers (36). Many genes expressed in endometriosis are also detected in endometrioid ovarian cancer, but do not overlap with genes expressed in high-grade serous cancers (37). In summary, endometriosis is associated with 3 type I (38) ovarian histiotypes: endometrioid, clear cell, and low-grade serous ovarian cancer (see also Pathology section).

A common mechanism linking endometriosis and PID to ovarian cancer risk may involve the intensive release of cytokines and infiltration of immune cells (macrophages) that accompany inflammation. Some (39,40), but not all (41) epidemiologic data suggest that the use of anti-inflammatory agents, including aspirin and nonsteroidal anti-inflammatory drugs, protects against ovarian cancer development.

Other Risk Factors: Diet, Smoking, Exercise

For the most part, the studies that have investigated whether diet affects ovarian cancer risk have had inconsistent and conflicting results. Any association between diet and cancer risk is likely difficult to decipher given the inaccuracy of food frequency questionnaires and seasonal differences in the supply of fresh food. Several studies have tried to determine whether vitamin A and β -carotene consumption affects ovarian cancer risk, but while some studies suggested a risk reduction, others could not confirm it.

In an Italian study, a diet favoring red meat was reported to confer an increased risk of ovarian cancer (42). However, the California Teachers Study, which had almost 100,000 participants, concluded that dietary factors are unlikely to play a major role in ovarian cancer development. In this study a RR reduction was only found with isoflavones, the phytoestrogens found in soy-based foods, some of which have antiestrogenic effects (RR, 0.6; 0.33–1) (43,44).

The Women's Health Initiative Dietary Modification Randomized Controlled Trial evaluated prospectively the effects of reducing fat intake by at least 20% and increasing consumption of vegetables, fruits, and grains on ovarian cancer incidence in 48,835 postmenopausal women (45). The overall ovarian cancer HR was not statistically different between the 2 groups; however, the HR decreased with increasing duration of intervention: For the first 4 years, the risk for ovarian cancer was similar in the intervention and control groups; but then over the next 4 years, the risk was lower in the intervention group (0.38 cases per 1000 person-years in the intervention group versus 0.64 per 1,000 person-years in the comparison group [HR 0.6; CI, 0.38–0.96]).

Indirect evidence for the effect of diet on the risk of ovarian cancer comes from the fact that women from geographic areas with a low incidence of ovarian cancer who relocate to a high-incidence region (North America, Europe) acquire the same risk as women who were born in that region, and by the increase of ovarian cancer incidence over time in Japan, which is transitioning to a more Westernized eating pattern (46).

Smoking is not generally considered a risk factor for ovarian cancer (47). However, current smoking seems to be associated with an increased risk of developing a mucinous ovarian cancer (OR, 1.78; 1.01–3.15) (48). Smoking cessation reduces this risk back to baseline over 20 years.

Currently, there is no convincing association between physical exercise and ovarian cancer risk and survival (49). An ongoing GOG trial is studying whether regular exercise, a low-fat diet, and high intake of vegetables after primary treatment for ovarian cancer affects recurrence (GOG #225).

In summary, factors that decrease the number of lifetime ovulations reduce the risk of developing ovarian cancer, while hereditary factors increase the risk. From a practical, clinical standpoint, only a positive family history will raise the suspicion of a predisposition to ovarian cancer in an asymptomatic woman.

HEREDITARY OVARIAN CANCER: BRCA AND HNPCC

Biology of BRCA-Associated Ovarian Cancer

The study of familial breast and ovarian cancer began in 1866 when the French physician Paul Broca noted a much larger than expected incidence of cancer in one family. Over 4 generations, 10 out of the 24 women in this family died from breast cancer, while several more individuals of both sexes developed other malignancies. Dr. Broca concluded that this excess of cancers could not reasonably be attributed to chance. Now that mutations in the high-penetrance *BRCA1/2* genes and the MMR gene group associated with Lynch syndrome have been identified, we know that these hereditary mutations are the strongest known risk factors for the development of ovarian cancer. Approximately 15% of invasive epithelial ovarian cancers are estimated to be the result of autosomal dominant genetic factors with high disease penetrance, predominantly germline mutations in the *BRCA1* or *BRCA2* genes (65% to 85%), or in MMR genes (10% to 15%) (50).

The *BRCA* genes are inherited in an autosomal dominant fashion, which means that every first-degree relative of a mutation carrier has a 50% chance of carrying a mutation. The *BRCA* genes function as classic tumor suppressors, with loss of the function of both alleles required for cancer formation. Carriers are initially heterozygous for the *BRCA* gene mutation(s) in all cells and then the sporadic loss of the wild-type allele in epithelial breast or fallopian/ovarian cells results in a predisposition to cancer. The 2 *BRCA* proteins regulate cell cycle checkpoints and gene expression. Their most important function is probably participation in a specific DNA repair pathway, homologous recombination, which is used for the high-fidelity repair of double-strand DNA breaks. Because cells with *BRCA1/2* mutations lack the ability to repair double strand breaks, they have increased genomic instability and a predisposition to malignant

transformation. The ability of cells with *BRCA* mutations to repair DNA cross-links induced by platinum salts is impaired, which is hypothesized to explain the improved chemosensitivity and survival of patients with *BRCA* mutations (see below).

The prevalence of *BRCA1* or *BRCA2* mutations (over 1,000 have been identified) in the general population is about 1:300 to 1:800. However, specific ethnic populations founded by small ancestral groups, such as French Canadians, Icelanders, and Ashkenazi Jews, have a higher mutation rate arising from spontaneous “founder mutations.” For example, 2% to 3% of all Jewish women of Eastern European descent have one of 3 founder mutations (2 in *BRCA1* 187delAG and 5382insC; 1 in *BRCA2* 6174 delT). The cumulative lifetime risk of developing ovarian cancer for women with a *BRCA1* mutation has been estimated at 39% to 54%, and for women with a *BRCA2* mutation, 11% to 23%. The number of *BRCA2*-associated ovarian cancers is smaller overall. In comparison, the lifetime risk for ovarian cancer for women in the general population is 1.4% (51,52). As we understand more about the *BRCA* genes, the various *BRCA1/2* genetic changes have been classified according to their functional effects. Class I mutations are present in 66% of *BRCA1* mutation carriers and class II mutations in 25%, while class II mutations are rare in *BRCA2* carriers (53) (see Table 24.2).

Also, loss of proteins in the homologous recombination pathway and loss of components for the Fanconi anemia pathway, will result in cells with defective homologous recombination that is comparable to cells with a *BRCA* mutation. This phenomenon is referred to as “*BRCAness*” (54). Therefore, while only 13% to 14% of women with ovarian cancer carry germ-line *BRCA1/2* mutations, the TCGA analysis of almost 500 patients revealed that close to half of them had functional defects in one component of the homologous DNA repair pathway (55). Cancers with such functional defects have been hypothesized to exhibit similar clinical behavior as cancers associated with *BRCA* mutations, and means of identifying “*BRCAness*” of a subset of tumors that occur in women who do not carry a germ-line *BRCA* mutation are being sought. However, none of these classifiers have been clinically validated.

Clinical Features of BRCA-Associated Ovarian Cancer

In general, *BRCA* mutation carriers who develop ovarian cancer have a younger age at diagnosis, are more likely to have cancers of high-grade serous histology originating in the fallopian tube, are less likely to have borderline or mucinous tumors, and have a better prognosis than matched controls with sporadic ovarian cancer (50,56–58). A breast cancer precedes the ovarian

Table 24.2 Different Types of *BRCA* Mutations

Mutation Type	Mutation Effect	Mechanisms
Class I mutations	Loss of function mutations	– mRNA nonsense-mediated degradation – Instability of truncated protein – Deletion of regions regulating transcription → These changes result in reduced mRNA transcript, protein level or a truncated nonfunctional protein
Class II mutations	Potentially stable mutant proteins: – dominant-negative functions – partially preserved normal function – loss of function	– missense substitutions – in-frame deletions and insertions – truncating mutations in the last exon of <i>BRCA1/2</i> → these genetic changes might still allow for the expression of a partially functional protein and might have less detrimental effect
Ovarian cancer cluster region mutations (OCCR)	Mutations within nucleotide region c.2831–c.3847; c.6275–c.6401	Mutations occurring in the central region are associated with a higher risk of ovarian and breast cancers compared to mutations outside this region

cancer diagnosis in 37% of *BRCA1*-associated cases and 37% of *BRCA2*-associated cases (53).

In 1996, Rubin and colleagues reported results of a retrospective analysis suggesting that there are distinct clinical and pathologic features of *BRCA1*-associated ovarian cancer (56). Among 53 patients with germline *BRCA1* mutations, the average age at diagnosis was only 48, and the vast majority of cancers were serous adenocarcinomas. Cancers associated with *BRCA1* mutations had a relatively favorable prognosis, with an actuarial median survival of 77 months compared to 29 months for matched controls (Fig 24.6). Boyd et al. performed a retrospective cohort study of invasive ovarian cancers in patients of Jewish origin (67 *BRCA1* and 21 *BRCA2*) (57). The average age at diagnosis was 54 for *BRCA1* mutation carriers, 62 for *BRCA2* mutation carriers, and 63 for Jewish women with sporadic ovarian cancers. The histology, grade, stage, and success of cytoreductive surgery were similar for hereditary and sporadic cases, although there were no mucinous tumors and only 2 clear cell tumors observed among 88 *BRCA*-associated cases, versus 5 mucinous and 7 clear cell tumors among 101 sporadic cases. The median disease-free interval after initial chemotherapy was 14 months for the *BRCA*-associated group and 7 months for the sporadic group ($p < 0.001$). While most series find that *BRCA*-associated cancers are most often of high-grade serous histology, one recent review suggested that *BRCA1* and *BRCA2* associated tumors are similar in histology and grade to sporadic cancers. A recent study of 1,119 *BRCA1/2* associated ovarian cancers (53) reported 67% serous, 12% endometrioid, 2% clear cell and 1% mucinous cancers; the important clinical implication was that women with a nonserous carcinoma should still be considered for *BRCA* mutation testing (59). In a series of *BRCA*-associated ovarian cancers with centralized pathology review (60), cancers in *BRCA* carriers were compared to those in noncarriers. Among 220 women, mutation-associated tumors were of significantly higher grade and stage and less often mucinous, when compared to non-mutation-associated tumors. No mucinous and no borderline tumors were found in the mutation-associated group. Primary peritoneal carcinoma occurred rarely in both groups.

Extending the findings of improved survival of *BRCA*-associated ovarian cancers, a pooled analysis of 26 prospective, international studies published in 2012 found a 5-year overall survival of 36% for noncarriers, 44% for *BRCA1*, and 52% for

BRCA2 mutation carriers. Even after adjusting for age, stage, grade, and histology, women with *BRCA*-mutations had a significantly longer survival, with *BRCA2* mutation carriers having the best prognosis (58). These studies suggest that ovarian cancer developing in *BRCA1/2* mutation carrier have specific clinical characteristics compared to sporadic ovarian cancer. It is probable that the improved survival of women with *BRCA*-associated ovarian cancers is related to the fact that loss of function of *BRCA* proteins, which participate in DNA damage repair, results in a more favorable response to platinum-based chemotherapy.

BRCA1/2 associated ovarian cancers are less likely to have platinum-resistant disease (14.9%) compared to sporadic ovarian cancer (31.7%), and when these patients recur, they tend to have a higher response to second-line platinum-based chemotherapy even in the setting of platinum-resistant disease (50). Platinum salts induce DNA crosslinks, which are recognized by DNA damage repair pathways, and are repaired by nucleotide excision repair and homologous recombination (61). It may be because *BRCA1/2* associated high-grade serous cancers harbor defects in homologous recombination that platinum compounds are more efficient in these cancers (56,58). Indeed, a decrease in *BRCA1* mRNA levels (PCR-based measurement) was associated with a significantly longer survival in 57 unselected ovarian cancer patients (62).

Deficiency in either *BRCA1* or *BRCA2* also causes profound cellular sensitivity to the inhibition of poly(ADP-ribose) polymerase (PARP) (63). The PARP enzyme is essential for the repair of DNA single-strand breaks. PARP inhibition blocks repair of single-strand breaks, and normal cells will compensate by using homologous recombination to bypass these lesions during DNA replication. Since *BRCA*-mutated cancer cells cannot perform DNA repair through homologous recombination, exposure to PARP inhibitors results in their death, while cells with intact homologous recombination pathways survive. This therapeutic mechanism is called “synthetic lethality,” and refers to the concept that 2 defective pathways that do not, individually, affect cell viability, will, in combination, be lethal (63,64). Several PARP inhibitors are in clinical development, and these drugs appear to have preferential single-agent activity in tumors of patients who carry germline *BRCA* mutations.

Genetic Testing/Counseling

BRCA1/2-directed genetic counseling is important because (a) it will help to identify women at risk of having a *BRCA1/2* mutation, (b) it will allow for the implementation of preventive strategies in patients with known *BRCA1/2* mutations and counseling of their families, and (c) it will guide therapy decisions in *BRCA1/2*-associated serous ovarian cancers. Given that a salpingo-oophorectomy significantly reduces the risk of developing ovarian and fallopian tube cancer, it is clinically meaningful to be aware if a woman carries a *BRCA* mutation. While the treatment (carboplatin/paclitaxel) for *BRCA* mutation-associated ovarian cancers is currently the same as treatment for sporadic ovarian cancers, the current development of PARP inhibitors may change this.

The following factors (59) are associated with a 20% to 25% chance of having an inherited disposition to breast and ovarian cancer and are recommended by the Society of Gynecologic Oncologists (SGO) for use in deciding which patients should be screened: Ashkenazi Jewish ancestry, young age at diagnosis, personal history of both breast and ovarian cancer, or a family history of ovarian cancer or breast cancer (particularly multiple first-degree relatives, or relatives with breast cancer at a young age, including paternal relatives), and a relative with a *BRCA1/2* mutation. Women at risk for a *BRCA* mutation should be referred for genetic counseling, since they will have to make difficult decisions about genetic testing, and, especially if a

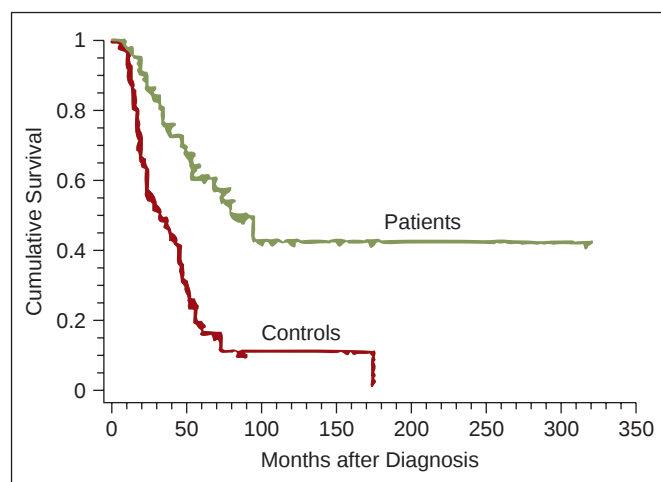


FIGURE 24.6. Actuarial survival among 43 patients with advanced ovarian cancer and *BRCA1* mutations compared to matched controls without known mutations.

Source: Reprinted with Permission from Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathological features of ovarian cancer in women with germline mutations of *BRCA1*. *N Engl J Med*. 1996;335:1413–1416.

mutation is found, ovarian and breast cancer screening and risk-reducing strategies including prophylactic surgery. Moreover, *BRCA* mutation carriers have an increased risk of pancreatic cancer (3% to 4%) and melanoma (5%). Considerable expertise and time is necessary to counsel these women well.

If a woman who is found to have a *BRCA1/2* mutation chooses screening rather than prophylactic surgery, most practitioners will follow her with clinical pelvic exams, CA-125 testing, and pelvic ultrasound, but there is no evidence that these are effective screening strategies. Patients should also have regular breast examinations as well as annual mammograms and breast magnetic resonance imaging (MRI). Prophylactic bilateral mastectomy should also be discussed with *BRCA* mutation carriers, and patients should be informed of the techniques available for removing and reconstructing the breast, and the expected psychosocial and sexual effects. Counseling about risk-reducing salpingo-oophorectomy (RRSO) should balance the risks and symptoms associated with surgical menopause with the morbidity and high mortality of advanced serous ovarian cancer.

Most studies have shown that the reproductive and hormonal factors that affect ovarian cancer risk in the general population also affect risk for women who carry *BRCA1* and *BRCA2* mutations. Narod et al., from Toronto, initially reported a 60% reduction in ovarian cancer risk for *BRCA1* or *BRCA2* mutation carriers with OCP use for 6 or more years (65). However, while smaller studies have confirmed this observation, a large population-based study from Israel did not find a protective effect (66); therefore, the use of OCPs as a means to prevent ovarian cancer in *BRCA* mutation carriers prior to oophorectomy has remained controversial. Later, the Toronto group reported results from a greatly expanded database, which included 670 women with a history of *BRCA1*-associated ovarian cancer, 124 with a history of *BRCA2*-associated ovarian cancer, and 2,424 mutation carriers with no history of ovarian cancer (67). Use of OCPs reduced the risk of ovarian cancer in both women with *BRCA1* mutations (OR, 0.56) and in those with *BRCA2* mutations (OR, 0.39). Breast-feeding was also found to be protective for carriers of a *BRCA1* mutation (OR, 0.74). An effect of similar magnitude was seen for breast-feeding in *BRCA2* mutation carriers, but it was not statistically significant (OR, 0.72). Although the Toronto group had previously reported that tubal ligation was protective against ovarian cancer in mutation carriers as well as noncarriers, the association in this expanded cohort was not significant for carriers of either a *BRCA1* (OR, 0.8) or a *BRCA2* mutation (OR, 0.63). Pregnancy, which had previously been reported to be protective for women carrying a *BRCA* mutation (66), was found to be protective for carriers of *BRCA1* mutations (OR, 0.67), but was associated with increased risk for carriers of *BRCA2* mutations (OR, 2.74). The reasons for this are not clear.

It is also important to offer genetic testing to patients with risk factors for a *BRCA1/2* mutation who have already developed ovarian cancer. The identification of a *BRCA* mutation may impact their treatment, since it might indicate an increased sensitivity to platinum compounds in the first- and second-line setting (50) and PARP inhibitors. Also, their unaffected first-degree female relatives have a 50% probability of carrying the same mutation, and can be specifically tested for it. Those first-degree relatives who are found to be *BRCA* negative can be told that they are not at a statistically significant risk of developing ovarian cancer (68), while those who carry the mutation can be counseled on risk-reducing strategies. The SGO criteria used to determine who should be screened for *BRCA1/2* mutations are generally applied to women who have been diagnosed with ovarian cancer as well as to unaffected patients (see above [59]). However, by using these criteria for patients with the disease, practitioners will miss many women who have a *BRCA* mutation. A large study, which screened 1,342 unselected patients from the province of Ontario diagnosed with epithelial ovarian cancer,

reported a mutation frequency of 13.4% (69). This study used multiplex ligation-dependent probe amplification, and, therefore, included the detection of large deletions that normally elude general sequencing. Women with ovarian cancer in their fourth life decade had the highest mutation rate (24%), as did women of Italian (43%), Jewish (30%), or Indo-Pakistani (29%) origin. Most importantly, 8% of the women in the study had no family history of ovarian cancer. Among Ashkenazi Jewish women with ovarian cancer, there is about a 29% to 40% chance that the disease is related to a *BRCA1* or *BRCA2* mutation (66,70). The Australian Ovarian Cancer group detected *BRCA1/2* germline mutations in 22% of patients with high-grade serous cancers, 44% of whom did not have a family history of cancer (50).

Given these findings (50,54,55,69), the current complicated criteria for testing (59), advances in sequencing technology (55), and potential implications for selecting treatments (50,54), it has been suggested that testing for germline *BRCA* mutations should be routinely offered to all women with nonmucinous high-grade epithelial or serous ovarian cancer, regardless of family history. Such strategies are already employed in some Canadian provinces (Ontario, British Columbia) and are being considered in Australia.

Finally, it is important to be aware of legislation that addresses issues of discrimination and privacy that are raised by the prospect of increasingly comprehensive genetic information on each patient. The Genetic Information Nondiscrimination Act (“GINA”) (2008) prohibits health insurers and employers from discriminating on the basis of genetic information (71). Rules governing patient privacy and confidentiality prevent a physician from disclosing genetic test results to a relative. ASCO guidelines suggest that the ethical duty to warn a relative of genetic risk is satisfied if the doctor explains to the patient that a hereditary cancer syndrome has implications for other family members, advises the patient to share information with them, and offers genetic counseling for those family members who are interested and at risk.

Prophylactic Salpingo-Oophorectomy for Prevention of *BRCA*-Associated Ovarian Cancer

Indication for Surgery

There is, at this time, no scientific evidence that the current methods of screening can detect ovarian cancer early. The currently widely used screening procedures (clinical exam, CA-125, pelvic ultrasound) have such low specificity and sensitivity that their utility in detecting ovarian cancer at a curable stage is highly questionable (72). Such screening is even less efficient in young premenopausal women because ovulating women may have functional cysts or a hemorrhagic corpus luteum mistaken for a suspicious mass.

In contrast, the evidence does support the efficacy of RRSO for the early detection of ovarian cancer and its prevention in unaffected patients (73–76). In 2002, 2 large prospective series clearly demonstrated that RRSO reduced the risk of developing müllerian carcinoma (ovarian, fallopian tube, and peritoneal cancer) in patients with *BRCA1/2* mutations (73,74). Kauff and colleagues from Memorial Sloan-Kettering prospectively studied 170 women with either *BRCA1* or *BRCA2* mutations for 6 years. Ninety-eight women who underwent RRSO were compared with 72 women who elected surveillance. As can be seen in Figure 24.7, the RRSO group had significantly fewer *BRCA*-related gynecologic and breast cancers than the surveillance group. Another prospective study, of a larger cohort of women, allowed us to understand the effects of RRSO in *BRCA1* and *BRCA2* patients separately. In this multicenter study of 1,079 patients, RRSO reduced ovarian cancer risk in

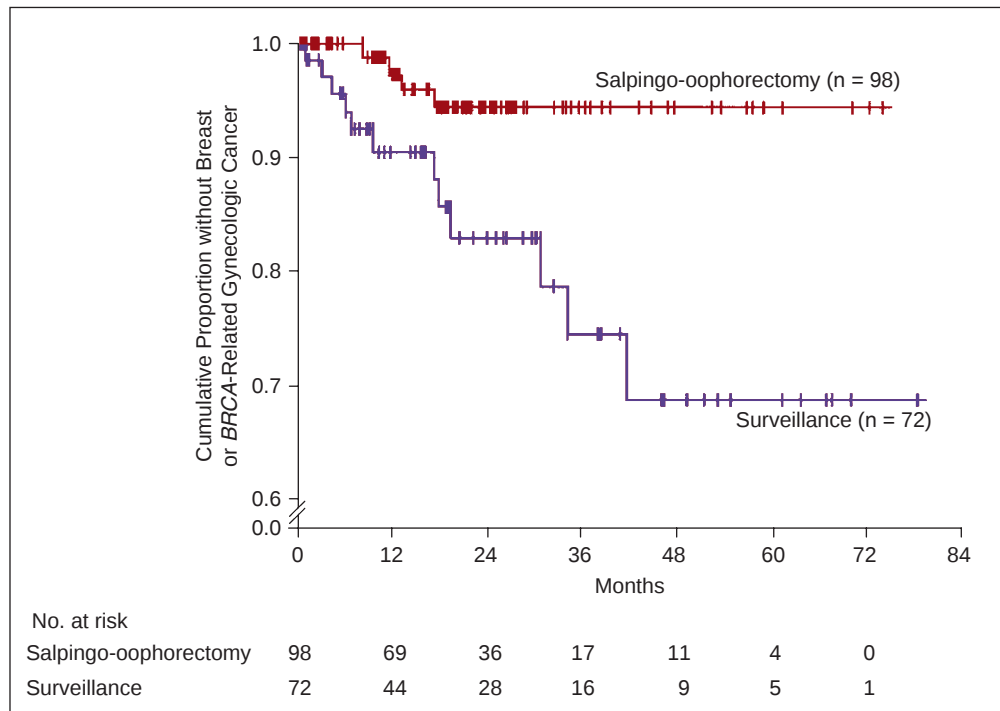


FIGURE 24.7. Kaplan–Meier Estimates of the Time to Breast Cancer or BRCA-Related Gynecologic Cancer among Women Electing Risk-Reducing Salpingo-oophorectomy and Women Electing Surveillance for Ovarian Cancer.. $P = 0.006$ by the log-rank test for the comparison between the actuarial mean times to cancer. A Cox proportional-hazards model for multiple end points, which took into account the different proportions of women in the 2 groups who had breast tissue at risk, yielded a hazard ratio for subsequent breast cancer or BRCA-related gynecologic cancer after risk-reducing salpingo-oophorectomy of 0.25 (95% confidence interval, 0.08 to 0.74). Source: From Kauff ND, Stagapan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2002;346:1609–1615, with permission.

women with *BRCA1* mutations by 85% and reduced breast cancer risk in women with *BRCA2* mutations by 72%. There was also a 39% reduction in breast cancer risk in women with *BRCA1* mutations, and a reduction in gynecologic cancers in women with *BRCA2* mutations but these were not statistically significant. The absence of a significant reduction in ovarian cancer in *BRCA2* mutation carriers was probably attributable to the fact that most women with *BRCA2*-associated ovarian cancer are over 60 years old, while the median age of the women in the study was 46 years (69,75). In another large study coordinated by the Toronto group, 1,828 known carriers of a *BRCA1* or *BRCA2* mutation were identified from an international registry of 32 centers. The overall reduction in risk of müllerian cancers with RRSO was 80%; the estimated cumulative incidence of peritoneal cancer at 20 years after oophorectomy was 4.3%, with most cases occurring less than 5 years after RRSO (76).

Given the strong evidence that RRSO is protective against the development of ovarian cancer, The National Comprehensive Cancer Network (NCCN), the American College of Obstetrics and Gynecology (ACOG) and the Society of Gynecologic Oncology (SGO) (59) have recommended that prophylactic oophorectomy be considered in women with ovarian cancer syndromes at age 40 years or after childbearing is completed. Because *BRCA2* mutation carriers will develop ovarian cancer at an average age of 58, and only 2% to 3% of these women will develop ovarian cancer by age 50 as compared to 10% to 21% of women with *BRCA1* mutations, delaying surgery in *BRCA2* mutation carriers could be considered (69). However, women with *BRCA2* mutations have a 26% to 34% risk of developing breast cancer by the age of 50, and the evidence suggests that the

breast-cancer risk reduction conferred by RRSO is greater when the ovaries are removed earlier (77).

Surgery

RRSO substantially decreases ovarian cancer risk. Some risk of primary peritoneal cancer remains after RRSO although that risk may largely arise from an ovarian remnant, an incompletely removed fallopian tube, or a microscopically metastasized, occult cancer that could not be recognized at the time of surgery.

The informed consent discussion for RRSO surgery should include not only information about the general risks of surgery, but also information about the likely side effects of bilateral salpingo-oophorectomy. Permission to perform a full staging or debulking procedure if cancer is found should also be obtained. The rate of occult cancer detected with RRSO (which requires an additional surgical procedure) can be up to 10% in a tertiary referral center (21,78) though the rate drops to approximately 3% when centers that do not perform an extensive pathologic review of the fallopian tube are included (79). Hysterectomies are not performed routinely, because there are no reports indicating that the intrauterine portion of the fallopian tube gives rise to a fallopian tube cancer. However, hysterectomy may be indicated if there is other uterine pathology, if the uterus contributes to incontinence or bleeding disorders, to reduce endometrial cancer risk for patients with Lynch syndrome who are also at risk for endometrial cancer (see below), or to simplify HRT.

It is usually possible to perform a RRSO laparoscopically as an outpatient procedure. Occasionally a laparotomy will be necessary due to extensive intra-abdominal/pelvic adhesions. After a thorough surveillance of the entire abdominal cavity including the

upper abdomen, peritoneal washings are performed and abnormal areas biopsied. The ureter is visualized and the infundibulopelvic vessels are transected about 2 cm superior to the ovary to assure that the entire ovary has been removed. The tube and the superior branch of the uterine artery are transected very close to the uterine cornu. A frozen section is only prepared if there is a gross abnormality of the ovary or any other suspicious tumor. Random biopsies of the omentum and peritoneum have not been found to lead to improved detection of occult cancers (78). Many patients presenting for RRSO will have had a previous reconstruction of their breast using some variation of a rectus abdominus myocutaneous flap. Since these procedures can lead to umbilical translocation in relation to the aortic bifurcation, higher camera port placement may be required (80). In general, RRSO is associated with a very low risk of operative complications. In a Memorial Sloan-Kettering study, four out of 80 RRSOs performed laparoscopically had complications caused by adhesions and trocar injuries, which are known complications associated with operative laparoscopy (74).

Because high-grade serous “ovarian cancer” is now believed to arise in the fallopian tube, the option of removing the fallopian tube and leaving the ovary *in situ* is being debated. As of this time, this approach is not supported by published data, and we believe that it remains strictly investigational.

Postoperative Results

Women who have chosen to undergo RRSO generally report a good overall quality of life. The surgery is often accompanied by a significant decrease in perceived risk, and therefore a decrease in anxiety (81). Acute surgical menopause, however, can have a significant negative effect on quality of life (82). Surgical menopause affects bone health and can cause a decrease in sexual desire, vaginal atrophy and dyspareunia, affecting sexual functioning and leading to decrease in sexual desire, discomfort, and avoidance of intimacy. Many patients suffer from vasomotor symptoms, such as hot flashes and night sweats, which lead to sleep disturbances. These symptoms can be alleviated but not completely eliminated by HRT (81). It has been reported that short term HRT (approximately 3 years duration) does not negate the protective effect of RRSO on the development of subsequent breast cancer (83). This was confirmed by Eisen et al., who showed that HRT after RRSO is not associated with an increase in breast cancer risk in *BRCA* mutation carriers (84). Still, decision-making regarding menopausal therapies in women with *BRCA* mutations who are at increased risk of breast cancer is challenging because of the theoretical risk that HRT will promote growth of occult breast tumors. Alternative treatments for vasomotor symptoms, such as venlafaxine and gabapentin, should be discussed in counseling.

The Pathologic Examination of Risk-Reducing Salpingo-Oophorectomy Specimens

A family history of ovarian cancer and/or *BRCA* mutation status should be shared with the pathologist, since in patients with benign gynecologic disease only one slide from the fallopian tube and ovary is normally reviewed (21,78). In the setting of a known history of genetic predisposition to breast and ovarian cancer, most pathologists will submit the entirety of the fallopian tubes and ovaries for microscopic examination. The SEE-FIM (sectioning and extensively examining the fimbriated ends) protocol is widely used. Basically, this involves serially sectioning the tube meticulously, stopping before the fimbriae. The fimbria is amputated and sectioned longitudinally, thereby maximizing exposure. Deeper sections need to be obtained if foci of atypia are to be identified histologically. Foci of *in situ* or invasive occult carcinoma may be very subtle, and are often less than 1 mm in maximum diameter. (See also Pathology section.)

Microscopic occult carcinomas have been identified in RRSO specimens in about 2% to 9% of *BRCA* mutation carriers,

generally involving the tubal fimbriae. In one prospective series, 7 ovarian, and 3 tubal carcinomas (and 1 case in which washings showed malignant cells but no primary cancer was identified) were found among 490 women who underwent RRSO (76). Powell and colleagues report that in 111 consecutive *BRCA*-positive patients treated at a single institution, 9% had occult neoplasia (78). Suspicious epithelial cells, clearly distinct from mesothelial cells, are occasionally identified in cytology specimens. Colgan et al. found malignant cells in 3 of 35 pelvic washings. One microscopic ovarian surface carcinoma and 1 *in situ* tubal carcinoma were found; no carcinoma could be identified in the third patient. Twenty-two percent of specimens showed endosalpingiosis (85). Positive cytology specimens only rarely lead to the discovery of early-stage tubal carcinomas (21,78) although sometimes, as mentioned, malignant cells are present in washings at RRSO and there is no identifiable carcinoma by histology (76).

Lynch Syndrome—Hereditary Nonpolyposis Colorectal Cancer Syndrome

Epithelial ovarian cancer is also a component of Lynch syndrome II (Hereditary nonpolyposis colorectal cancer syndrome—HNPCC). In addition to a predisposition to develop colorectal and endometrial cancer, women with this syndrome have a 10% to 13% lifetime risk for developing ovarian cancer (86). Women at risk for Lynch syndrome are identified using either the Amsterdam II or the revised Bethesda criteria, attempting to enrich for patients who are likely to have a hereditary origin of their cancer. However, even though the Bethesda criteria have been revised to improve identification, they may still miss as many as 28% of patients with Lynch syndrome.

Lynch syndrome-related tumors exhibit a lengthening or shortening of DNA repeat sequences, which leads to microsatellite instability (MSI), caused by an inability to repair DNA replication errors. This syndrome is a result of germline mutations in genes involved in the DNA mismatch repair pathway, such as *MSH2* and *MLH1* which account for about 90% of the mutations detected in families with Lynch syndrome, with *MSH2* being particularly associated with an excess of endometrial and ovarian carcinomas. Other genes in the MMR family, including *MSH6*, *PMS1*, and *PMS2*, account for 10% of HNPCC-related cancers (86). To identify patients with HNPCC 2 approaches are used: For MSI analysis, DNA is extracted from macrodissected tumors using paraffin sections, and short tandem repeats are amplified. Immunohistochemical stains are performed for *MSH2*, *MSH6*, *MLH1*, and *PMS2*. If a MMR protein is absent, despite appropriate controls, confirmatory sequencing is performed. MSI can be due to epigenetic changes as well as to Lynch syndrome. For example, *MLH1* promoter hypermethylation or *BRAF* gene mutations can result in MSI.

A recently published French multicenter study reviewed the cancer incidence in 537 families with Lynch syndrome (87). For women in the study, the cumulative risk for Lynch syndrome-associated cancers was 19% by age 50 and 54% by age 70. The age specific cumulative risk for ovarian cancer by age 70 was 20% for *MLH1* mutation carriers, 24% for *MSH2* mutation carriers, and 1% for those with *MSH6* mutations (Fig. 24.8). This study clearly showed that *MSH6* mutation carriers have much lower cancer risks than *MLH1* and *MSH2* mutation. These findings raise the question of whether women with a *MSH6* really need prophylactic surgery, especially if no other family member has been affected by cancer. However, a smaller cohort study did not confirm this low ovarian cancer risk in women affected by *MSH6* mutations and found that a third of cases of ovarian cancer identified among MMR mutation carriers were affected by a *MSH2* mutation (88). This study from the combined Swedish/Danish cancer registry found that the distribution of ovarian

Cumulative Risk,% (95% Confidence Interval)												
Age, y	Colorectal Cancer				Endometrial Cancer				Ovarian Cancer			
	Carriers				Carriers				Carriers			
	All	MLH1	MSH2	MSH6	All	MLH1	MSH2	MSH6	All	MLH1	MSH2	MSH6
20	0 (0-1)	0 (0-1)	0 (0-1)	0	0	0	0	0	0	0	0	0
30	2 (1-3)	1 (0-3)	2 (1-5)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0	0	0	0 (0-1)	0
40	5 (3-8)	6 (3-11)	8 (4-13)	1 (0-3)	2 (1-4)	1 (0-4)	2 (0-7)	1 (0-2)	1 (0-1)	0 (0-2)	1 (0-3)	0
50	13 (9-19)	14 (8-27)	20 (13-30)	3 (2-6)	8 (4-15)	9 (3-19)	8 (3-21)	3 (1-8)	3 (1-5)	4 (0-11)	4 (1-9)	0 (0-1)
60	24 (17-35)	28 (16-49)	36 (23-54)	6 (4-12)	23 (12-38)	32 (12-55)	18 (8-53)	9 (5-19)	7 (2-21)	15 (1-45)	11 (2-28)	1 (0-2)
70	35 (25-49)	41 (25-70)	48 (30-77)	12 (8-22)	34 (16-58)	54 (20-80)	21 (8-77)	16 (8-32)	8 (2-37)	20 (1-65)	24 (3-52)	1 (0-3)
80	42 (30-60)	49 (29-85)	52 (31-90)	18 (13-30)	35 (17-60)	57 (22-82)	21 (9-82)	17 (8-47)	8 (2-39)	20 (1-66)	38 (3-81)	1 (0-3)

^aSee eTable 3 (available at <http://www.jama.com>) for the number of affected individuals and the number of family members contributing to the likelihood for risk estimation.

FIGURE 24.8. Age-Specific Cumulative Risks of Colorectal Cancer, Endometrial Cancer, and Ovarian Cancer According to Gene for Mismatch Repair Mutation Carriers.

Source: From Bonadona V, Bonaldi B, Olschwang S, et al. Cancer risk associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. 2011;305:2304–2310, with permission.

cancer histologic subtypes in patients with Lynch syndrome differed considerably from the sporadic ovarian cancer population. They reported that 35% of the ovarian cancers associated with Lynch syndrome were endometrioid, and 17% were clear cell, both much higher percentages than are seen in sporadic cases.

As with *BRCA1/2* patients, RRSO is a very effective method for the prevention of ovarian cancer in patients with a Lynch syndrome mutation. Preoperatively patients should have a colonoscopy to detect colon cancer, an endometrial biopsy to exclude an occult endometrial cancer, and a vaginal ultrasound to detect any ovarian masses that will affect the surgical approach (minimally invasive vs. open surgery). In a large study combining all Lynch syndrome patients followed at MD Anderson, UCSF, and Creighton University, none of 61 patients who underwent RRSO and a hysterectomy developed ovarian or uterine cancer. However, 12 (5.5%) of the 223 patients who chose surveillance developed ovarian cancer and 33% developed endometrial cancer (89). Consistent with the French study (87), half of the patients who developed ovarian cancer had a *MLH1* mutation and the other half a *MSH2* mutation, while none had a *MSH6* mutation. Clearly RRSO and hysterectomy are efficient in preventing gynecologic cancers in women affected by HNPCC.

A critical question for patients with Lynch syndrome is at what age a hysterectomy/BSO should be performed. Two studies reported that the median age for endometrial and ovarian cancer in these patients is 46 to 48 years and 42 to 48 years, respectively. Moreover, a significant number of the women studied (21% to 42%) developed ovarian cancer before age 40 (88,89). In contrast, the French study found that the risk of developing ovarian cancer for all Lynch syndrome mutation carriers by age 40 does not exceed 2% to 3%. Still, a prudent approach is to perform the hysterectomy and RRSO after the age of 35 (or once childbearing is completed). Obviously, such an early intervention requires extensive counseling, balancing the consequences of surgical menopause treated with HRT with the benefits of avoiding ovarian and endometrial cancer.

For patients with Lynch syndrome who prefer not to undergo prophylactic surgery there is no scientifically proven screening option. Still, according to the NCCN guidelines and most experts, transvaginal ultrasound and CA-125 are acceptable exams in patients with mutations, if the patient is fully aware that these interventions will not necessarily diagnose ovarian cancer early and might even be harmful, due to possible complications of surgical follow-up for a false-positive result (72). However, given that two-thirds of HNPCC-associated ovarian cancers are diagnosed during stage I and II because of their endometrioid and clear cell histology (88,89), a vaginal ultrasound is a reasonable choice for surveillance in a woman who declines prophylactic surgery.

NATURAL HISTORY OF THE DISEASE: PATTERNS OF SPREAD

Mucinous and Endometrioid Ovarian Cancer

Mucinous neoplasms are the largest of all known ovarian tumors. They can reach diameters of 30 to 40 cm, often compressing adjacent organs (Fig. 24.9). Intact removal may be challenging because of the weight and the large veins that drain from the tumor, and because of difficulties visualizing the ureter. Interestingly, the largest tumors are often benign. Indeed, invasive mucinous ovarian cancer is rare because most of the tumors are low grade, or are benign mucinous cystadenomas (80%). High-grade invasive mucinous cancers, however, are very aggressive and resistant to chemotherapy (90). Of all advanced ovarian cancers, 0.5% to 1.5% have a mucinous histology. Most (71%) invasive mucinous tumors found in the ovary are metastasis from the gastrointestinal tract (colon, pancreas, and appendix) so only 29% of all mucinous carcinomas found in the ovary are truly primary mucinous ovarian cancers (90,91).



FIGURE 24.9. A 42-year-old patient with a multicystic adnexal mass originating from the left ovary. The specimen was 20 × 15 cm, weighed 5 pounds. The frozen section returned as a mucinous borderline tumor.

These primary invasive mucinous tumors are often confined to the ovary without surface involvement, and are unilateral (metastases are bilateral) and of a significant size (≥ 13 cm) (91). Often patients with mucinous tumors have an elevated CEA or CA19-9.

Pseudomyxoma peritonei is a condition caused by the production of mucin by glandular cells in the peritoneal cavity. These cells have a benign glandular histology, but their behavior is biologically malignant, since the mucin-producing cells implant diffusely on the abdominal and pelvic peritoneum. They then produce thick mucin that can encase the bowel and pelvic organs, leading to tumor cachexia and bowel obstruction. Usual origins of pseudomyxoma peritonei are currently thought to be appendiceal neoplasms or ruptured benign mucocles of the appendix with secondary involvement of the ovary. Patients with pseudomyxoma peritonei can progress for months or years without symptoms. Although their disease often has an indolent course, it cannot be cured (10-year survival is 60%) (92). Currently, it is recommended that patients receive very aggressive cytoreductive surgery with complete peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) in a specialized center, although there are no randomized data to support this strategy.

Invasive endometrioid ovarian cancer accounts for about 10% of all ovarian carcinomas and occurs most often in perimenopausal patients. These cancers are often associated with endometriosis (33–35). Up to 25% of young premenopausal patients of reproductive age with an endometrioid endometrial cancer have a synchronous early-stage endometrioid ovarian cancer (93).

Because of their size, both mucinous and endometrioid ovarian cancer are likely to be discovered at an early, FIGO I/II, stage. These cancers do not have the pattern of transcoelomic spread along peritoneal surfaces seen with serous cancers. Locally, they are characterized by thick adhesions to the pelvis and can invade adjacent pelvic organs including the muscularis of the colon and the pelvic sidewall. Advanced metastatic endometrioid and mucinous tumors (FIGO III/IV) implant into the abdominal wall, and metastasize to the parenchyma of intra-abdominal organs such as liver and spleen. They can also have early distant extra-abdominal metastases.

Serous Ovarian Cancer

Serous carcinomas originating from müllerian epithelium, including ovarian, peritoneal, and fallopian tube cancers, are characterized by transcoelomic spread (16,94,95). Recently there have been new insights into the origin of serous “ovarian” cancer, and a putative precursor lesion in the fallopian tube, serous tubal intraepithelial carcinoma (STIC), has been identified. It is now believed that most serous “ovarian” cancer originates in the fallopian tube as STIC (21). Often, it is not possible to clearly identify where the serous tumor originated. However, this is not very important from a practical, clinical standpoint since the dissemination pattern and patient survival of the 3 serous-papillary subtypes (ovarian, fallopian tube, peritoneal) are very similar. A recent study (96), as well as clinical experience, suggests that all 3 tumor subtypes grow quickly and disseminate on mesothelial cell-covered body cavities including the peritoneal cavity or pleural space. Extensive surface involvement of the abdominal or pleural cavity will cause ascites and a pleural effusion, respectively. Rarely, serous tumors will metastasize to the mesothelial cell covered pericardium, causing a pericardial effusion.

Ovarian, peritoneal, and fallopian tube cancers have a very distinctive presentation, by virtue of their propensity to exfoliate malignant cells into the peritoneal cavity. The exfoliation of neoplastic cells from the ovarian tumor or the distal fimbriated

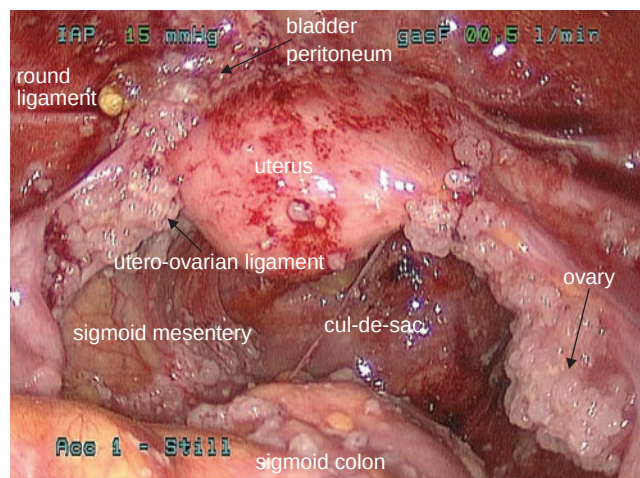


FIGURE 24.10. Laparoscopic intraoperative image of the pelvis of a patient with disseminated high volume disease suggestive of ovarian cancer on CT scan. Tumor implants on the sigmoid colon, sigmoid mesentery, pelvic sidewall, ovary, utero-ovarian ligament, bladder peritoneum.

end of the tube is the probable starting point for the cells (21,94). The most common sites involved in locoregional metastasis are the contralateral ovary, the peritoneum of the cul-de-sac, the rectosigmoid colon and its mesentery, which often results in an obliteration of the rectouterine space.

In patients with extensive pelvic disease (Fig. 24.10) the uterus, bladder, peritoneum, sigmoid colon, ovarian tumor masses and appendix become a conglomerate pelvic tumor, and it is very difficult to identify the individual organs or any anatomic borders (97,98). Sometimes the appendix becomes part of a right adnexal tumor mass.

Once the cancer cells detach from the ovarian or fallopian tube tumor, they float in the ascites as single cells or as multicellular spheroids (16). The cells follow the normal clockwise circulation of peritoneal fluid up the right paracolic gutter and to the undersurface of the right hemi-diaphragm, where they may implant and grow as surface nodules. All intraperitoneal mesothelial covered surfaces are at risk, with frequent involvement of the peritoneum, diaphragm, omentum including the hepatic and flexure and splenic hilum, bowel and bowel mesentery, and appendix (95,99). The most frequent site of distant metastasis is the omentum. Other than the contralateral ovary, an omental metastasis is often the largest tumor in the abdominal cavity. Serous cancers initially transform the infracolic omentum, but as the cancer progresses the entire omentum is replaced by tumors (95,100) reaching from the hepatic to the splenic flexure (Fig. 24.11). Because the omentum reaches the spleen in the left upper quadrant there is often a solid tumor at the lower pole of the spleen and at the splenic hilum directly adjacent to the distal pancreas, requiring an *en bloc* resection of the distal pancreas and the spleen to completely clear the left upper abdomen (101–104). In patients affected by extensive disease, the lesser omentum, which is attached to the lesser curvature of the stomach, is also involved. Despite extensive involvement of the omentum by the serous carcinoma there is almost never invasion of the gastric or transverse colon muscularis and it is always possible to remove the tumors without a colon or gastric resection. Also, there is almost never a tumor in the retroperitoneal lesser sac.

Large tumor masses often develop in the right lower quadrant involving the ileocecum, appendix and right ovary. Patients with extensive intra-abdominal tumor involvement sometimes have extensive involvement of the small bowel mesentery, with tumor constricting the blood supply to the bowel and limiting

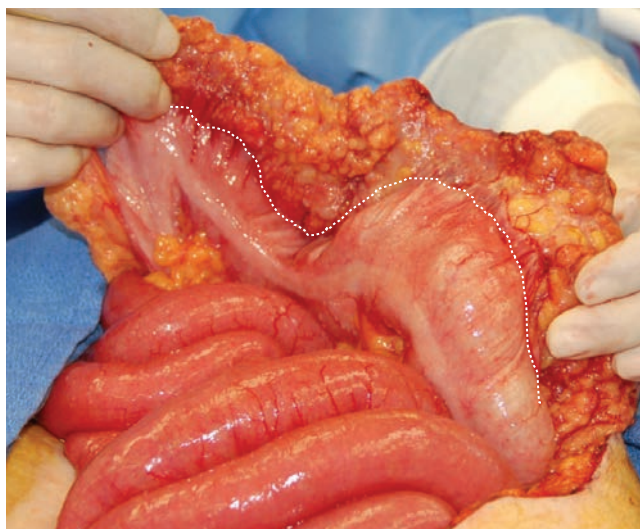


FIGURE 24.11. Patient with FIGO stage IIIC ovarian cancer with an omental cake. The omentum is completely transformed by tumor nodules. The omentum is lifted superior, towards the patient's head. The omental tumor can almost always be dissected off the transverse colon along an avascular plane (white dotted line) allowing entry into the lesser sac.

mobility of the bowel because of the short mesenteric root, a condition described by its appearance as “rose budding”. Often these tumors are unresectable because they compromise the entire blood supply to the small bowel from the superior mesenteric artery. In very advanced disease, serous cancers tend to agglutinate the loops of small bowel and cause a high-grade bowel obstruction at many levels (jejunum, ileum).

Women with advanced serous ovarian cancer, who have disseminated miliary disease covering the entire peritoneal surface, including the diaphragms, have extensive ascites (105). The ascites contains mostly mesothelial, inflammatory and ovarian cancer cells (16).

Patients with FIGO stage IV disease are a very heterogeneous group because several anatomic locations in the upper abdomen and a malignant pleural effusion define a patient as having a stage IV cancer. Peritoneal-pleural lymphatic communication through the diaphragm allows trans-diaphragmatic spread of tumor into the mesothelial covered pleural space, causing a malignant pleural effusion. Because serous cancers have a preference for implantation on the right diaphragm, most patients have a right sided malignant pleural effusion (37–48%) (106,107). Other FIGO stage IV defining metastasis patterns include parenchymal liver metastasis, supraclavicular/axillary lymphadenopathy, parenchymal lung metastases, mediastinal adenopathy, and distal vaginal or perineal metastasis (106,107). While serous ovarian cancer disseminates extensively within the abdominal cavity, intra-pulmonary metastasis, or other intra-parenchymal or retroperitoneal metastases for example into the liver, spleen, or kidney are rare, and should broaden the differential diagnosis to include a different ovarian cancer histiotype (clear cell, mucinous or carcinosarcoma) or a different tumor origin (gastrointestinal, breast cancer). Advanced low-grade serous cancers, which represent about 9% of all epithelial ovarian cancers (108,109), have a very similar tumor distribution to high-grade serous cancers, with metastasis to the omentum (83%), fallopian tube (63%), pelvic peritoneum (49%), and uterine serosa (46%) (110).

Fallopian tube cancers have a similar spread pattern to ovarian cancer but first invade the tubal muscularis, which is why staging for fallopian tube cancer includes depth of invasion. Schiller and Silverberg (111), in a retrospective review of 76 published cases of obvious early stage fallopian tube

carcinoma, documented the important relationship between the depth of invasion by tumor and survival. A crude 5-year survival of 91% was found for intramucosal lesions, 53% for tumors with mucosal wall invasion, and 25% or less for cases in which the tumors penetrated the tubal serosa. A study by Peters et al. (112) confirmed the importance of the depth of invasion in predicting survival. The pathologist who examines a fallopian tube that contains invasive tumor should provide information on the depth of invasion, the presence of lymphatic or capillary space involvement, and the degree of histologic differentiation. Some studies have reported a higher incidence of lymph node spread in fallopian tube cancers.

Lymph Node Metastasis

Exfoliation and implantation is 1 of 2 primary modes of spread of ovarian cancer. The other is via the retroperitoneal lymphatics that drain the ovary. These follow the superior ovarian blood supply in the infundibulopelvic ligament, which contains the ovarian artery and vein as well as extensive lymphatics, which terminate in lymph nodes lying along the aorta and vena cava up to the level of the renal vessels. The next lymph node stations are at the celiac trunk from where tumor cells may continue up to the mediastinal and supraclavicular lymph nodes. Lymph channels also pass laterally through the broad ligament and parametrial channels to terminate in the pelvic sidewall lymphatics, including the external iliac, obturator, and hypogastric chains (113). Spread may also occur along the course of the round ligament, resulting in involvement of the inguinal lymphatics (these patients are still considered to have FIGO IIIC disease). The principal lymphatic drainage of the ovary and fallopian tube appears to be via the paraaortic lymph nodes. Lymph node metastases are correlated with extent of intra-abdominal disease involvement, and retroperitoneal node involvement has been found in the majority of advanced ovarian cancer cases (114–117).

The initial spread of ovarian cancer, by both the intraperitoneal and lymphatic routes, is clinically occult. As many as 20% of women with what appears to be stage I/II ovarian cancer have widespread disease. The extent of their disease can be detected only by histologic examination of visually normal tissues sampled during careful surgical staging (118). Approximately 10% of patients with cancer that appears to be confined to the ovaries will have metastases to the paraaortic nodes. Many patients with apparently localized disease will also have occult disease in peritoneal washings or in biopsies of the diaphragm and omentum (Table 24.3).

Table 24.3 Subclinical Metastases in Apparent Early Ovarian Cancer

Site	No. of Patients with Involvement	Total Patients	% Involved
Diaphragm	17	223	7.6
Omentum	21	294	7.1
Cytology	13	69	18.8
Peritoneal	6	61	9.8
Pelvic nodes	18	202	8.9
Paraaortic nodes	35	285	12.3

Source: Modified with permission from Moore DH. Primary surgical management of early epithelial ovarian carcinoma. In: Rubin SC, Sutton GP, eds. *Ovarian Cancer*. New York, NY: McGraw-Hill; 1993.

Recurrent Ovarian Cancer

The majority (80%) of patients with advanced ovarian cancer who undergo a combination of platinum- and taxane-based chemotherapy will have a recurrence, despite an initial complete response to primary treatment (106,119,120). Seventy-five percent of all patients have an intraabdominal recurrence; the remainder have extraperitoneal/intrahepatic or distant metastasis with or without intrabdominal recurrence (121). Twenty-two percent of recurrences occur outside the peritoneal cavity. The location of intraabdominal recurrences include the remnants of the omentum, especially at the splenic flexures, the small and large bowel mesentery, and the epiploic appendices, which are peritoneal pouches filled with fat and located along the colon and intraperitoneal rectum.

Following the increased use of intraperitoneal chemotherapy with the publication of GOG #182 (122) several retrospective studies reported a change in the pattern of recurrence. Women treated with intraperitoneal, rather than intravenous, chemotherapy were found to have a higher rate of extraabdominal recurrences, including brain metastasis, pleural effusions, and mediastinal disease (101). Robinson et al. found that women with recurrent ovarian cancer treated with intraperitoneal chemotherapy had a 26% risk of extraabdominal metastasis, while women treated with intravenous chemotherapy had a 7% risk (123). Two further retrospective studies reported even higher extraperitoneal recurrence rates of 41% to 45% with intraperitoneal chemotherapy (101,124). If intraperitoneal chemotherapy is combined with bevacizumab more patients present with recurrent disease in the central nervous system or the skin (123), indicating that bevacizumab also affects the recurrence pattern of ovarian cancer. Since most patients with intraperitoneal chemotherapy receive bevacizumab at some point during their treatment for recurrent disease, it is possible that the variation in pattern of metastasis reported for intraperitoneal chemotherapy is actually caused by bevacizumab.

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

The diagnosis and treatment of patients with ovarian masses is difficult because of the diversity of clinical presentations, the plethora of differential diagnoses, and the wide range of therapeutic options.

Clinical Presentation of Patients with a Benign Adnexal Mass or Early-Stage Ovarian Cancer

Almost all patients with small adnexal tumors are asymptomatic, and the mass is usually discovered incidentally during a work-up for other conditions. With increasing size, adnexal masses cause pelvic pressure and pain by compressing surrounding structures. A larger pelvic tumor can cause genitourinary symptoms including urgency, frequency, and dyspareunia. Posteriorly, a fixed pelvic tumor compresses the sigmoid colon, causing severe constipation. These symptoms are essentially similar in both benign disease and early ovarian cancer, and it is impossible to differentiate a benign from a malignant ovarian mass by clinical examination alone. Borderline ovarian tumors, nonserous malignant epithelial ovarian cancer (endometrioid, clear cell, mucinous), and nonepithelial (germ cell, stromal cell) malignant tumors present as large adnexal masses at an early-stage without any further abdominal dissemination.

An ovarian mass becomes a surgical emergency if a patient with an adnexal mass has sudden onset of abdominal pain. The differential includes torsion and possible infarction of the ovarian mass. But severe abdominal pain can also be caused by a hemorrhage inside a cyst, which distends it, or by the rupture of a blood-filled cyst, causing hemoperitoneum. Sudden abdominal pain associated with an adnexal mass is often accompanied by malaise, nausea and vomiting, low-grade fever, and an elevated white blood cell count and C-reactive protein, which are all caused by the peritoneal irritation. In the presence of acute pain, peritoneal signs, rigidity, and rebound tenderness, urgent expert surgical evaluation should be considered. Evaluation is most often performed laparoscopically. Delaying surgery can result in infarction, hemorrhage and peritonitis.

Vaginal bleeding in a patient with an adnexal mass could be an indication of synchronous endometrial and ovarian cancers (93) or a granulosa cell tumor that produces estrogen, causing abnormal bleeding. Sertoli-Leydig cell tumors can lead to virilization.

Clinical Presentation of Patients with Advanced Ovarian Cancer

The clinical presentation of advanced ovarian cancer is varied, and it is often surprising to the treating physician how few symptoms women with advanced ovarian cancer sometimes experience. General, nonspecific symptoms associated with advanced ovarian cancer include anorexia, fatigue, early satiety and loss of appetite. While weight loss is unusual in ovarian cancer because of diffuse ascites production, tumor cachexia can be a presenting sign in patients with high-volume disease and long standing partial bowel obstruction.

Often patients complain of nonspecific pelvic and abdominal symptoms, including bloating and diffuse, dull, constant abdominal pain caused by the infiltration of the peritoneum and the bowel mesentery, or by extensive ascites. Involvement of the small bowel can cause changes in frequency of bowel movements alternating constipation with diarrhea. If the tumor has metastasized to the omentum, patients complain of upper abdominal discomfort with nausea, belching, early satiety and fullness. The abdominal cavity may also be distended by several liters of ascites, which can cause a significant increase in abdominal circumference leading to marked discomfort. Extensive ascites can cause significant fatigue, anorexia, pain, nausea/vomiting, and incontinence. In addition, ascites can cause dyspnea, because the lower lung lobes are compressed by the abdominal distension (105). Signs of bowel obstruction, severe urinary symptoms, intense pelvic pain, and ascites are likely to indicate miliary dissemination on the peritoneal surfaces and large-volume advanced disease.

Because symptoms often develop late, when the cancer is already advanced, ovarian cancer has been called the “silent killer” or “the cancer that whispers”. However, a careful review of symptoms in woman with ovarian cancer has shown that many women have abdominal symptoms, urinary frequency, and pain for 3 months or longer before diagnosis (125). One study suggested that ovarian cancer patients seem to have several symptoms at once (e.g., increased abdominal size/bloating, early satiety, pelvic/abdominal pain, incontinence), which are more severe, more frequent, and of more recent onset than those symptoms reported by patients without cancer who presented to a primary care clinic (125). Other studies have disputed that symptom clusters can aid in recognizing ovarian cancer earlier, and showed that screening for these symptoms adds little to the use of CA-125 and ultrasound (126), indicating that the appraisal of symptoms alone will not lead to an earlier diagnosis (127,128).

The ACOG and SGO (129) consensus guidelines recommend referral to a gynecologic oncologist for postmenopausal women with elevated CA-125, ascites, a nodular/fixed pelvic mass, or evidence of abdominal/distant metastasis. In premenopausal women, a very elevated CA-125, ascites, and evidence of abdominal or distant metastasis should trigger a referral. The guidelines have a positive predictive value of 39.6% for premenopausal women and 64.6% for postmenopausal women (130).

Meigs syndrome is defined as a cytologically benign pleural effusion and ascites, which resolves upon removal of a concomitant ovarian tumor, usually an ovarian fibroma or thecoma. Patients with advanced ovarian cancer sometimes present with a DVT from large tumors pressing on pelvic veins or as part of the hypercoagulopathy associated with advanced-stage cancer (131).

Clinical Exam

A focused clinical exam should begin with an assessment of supraclavicular lymph nodes, a breast exam, and percussion of the lungs to detect a pleural effusion. The abdomen should be evaluated for the presence of an umbilical hernia. The involvement of the umbilicus by an ovarian cancer is colloquially called “*Sister Mary Joseph nodule*,” named after an assistant to Dr. William Mayo, who identified the lesion as a sign of advanced malignancy (132). The abdomen should also be inspected for surgical scars and visible veins (“*caput medusae*”) caused by impaired central venous return from extensive intraabdominal disease, and examined for the presence of ascites, the size and mobility of the adnexal mass, costovertebral angle tenderness from hydronephrosis, and the presence of enlarged inguinal lymph nodes. In a patient with extensive ascites, the bowel floats on top of the ascites leading to central tympany on exam, while in patients with a large tumor the tympany is lateral.

On gynecologic exam, a prominent cystocele could be indicative of ascites. The bimanual and rectovaginal exam should attempt to evaluate and characterize the adnexal mass in respect to size, borders (smooth/irregular), mobility (fixed/mobile), and location. Invasive ovarian cancers often have irregular borders and are often fixed to the pelvic sidewall and fill the cul-de-sac. Pelvic examination findings may also include involvement of the parametrium by tumor, or nodularity of the rectovaginal septum. It may not be possible to differentiate the uterus from the tumor and the cervix is sometimes dislocated anteriorly behind the pubic symphysis. Some ovarian tumors are behind the uterus and can be best palpated with a rectovaginal exam after the bladder is emptied.

Laboratory Tests

A pregnancy test should be part of the work-up for premenopausal women, since uterine enlargement could be due to pregnancy. The laboratory work-up for patients with suspected ovarian cancer generally includes a complete blood count. Patients with ovarian cancer are often hemoconcentrated, while patients with gastrointestinal malignancies are frequently anemic. Patients with ovarian cancer also often have thrombocytosis (a poor prognostic marker) (131) and may have a low albumin level, which is indicative of tumor cachexia and malnutrition and is associated with higher peri- and postoperative morbidity.

The CA-125 tumor marker is elevated in 80% of all patients with advanced epithelial ovarian cancer. In stage I disease, the sensitivity is much lower at 50%, which is one reason that CA-125 is not a good screening method for

early-stage disease (133). However, 80% of patients with ovarian cancer of any stage, who are over 50 years old, have an elevated CA-125. The CA-125 is highest in serous and lowest in mucinous epithelial cancers. Clear cell and endometrioid ovarian cancer often have lower CA-125 values, around 200 U/mL. In premenopausal women, the differential of an elevated CA-125 includes many diseases associated with acute or chronic inflammation, and generally speaking, CA-125 can be regarded as an acute phase reactant. It can be elevated in patients with endometriosis, fibroids, PID, cirrhosis of the liver, systemic lupus erythematosus, and inflammatory bowel disease. Moreover, as a tumor marker, CA-125 is not specific to ovarian cancer, since it is increased, albeit modestly, in most metastatic solid tumors, including gastrointestinal and endometrial cancer. A mathematical, computer-based algorithm, ROCA (Risk of Ovarian Cancer Algorithm), was devised to increase the sensitivity and specificity of CA-125 when it is used for screening. The algorithm involves looking at the changes in levels of CA-125 over time for an individual instead of a single cut-off value as the basis for deciding whether additional tests are needed to look for ovarian cancer. A large UK-based study is currently evaluating this algorithm prospectively.

Patients with mucinous ovarian cancer often have elevated CEA values, but this tumor marker is not specific for ovarian cancer either and is increased in patients with gastrointestinal malignancies, especially colon and gastric cancer.

Imaging of Adnexal Masses, Early and Advanced Ovarian Cancer

In patients with adnexal masses a complete history, physical examination, pelvic ultrasound, and a CA-125 will provide the necessary data to determine if surgery is required. Because history and the clinical exam alone cannot reliably differentiate between benign and malignant masses, imaging is generally performed to help establish a diagnosis.

Ultrasound

Ultrasound can detect and characterize ovarian size and morphology. Benign tumors often appear on ultrasound as unilateral with smooth walls, with a few cysts, no solid elements and an absence of ascites. In general, most benign tumors are cystic and mobile. Defined ultrasound criteria can diagnose functional cysts, dermoids, and endometriomas with a high degree of certainty, allowing the choice of conservative, nonoperative treatment. Functional cysts have thin walls and are fluid filled. Dermoids are often cystic with hyper-echoic areas (teeth). Endometriomas have low level, layered echos (blood) and thick walls. Vaginal ultrasound allows a very good resolution of the ovary but for large ovarian masses, an abdominal scan will complement the vaginal scan.

In contrast, malignant tumors are partially solid and cystic, often bilateral, irregular, fixed, and often accompanied by ascites. Patients with tumors that display these features require surgical exploration. Homogenous solid tumors also require surgical exploration, but the most common finding is an ovarian fibroma.

Sassone developed a model integrating inner wall structure, wall thickness, septa, and echogenicity as sonographic markers of malignancy, and found that in premenopausal women cysts greater than 6 cm should be further investigated for malignancy (134). Indeed, malignant tumors often present as complex masses with partially solid and partially cystic components. Diagnostic models have been developed that integrate grayscale ultrasound, color Doppler ultrasonography, and CA-125. In a pooled estimate of 18 cohort studies of the Sassone model, it

was calculated that its sensitivity and specificity in differentiating between a benign and malignant ovarian mass are 84% and 80%, respectively (135). DePriest presented a model integrating tumor volume, wall structure, and septal structure (136), which was tested in 10 studies and was found to have a pooled estimated sensitivity of 91% and specificity of 69% (135). In 1990, Jacobs introduced the Risk of Malignancy Index (RMI) based on logistic regression analysis that was adjusted 4 times (RMI I–IV) without significant improvements in sensitivity/specificity (137). It uses the product of CA-125 (U/mL), ultrasound scan results, and menopausal status. If a score of 50 is used as a cutoff, the pooled estimate for sensitivity was 91% and for specificity 74% (135).

Sometimes ovarian masses are indeterminate on gray-scale ultrasound providing insufficient rationale to proceed to surgery but are concerning enough that a second imaging test is considered for further characterization.

MRI can contribute to differentiate the nature of a mass as it can differentiate between simple fluid, atypical fluid (mucinous), fresh blood, old hematoma, solid tissue, stromal tissue, and fat. This is why MRI is of help to further characterize a mass when an ultrasound is suboptimal or indeterminate (138,139). As with ultrasound, several criteria have been established to differentiate a benign from a malignant mass, including the presence of septations, solid elements and papillary projections, and solid tissue intensity on T2-weighted MRI. Injection of gadolinium contrast agents further assists to characterize an adnexal mass because solid malignant components within a mass take up the contrast. This allows for better resolution aiding in the differentiation of cystic from solid lesions, especially endometriomas, stromal cell tumors, and teratomas. The pretest probability to detect a borderline/malignant tumor increased from 32% to 77% (95% CI, 69% to 85%), with a positive result for malignancy in the MRI diagnosis, and decreased to 4.8% (95% CI, 3% to 6%), with a negative result (140). Given these sensitivity and specificity, MRI is a reasonable test to predict if a mass is benign or malignant but will not be able to differentiate between borderline and invasive tumors. A meta-analysis found that the average sensitivity and specificity to identify a borderline/malignant tumor from a benign tumor was 92% (95% CI, 89% to 94%) and 85% (95% CI, 82% to 87%), respectively. While the sensitivity is similar to that reported by ultrasound, the specificity of MRI outperforms that of ultrasound imaging. A comparison of color Doppler, CT scans, and MRI showed that of all 3 modalities, contrast-enhanced MRI is most helpful in further characterizing an adnexal mass (138). In a premenopausal woman with an indeterminate ultrasound and a negative contrast-enhanced MRI, the risk of malignancy is 2%, while a positive MRI increases the risk of malignancy in the same patient to 80%.

Given the higher *a priori* probability that a mass in a premenopausal patient suggests a benign mass, a reasonable approach is to further characterize an indeterminate mass by MRI (138,139). If the MRI suggests a benign mass, the patient can be followed with a combination of clinical exam, serial ultrasounds, and CA-125 every 3 to 6 months to capture a malignant adnexal tumor not detected during the initial work-up. If the mass is stable, the follow-up interval can be extended. Still, it is important to stress to the patient that while gray-scale ultrasound can be used to characterize many ovarian masses reliably, only histological examination can confirm the diagnosis.

Computed Tomography/CT–Positron Emission Tomography Scan

Computed Tomography allows for detection and further characterization of an adnexal mass but performs less well than MRI

as a secondary imaging modality after gray-scale ultrasound. Even when intravenous contrast is given, CT offers lower soft tissue contrast than MRI (138,139). CT has a sensitivity of 87% and a low specificity of 16% in differentiating a benign from a malignant ovarian mass (141).

Because of reasonable costs and wide availability, CT scanning is currently the preoperative imaging modality most often used in patients with a high clinical suspicion for ovarian cancer. Frequently patients are discovered to have an adnexal mass or advanced disease after a CT scan of the abdomen and pelvis performed to work up unspecific clinical symptoms. In the pelvis, a CT scan allows for characterization of the adnexal mass and any involvement of surrounding organs (bladder, sigmoid, ureter, pelvic sidewall involvement). In the upper abdomen retroperitoneal adenopathy, omental involvement, and intrahepatic liver involvement can be detected reliably by CT scans with intravenous contrast (132,142).

Preoperative CT scans can identify the presence of disease in anatomic regions that are difficult to resect (e.g., stomach, lesser sac, liver, small bowel mesentery, adenopathy above the renal vessels). Bristow and colleagues identified 13 diagnostic features and calculated a predictive score to predict the chances of optimal cytoreduction (143). The score integrated 13 factors: peritoneal thickening, peritoneal implants greater than 2 cm, small and large bowel mesenteric disease greater than 2 cm, omental extension to stomach, spleen, or lesser sac, extension of the tumor to the pelvic sidewall/parametria/hydroureter, large-volume ascites, supra- and infrarenal lymph-adenopathy, diaphragm involvement, inguinal canal disease, liver lesions greater than 2 cm, and porta hepatis/gall bladder disease. Using this model, the authors were able to predict surgical outcome with 93% accuracy (143). However, multi-institutional validation showed an accuracy of only 34% to 46% (144). This study identified disease on the diaphragm and large bowel mesentery implants as the only statistically significant predictors of suboptimal cytoreduction, but even limiting the score to these 2 factors there was still a 33% false-positive rate (144). A Japanese study from Osaka University has combined diffuse peritoneal thickening, pelvic lymph node involvement, bowel encasement, and cul-de-sac implants to predict suboptimal debulking and found an improved accuracy of 88% (145), but their score has not yet been validated. Because surgical outcome depends on so many other factors than anatomical disease distribution (comorbidities, surgeon philosophy, advanced surgical techniques) preoperative CT scanning poorly predicts surgical resectability. Therefore, for most patients surgical evaluation of the peritoneal cavity is required to evaluate resectability of disease (146). Still, a patient whose CT scan indicates clearly high-volume ovarian disease should be evaluated carefully before a decision is made to proceed with primary debulking.

Positron emission tomography (PET) has been integrated with CT scan for the diagnosis of ovarian cancer and evaluating disease recurrence (142,147). CT/PET combines the high anatomic resolution afforded by the CT scan with a functional study of tumor fluoro-deoxy glucose (FDG) uptake. While PET scans have very high sensitivity, the low specificity leads to false-positive results because of increased FDG uptake in benign metabolically active tissues and inflammatory changes. In a single institution prospective study with 101 patients, a combined CT/PET scan had a sensitivity of 100% and specificity of 92% in diagnosing a tumor that had a high RMI score correctly (148). CT/PET scans seem to be especially useful in further characterizing recurrent disease in patients with rising CA-125 levels. In a retrospective study PET/CT showed a sensitivity of 82% and a specificity of 87% in correctly identifying recurrent disease which was superior to CA-125 or CT/MRI scans used alone (147).

Magnetic Resonance Imaging—MRI

While CT provides good spatial resolution, MRI is a nonradioactive imaging modality allowing for excellent soft tissue contrast resolution. In addition to being useful in diagnosis of an indeterminate ovarian mass (138,139), as described above, MRI is also an excellent modality to characterize nonadnexal pelvic pathology (e.g., diverticulitis) and to further characterize the upper abdominal disease extent of an ovarian cancer. The T1-weighted MRI images after administration of contrast (gadolinium) allow for detection of peritoneal metastases and bowel implants. It also allows determination whether the bowel mesentery is involved by cancer, whether a liver tumor is benign or malignant, is on the surface of the liver or intrahepatic, and whether the cancer involves the diaphragm. MRI is better than CT or ultrasound in the diagnosis of small peritoneal metastases, but CT imaging is superior in identifying involvement of the omentum by ovarian cancer (141).

In recurrent cancer, MRI is especially useful for differentiating between postsurgical changes and a recurrence on the vaginal dome, small bowel mesentery, splenic hilum, liver surface, or diaphragm. The reported sensitivity of MRI for recurrent ovarian cancer ranges from 62% to 91% and the specificity is between 40% and 100% and is mostly dependent on tumor size (142).

A new MRI technique dynamic, diffusion-weighted MRI (DWI), measures the diffusion of water molecules in the tissue. It is used in imaging of prostate cancer and is currently being tested for the evaluation of indeterminate ovarian masses, to evaluate small tumors and peritoneal implants for early recurrence, and follow chemotherapy treatment response (149).

Screening

No current screening modalities either individually or in combination (CA-125, pelvic ultrasound, pelvic examinations) have been shown to decrease the risk of death from ovarian cancer. Because ovarian cancer has such a low prevalence (1 case/2500 women per year), screening low-risk asymptomatic women would require a test or combination of tests with high sensitivity, specificity, and both positive and negative predictive value. Several studies have shown that if asymptomatic women were screened for ovarian cancer, between 5 and 33 operations would be required to find one invasive ovarian cancer (72,126,148,150). This situation is primarily caused by the high false-positive rate of ultrasound.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial randomized 78,216 women to either undergo annual screening with CA-125 and ultrasound or to have usual medical care (72). The results showed that screening does not improve mortality from ovarian cancer and found a greater cause-specific mortality in the intervention group (RR, 1.18; 0.82–1.71), driven by the morbidity associated with undergoing more operations. False-positive screening results were returned in 3,285 patients, 1,080 (32.9%) underwent surgery and of these 15% or 163 women had a major complication. The number of patients diagnosed in late stage ovarian cancer was similar in the screening and observation group, suggesting that screening does not detect ovarian cancer at an early stage. The absence of an expected stage-shift was also confirmed by a large Japanese screening study (150).

Even in women who carry a *BRCA1* or *BRCA2* mutation, annual pelvic exams, CA-125, and ultrasound have not been shown to be useful for screening (76). However, such screening is still recommended by the NCCN for high-risk women, and is carried out by many clinicians in the absence of an alternative. The inability to detect early ovarian cancer using a yearly

screening approach is probably due to the very fast growth rate of serous carcinoma once it is fully transformed, which reduces the time during which screening can detect preinvasive or early invasive ovarian cancer (96). Another reason that screening tends to be ineffective may be the extent of ovarian cancer disease heterogeneity. Large-scale screening trials using the ROCA algorithm described above are still underway.

In summary, pelvic exams, CA-125, and ultrasound have not been shown to prevent mortality from ovarian cancer. If a woman wants to reduce her risk, tubal ligation, or OCP may currently be her best chance of primary prevention.

Diagnosis

The correct clinical diagnosis of an ovarian mass is difficult and requires considerable experience and clinical judgment (Table 24.4). Age is a very important factor in assessing an adnexal mass, since many ovarian tumors have a predilection for a particular age group. In premenarchal girls, an adnexal mass is often germ cell in origin, while young women in their reproductive years are most likely to have benign disease. In postmenopausal patients, a complex adnexal mass is particularly concerning for an epithelial cancer, as a normal postmenopausal ovary is atrophic and small ($1.5 \times 1 \times 0.5$ cm) (Table 24.5). These clinical situations will most often result in surgery.

The adnexal mass in the reproductive age woman causes the biggest differential challenge. The differential diagnosis of an adnexal mass/cyst is described in Table 24.4. There are several categories of benign masses, including functional cysts, adenomas, germ cell tumors (mature teratomas), sex cord stromal tumors (fibromas), and endometriosis. A pedunculated fibroid is often interpreted as an adnexal mass. Infectious causes include PID, appendicitis, and diverticulitis. For women in their reproductive years, the decision to pursue surgery will depend on clinical suspicion as detailed above and desire for future fertility.

In some patients there is no distinct adnexal mass but a conglomerate tumor in the lower abdomen. The differential for this includes an advanced ovarian cancer, an advanced endometrial cancer/sarcoma, colon, and retroperitoneal tumors. A metastatic breast, colon, or lung cancer tumor should be considered in the presence of an atypical pattern of metastasis, abnormal mammogram or chest x-ray. While ovarian cancer is much more prevalent in postmenopausal women, the most common cause of an adnexal mass in a postmenopausal patient is still a benign cyst. This is either caused by the hormone imbalance during perimenopause or develops postmenopausally driven by hormones secreted by the postmenopausal ovary. In postmenopausal women, simple unilocular cysts could be monitored but women with solid or complex masses are offered surgery. Depending on the level of suspicion for cancer, surgery may begin with a minimally invasive approach that can be converted to an open procedure if the frozen section suggests a borderline tumor or malignancy.

When formulating a diagnosis, the most important factors to consider are the patient's age, history, clinical exam, serum, and imaging studies. However, the fear of not detecting a malignancy, which could delay diagnosis or lead to inadequate surgery has shaped the clinical response to adnexal masses. The current treatment paradigm is that every postmenopausal woman with a solid adnexal mass should have a surgical exploration to obtain histology.

Given that early-stage ovarian cancer has a much better prognosis than advanced-stage disease, many operations are performed with the goal of “catching” a cancer early. Because only histology can exclude the presence of an ovarian cancer, about 5% to 10% of all women will, sometime during their lifetime, undergo surgery to rule out an ovarian cancer despite the fact that most adnexal masses are benign.

Table 24.4 Differential Diagnosis of an Adnexal Mass

Definition	Description	Mean Age	Clinical Presentation	Imaging	Therapy	Comments
Ectopic pregnancy	Tubal pregnancy, most common in the fimbriated end	Reproductive age women	Positive pregnancy test. History of PID, tubal surgery, fertility treatment or previous ectopic pregnancies. Pelvic pain, anemia	Pelvic ultrasound	Methotrexate or laparoscopy with salpingectomy or salpingostomy, laparotomy if hemodynamically unstable	Clinical emergency. 10%–15% recurrence risk
Physiologic, functional cysts	Follicular cyst—preovulatory cyst Corpus luteum cyst—postovulatory cyst caused by hemorrhage or cyst formation. Theca lutein cysts are caused by hCG stimulation of the ovary. “Other”: paratubal cysts, hydrosalpinx	Reproductive age women	Depending on size, lower abdominal pain, dyspareunia, signs of latent torsion. On exam freely mobile and unilateral. May present as an acute abdomen when ruptured, torsed or infarcted	Pelvic ultrasound. Often > 7cm	Persists for weeks. Oral contraceptives might cause involution/resolution and help with the diagnosis. If a cyst does not resolve within 8 weeks, laparoscopy should be considered	Most frequent benign masses in reproductive age woman. A bleeding corpus luteum can cause an acute abdomen, anemia, and hemoperitoneum. Hydrosalpinx is acystic dilatation of the fallopian tube caused by PID, ectopic pregnancy, endometriosis or fallopian tube cancer
Polycystic ovaries	Endocrine disorder: Multiple follicle cysts enlarging the ovaries to 2–5 their normal size	Reproductive age woman	Irregular menstrual cycles, anovulation, amenorrhea, acne, hirsutism, subfertility, metabolic syndrome	Pelvic ultrasound, hormonal tests (DHEA-S, androstenedione, testosterone, FSH). Glucose-tolerance test	Oral contraceptives, metformin, glitazones, weight loss, clomiphene, spironolactone	Often associated with peripheral insulin resistance. Higher risk of endometrial hyperplasia and endometrial cancer
Serous and mucinous cystadenomas	Serous—Cystic: Thin walled, unilocular. Mucinous – cystic thin walled but may be multicystic		Serous 5–20 cm, mucinous up to 40 cm	Pelvic/abdominal ultrasound	Laparoscopic drainage and removal or laparoscopic cystectomy	May present with torsion or rupture. Cystadenofibroma is a mixed tumor
Germ cell tumors	Benign: Teratomas/Dermoids. Malignant: immature teratoma/dysgerminoma	Young reproductive age patients	Bilateral in 20%	Ultrasound. Might show calcifications on X-ray or CT. Solid, partially cystic	Laparoscopic cystectomy removing the entire capsule. If malignant salpingo-oophorectomy, staging	
Sex cord stromal cell tumors	Benign: Fibromas, Thecomas, Brenner cell tumors Malignant: Granulosa cell tumor, Sertoli-Leydig cell tumor	30–menopause, but also postmenopausal patients	Solid, firm tumors resembling fibroids. May produce hormones: estradiol, inhibin. May cause irregular bleeding, uterine hyperplasia	Ultrasound/CT: Solid homogeneous tumors. Granulosa cell tumors are heterogeneous and often rupture	Laparoscopic or laparotomy for ovarian cystectomy or oophorectomy depending on size	In a postmenopausal patients benign stromal cell tumors are preoperatively often interpreted as being malignant. Often the CA-125 is normal or not too high
Peritoneal inclusion cysts	Cystic	Any age	History of multiple pelvic/abdominal surgeries or recurrent pelvic infections or peritoneal dialysis	Ultrasound: multiple thin walled cysts, CT, MRI	Observation <i>versus</i> ultrasound or CT-guided aspiration with cytology. Surgical intervention for severe symptoms or hydronephrosis. High perioperative morbidity (bowel, ureter injury)	
Fibroids	Benign. Broad ligament or pedunculated fibroids misdiagnosed	30–55 yr	Often asymptomatic. Degeneration or infarction can occur and cause acute pain	Ultrasound, rarely CT or MRI	Observation versus surgical intervention with myomectomy or hysterectomy	Common in African-American women. Often pedunculated fibroids are mistaken for an adnexal mass

Endometriosis	1–10 cm endometriotic cysts filled with blood, adherent to surrounding organs. Often bilateral. Endometriotic implants occur in the pelvic peritoneum including the cul-de-sac and bladder peritoneum. Nodularity of the uterosacral ligaments	30–45 yr	Pelvic pain. Dyspareunia. May have cyclical pain with menses, infertility, and dyspareunia. May present with acute pain from rupture, rarely torsion. CA-125 100–300 U/mL	Pelvic/abdominal ultrasound. Diagnostic laparoscopy	Conservative treatment. Anti-inflammatory drugs, OCP, GnRH analogues. Laparoscopy with removal of endometriotic nodules. Extent of surgery depends on symptoms and desire for future fertility	Common in White nulliparous women. Ovarian endometrioma is also called a “chocolate cyst”
PID/Salpingitis	Tubo-ovarian abscess complicate PID in 15% of all women	Young sexually active patients	History of PID, Pelvic pain, malaise, vaginal discharge, cervical motion tenderness. Fever, leukocytosis, CRP ↑, CA-125: 100–500 U/mL. Coagulopathy if septic	Ultrasound showing one or more masses that are homogenous, cystic, possibly with air fluid levels and septations	Combination antibiotic treatment, CT-guided abscess drainage. Laparoscopy or laparotomy if abscess cannot be drained or if the patient has signs and symptoms of sepsis	High recurrence risk
Appendicitis and appendiceal abscess	Appendicitis right sided tenderness, rebound	Younger patients	Fever, guarding, rebound tenderness. Malaise, RLQ pain, nausea, vomiting, absence of vaginal discharge. Pain migration. leukocytosis, CRP ↑, CA-125–100 U/mL	Ultrasound and CT imaging with contrast. No distinct mass. Features consistent with abscess: enhancement, irregular borders	Laparoscopic surgery.	Difficult differential in children and young woman. Consider PID and pregnancy.
Diverticulitis and diverticular abscess	Diverticulitis mostly in the sigmoid colon causing left sided pain	Elderly patients			Combination antibiotic treatment, CT-guided abscess drainage. Surgery if patient has signs and symptoms of sepsis and for definitive treatment	Presentation in very old patients might be subtle. High recurrence risk
Colon cancer			Anemia, irregular stools. Induration and irregularity. Family history.	Sigmoidoscopy/ colonoscopy		60–70% occur on the left side but cecal cancer can present as right adnexal mass
Early invasive epithelial ovarian cancer	Early serous ovarian cancer, endometrioid or clear cell ovarian cancer		CA-125 ↑ only in 50%	Papillary surface excrescences, areas of necrosis, internal solid elements	Surgical intervention: Consider starting with a laparoscopy to establish a diagnosis. Referral to Gynecologic Oncologist for full staging	Differential of ovarian malignancy: invasive serous cancer, endometrioid, clear cell cancer. Borderline tumors
Advanced invasive epithelial ovarian cancer	Serous carcinoma with ascites and metastasis to upper abdomen	Postmenopausal women	CA-125 ↑ in 80%	Suspicious adnexal mass and ascites, upper abdominal disease	Exploratory laparotomy, staging, tumor debulking. Referral to Gynecologic Oncologist	
Metastasis	Gastric, colon, breast, and uterine cancer		CA-125 can be elevated. Other tumor markers might be helpful (CEA, CA19-9, CA15-3)	Bilateral solid complex masses in patient with prior cancer history	Excision can be considered for symptomatic relief or if it is the only site of metastatic disease	Poor prognosis compared to ovarian cancer
Rare differential diagnoses	– Pelvic kidney – Disseminated abdominal tuberculosis: Young woman unlikely to have ovarian cancer from endemic areas, populations at risk, ascites, CA-125 ↑, absence of a dominant adnexal mass.					

Table 24.5 Age Considerations When Deciding if a Mass is Malignant

History		
Age Pregnancy Menopausal status	Premenarchal	Germ cell tumors, mature teratomas, rhabdomyosarcomas
	Young reproductive age (15–25 yr)	Functional cysts, ectopic pregnancy, PID/salpingitis/TOA, dermoid, appendicitis/appendiceal abscess, polycystic ovaries, juvenile granulosa cell tumor, dysgerminoma, endodermal sinus tumor, tuberculosis
	Middle reproductive age (25–35 yr)	Endometriosis, functional cysts, polycystic ovaries, serous/mucinous cystadenomas, PID/salpingitis/TOA Sertoli-Leydig cell tumor
	Advanced reproductive age (35–45 yr)	Stromal cell tumors, fibroids, peritoneal cysts, adult granulosa cell tumor
	Perimenopausal (46–52 yr)	Functional cysts, fibroids, ovarian cancer, endometrial cancer
	Postmenopausal (<52 yr)	serous/mucinous cystadenomas, ovarian cancer, colon cancer, benign stromal cell tumors, diverticulitis/diverticular abscess, fibroids

Differential Diagnosis

Malignant ascites is most often found in women with ovarian cancer, but patients with metastatic breast, pancreatic, and gastric cancer can also present with ascites. Patients with gastrointestinal malignancies and ascites tend to have concomitant intrahepatic metastasis. Therefore, in patients with extensive ascites and CA-125 values around 200 U/mL, other cancers should be considered. Reviewing patients with ascites who presented to an oncology clinic, Ayantunde (105) found diagnoses to be, ovarian cancer (37%), pancreaticobiliary cancer (21%), gastric cancer (18%), colon cancer (4%), and breast cancer (3%). Nonmalignant causes of ascites include pancreatitis, tuberculosis, hepatitis, systemic lupus erythematosus, cirrhosis, and Meigs Syndrome. A paracentesis will both establish a diagnosis of malignancy, and improve the dyspnea, pain, nausea, and vomiting that the patient may be experiencing as a result of large-volume ascites.

While serous ovarian cancer disseminates extensively within the abdominal cavity, it rarely metastasizes elsewhere. Imaging studies that suggest intra-pulmonary metastasis or intra-parenchymatous metastases in the liver, spleen or kidney especially in the absence of significant intraperitoneal disease, should broaden the differential diagnosis to include a different ovarian cancer histotype (clear cell, mucinous or carcinosarcoma) or a different tumor origin (gastrointestinal, breast cancer). Bilateral ovarian tumors may also be a sign that the ovarian tumors are of metastatic origin. Gastric cancers tend to cause drop metastases to the ovary, referred to as a Krukenberg tumors. Gastrointestinal malignancies can metastasize to the ovary due to its extensive blood supply, and these cancers are important differential diagnoses for women presenting with disseminated intra-abdominal disease on imaging. Indeed, 10% of all colon cancers are metastatic to the ovary and the ovarian tumor is often bigger than the primary colonic tumor. Patients who present with predominantly gastrointestinal symptoms, anemia, a high CEA, low CA-125, and a positive hemocult test should undergo an esophagogastroduodenoscopy (EGD) and a colonoscopy with

biopsies. A CA-125/CEA serum ratio greater than 25 has high discriminative power to differentiate between ovarian and colon cancer (151,152). In patients presenting with colon cancer with peritoneal and ovarian metastasis, the median survival is 10 months.

Ovarian cancer is the most common primary nonbreast second malignancy after treatment for breast cancer. Indeed, a history of breast cancer is associated with a 2- to 4-fold increase in the risk of developing ovarian cancer. However, breast cancer can also metastasize to the ovary, and is the most frequent (84%) primary cause of ovarian metastasis of non-GI origin (153,154). Metastasis of breast cancer to the ovary was found at autopsy in 23% to 39% patients dying of breast cancer.

When evaluating a patient with a history of breast cancer and an adnexal mass to determine if an ovarian mass is a breast cancer metastasis or a new ovarian cancer, the stage and histology of the previous breast disease should be considered. Patients with stage IV breast disease are much more likely to have distant metastasis, and lobular breast cancer metastasizes more often to the ovary than invasive ductal cancers. Most patients with ovarian metastasis from breast cancer are premenopausal (77%) and present with abdominal distension in the absence of ascites. Often these patients have bilateral ovarian involvement (64%) a high CA15-3 and a low CA-125. On the other hand, patients with breast cancer and abdominal carcinomatosis can have a high CA-125, which makes the differentiation from ovarian cancer challenging. On pelvic ultrasound, breast cancer metastases to the ovary are more solid appearing than primary ovarian cancer, which is often multicystic. The benefit of surgery in the treatment of breast cancer metastatic to the ovaries has not been proven, and may be limited to the palliation of symptoms by removing a single mass. Retrospective studies have suggested a possible survival benefit for surgery in patients with no residual disease after the operation, but found no benefit in the setting of widely metastatic disease (155). The 5-year survival for women with ovarian metastasis from breast cancer is 26%, while it is 8% and 1% for those with ovarian metastasis from colorectal and gastric cancer, respectively, much lower than the median survival for primary ovarian cancer (153).

STAGING

The widely used 1988 FIGO staging system for ovarian cancer is presented in Table 24.6. Of note, both paraaortic and inguinal lymph nodes are included in FIGO stage IIIC disease, whereas mesenteric lymph nodes (e.g., nodes in the mesentery of the colon) are considered FIGO stage IV disease. Details of surgical staging are discussed in section “Surgery.”

A slight modification of the FIGO staging for fallopian tube carcinoma, as proposed by Alvarado-Cabrero et al. (156) is presented in Table 24.7. This is similar to staging of ovarian cancer for advanced stages, and emphasizes the importance of tumor invasion into the muscular wall.

SURGERY

Introduction and Definitions

Surgery is a cornerstone of therapy for women with ovarian cancer and plays an important role at every treatment stage. Surgery is usually performed during the initial treatment of patients newly diagnosed with ovarian cancer for the purpose of pathologic diagnosis, cytoreduction, symptom relief, and staging. Indeed the FIGO staging system requires that

Table 24.6 Carcinoma of the Ovary: FIGO Nomenclature (Rio De Janeiro, 1988)

Stage I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact
IC ^a	Tumor either stage IA or IB, but with tumor on surface of one or both ovaries, or with capsule rupture, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC ^a	Tumor either stage IIA or IIB, but with tumor on surface of 1 or both ovaries; or with capsule(s) rupture; or with ascites present containing malignant cells or with positive peritoneal washings
Stage III	Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel or mesentery
IIIB	Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, not exceeding 2 cm in diameter; nodes are negative
IIIC	Peritoneal metastasis beyond the pelvis >2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV

^aIn order to evaluate the impact on prognosis of the different criteria for allotting cases to stage IC or IIC, it would be of value to know if rupture of the capsule was spontaneous or caused by the surgeon, and if the source of malignant cells detected was peritoneal washings or ascites.

surgery be performed to confirm the histologic diagnosis and to determine the true extent of the disease. In the recurrent disease setting, surgical biopsy can confirm a diagnosis and the removal of an isolated mass may render a patient macroscopically tumor-free. In patients with the extensive tumor dissemination typical of advanced disease, removal of tumor masses (“debulking”) accomplishes significant symptom relief from tumors externally pressing on organs in the pelvis or the upper abdomen. Finally, limited surgery may have a role for palliation of bowel obstruction in select patients with recurrent disease.

Because the most important prognostic factors in ovarian cancer are the FIGO stage and the success of debulking surgery, patients with ovarian cancer will benefit from treatment by physicians familiar with the surgical management of this disease.

Table 24.7 Modified FIGO Staging for Fallopian Tube Carcinoma^a

Stage 0	Carcinoma <i>in situ</i> (limited to tubal epithelium ^b)
Stage I	Growth limited to tube
Stage IA	Growth limited to one tube without extension through or onto serosa, ascites containing malignant cells, or positive peritoneal washings
Stage IA-0 ^c	Growth limited to one tube with no extension into lamina propria ^b
Stage IA-1 ^c	Growth limited to one tube with extension into lamina propria ^a but no extension into muscularis
Stage IA-2 ^c	Growth limited to one tube with extension into muscularis
Stage IB	Growth limited to both tubes without extension through or onto serosa, ascites containing malignant cells, or positive peritoneal washings
Stage IB-0 ^c	Growth limited to both tubes with no extension into lamina propria ^b
Stage IB-1 ^c	Growth limited to both tubes with extension into lamina propria ^a , ^b but no extension into muscularis
Stage IB-2 ^c	Growth limited to both tubes with extension into muscularis
Stage IC	Tumor either stage IA or IB but with extension through or onto tubal serosa or with ascites containing malignant cells or with positive peritoneal washings
Stage I(F)	Tumor limited to fimbriated end of tube(s) without invasion of tubal wall
Stage II	Tumor involving one or both fallopian tubes with pelvic extension
Stage IIA	Extension and/or metastasis to uterus and/or ovaries
Stage IIB	Extension to other pelvic tissues
Stage IIC	Tumor either stage IIA or IIB with ascites containing malignant cells or with positive peritoneal washings
Stage III	Tumor involving one or both fallopian tubes with peritoneal implants outside pelvis, including superficial liver metastasis, and/or positive retroperitoneal or inguinal nodes. Tumor limited to pelvis except for histologically proven extension to small bowel or omentum
Stage IIIA	Tumor grossly limited to pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
Stage IIIB	Tumor involving one or both fallopian tubes with grossly visible, histologically confirmed implants of abdominal peritoneal surfaces, none >2 cm in diameter. Lymph nodes are negative
Stage IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both fallopian tubes with distant metastases including parenchymal liver metastases. If pleural effusion is present, fluid must be positive cytologically for malignant cells

^aAs suggested by Alvarado-Cabrero et al. (156).

^bModification in terminology.

^cModifications to accommodate subsets of tumors that otherwise cannot be assigned a stage or to distinguish among subsets that may differ in their associated prognosis.

Table 24.8 Terms for Common Surgical Procedures, as they are used in this Chapter

Procedure	Definition
Paracentesis	Drainage of presumed malignant fluid/ascites in a patient with intra-abdominal tumor masses to establish a diagnosis before initiation of chemotherapy with cytology or to provide symptomatic relief.
Biopsy	Biopsy of disseminated disease or an adnexal mass to establish a pathologic diagnosis before initiation of chemotherapy.
Primary cytoreductive surgery	Initial laparotomy to establish a diagnosis, stage and attempt maximal tumor debulking to microscopic disease before the initiation of first-line chemotherapy. Also called “primary debulking” by some physicians.
Interval cytoreduction or Interval debulking	Cytoreductive surgery after a biopsy only or a primary suboptimal debulking followed by induction chemotherapy.
Second-look surgery	Surgery performed at the completion of primary chemotherapy in patients who do not have evidence of disease by CT scan or CA-125 to determine if there is residual disease in order to plan for additional chemotherapy. Currently rarely performed.
Secondary cytoreductive surgery	Surgery in a patient with recurrent disease who has completed primary treatment, including primary debulking ± chemotherapy, and had been without evidence of disease. The procedure is most commonly performed for platinum-sensitive patients with oligometastatic disease. Also called “primary debulking” by some physicians.
Palliative surgery	Surgery performed to relieve symptoms, most commonly performed for a malignant bowel obstruction with the goal to remove the obstruction or perform a diversion. Not primarily intended to remove tumors.
Complete debulking Result: no macroscopic disease	Complete resection [156]: Cytoreduction of all tumors independent of preoperative tumor load to microscopic residual disease at the completion of surgery – no gross residual tumors left. R0 resection.
Optimal debulking. Result: macroscopic disease up to 1 cm	Minimal residual [156]: Macroscopic disease up to 1 cm in diameter after primary surgery. Also called by some physicians “optimal cytoreduction”. R1 resection.
Sub-optimal debulking. Result: macroscopic disease >1 cm	Gross residual [156]: Primary cytoreduction resulting in macroscopic disease larger than 1 cm in size at the end of surgery. R2 resection.

The terms for common surgical procedures, as they are used in this chapter, are defined in Table 24.8.

Early-Stage Ovarian Cancer

In current clinical practice, optimal staging in early ovarian cancer includes careful inspection, palpation, and biopsies of peritoneal surfaces (diaphragm, paracolic gutters, bladder and cul-de-sac peritoneum), pelvic and diaphragmatic washings,

removal of the affected ovary, an infracolic or infragastric omentectomy, and a systematic pelvic and paraaortic lymph node dissection (157). An appendectomy can, though rarely, change the final staging (158). Preserving the contralateral ovary and the uterus in young patients desiring fertility is considered acceptable in the treatment of early-stage epithelial ovarian cancer.

The thorough surgical staging of early-stage ovarian cancer is important to establish the correct stage for determining prognosis and choice of therapy (chemotherapy vs. observation). A prospective randomized trial of patients with FIGO stage I-IIA disease (ACTION trial: (159,160)) indicated that complete surgical staging was statistically significantly associated with better outcomes. In this trial, patients were randomly assigned to adjuvant chemotherapy or observation after they had undergone either complete or incomplete staging surgery. Although the trial was not designed to compare different surgical staging procedures (and extent of surgical staging was not randomized), a subgroup analysis found that patients with a poorly differentiated tumor in the optimally surgically staged group (n=78) had a significantly longer ($p<0.009$) 10-year cancer-specific survival of 85% compared to 56% in patients who were not completely staged (n=78) which is logically attributable to their higher risk of undetected residual disease. This improved outcome was independent of age, presumed stage, histology and whether or not chemotherapy was given (160). The benefit of adjuvant chemotherapy was found to be restricted to patients with incomplete surgical staging, and incompletely staged patients with a poorly differentiated grade III tumor were found to derive the greatest benefit from adjuvant chemotherapy. Predictors of unappreciated residual disease after primary surgery, which leads to upstaging, include a high preoperative CA-125 level, positive cytology, and grade III disease (158).

The surgical approach to staging of early ovarian cancer will depend on patient comorbidities and the number of previous abdominal surgeries, as well as on the minimally invasive surgery training and skills of the surgeon. Retrospective studies suggest that both a minimally invasive approach and an open laparotomy allow for comprehensive surgical staging. Lymph node counts and the size of the omental specimen obtained are similar for both procedures. Given that bulky disease is only rarely detected in early-stage ovarian cancer patients, a minimally invasive surgical approach, which tends to involve more time in the operating room, but less blood loss and a shorter hospital stay than open surgery (161). A concern with laparoscopy is the possibility of port site metastasis, although this risk seems to be small (>1%) and such metastases are often a sign of disseminated intra-abdominal disease (162). Open surgery may have benefits including shorter operating room time, less advanced equipment, and less requirement for specialized surgical training. In early ovarian cancer, restaging involves multiple biopsies of the abdominal and pelvic peritoneum, as well as an oophorectomy, omentectomy, pelvic and paraaortic lymph node dissection, and pelvic and diaphragmatic washings for cytology. Patients who do not want to preserve fertility will have a hysterectomy and removal of the contralateral ovary.

In conclusion, in most cases unstaged patients with presumed early-stage ovarian cancer should be restaged or given adjuvant chemotherapy if staging is not feasible.

Role of Lymph Node Dissection in Early Ovarian Cancer

When treating both early and advanced ovarian cancer, a surgeon must decide whether to perform a lymph node sampling, limited to the removal of enlarged or palpably suspicious lymph nodes or a systematic lymph node dissection, removing

all visible lymph nodes within defined anatomic borders (113). Dye studies have shown that the lymphatic drainage of the ovaries originates under the ovarian surface. Lymph fluid drains predominantly superiorly, along both ovarian vascular pedicles (163,164). On the left side the lymphatics follow the infundibulopelvic vein until it drains into the left renal vein. The high left infrarenal, paraaortic lymph nodes often harbor lymph node metastasis and are a known site of (isolated) recurrence. The right infundibulopelvic vein and its accompanying lymphatics reach the inferior vena cava about 1 cm below the right renal vein. Cancer cells are then able to continue traveling along a net of lymphatic vessels covering the inferior vena cava and the interaortocaval space to lymph nodes at the base of the celiac axis, and then through the caval opening in the diaphragm into the chest reaching mediastinal or prescalene lymph nodes. Secondary lymph drainage routes are along lymphatics draining inferiorly through the utero-ovarian ligament to lymph nodes in the broad ligament, and along the external iliac artery to the round ligament to inguinal lymph nodes. This spread pattern explains why one sometime detects inguinal lymph node metastasis in patients with ovarian cancer. Minor lymph drainage is also to lymphatics along the internal iliac artery or lymph nodes in the obturator fossa (163,164). Ovarian lymph drainage does not reach the uterus, possibly explaining why one rarely sees intrauterine or cervical metastasis in serous ovarian cancer.

In patients with early ovarian cancer, it is recommended that both the pelvic and paraaortic lymph nodes should be removed when a systematic lymph node dissection is performed. However, given the lymphatic drainage of the ovaries, the removal of high paraaortic lymph nodes is the most important (116). The anatomic borders of a pelvic lymph node dissection are laterally, the external iliac artery and the genitofemoral nerve that travels on the psoas muscle; superiorly, the bifurcation of the external and internal iliac artery to the inguinal ligament; and medially, the anterior division of the hypogastric artery and the ureter (Fig. 24.12). After elevating the external iliac vein, the obturator fossa and the obturator nerve are exposed and then cleared of lymph nodes superior to the nerve. To enable the right paraaortic lymph node dissection the descending colon and terminal ileum are mobilized by incising the peritoneum

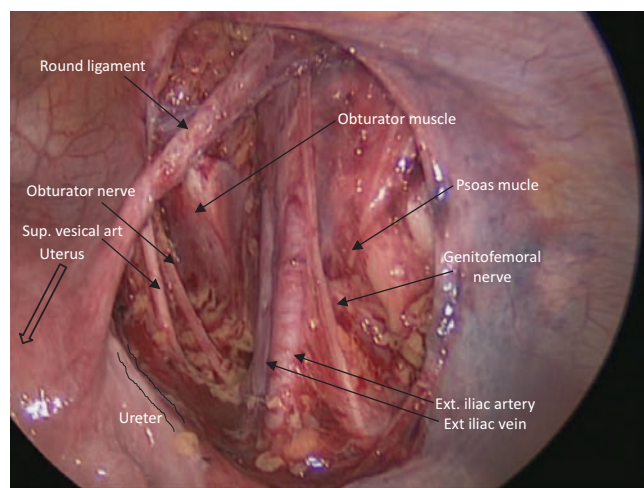


FIGURE 24.12. View into the right pelvis after a laparoscopic pelvic lymph node staging. The borders of a pelvic lymph node dissection are lateral the genitofemoral nerve, medial the superior vesical artery, posterior the obturator nerve, and superior the bifurcation of the external and internal iliac artery. In this specific patient 13 pelvic lymph nodes were removed from this side.

around the cecum to expose the inferior vena cava and interaortocaval space. Starting the dissection on the right common iliac artery, the precaval fatty tissue containing lymph nodes is removed from the common iliac artery up to the right renal vein, taking great care not to injure the ureter, renal vessels, and duodenum. To remove the left paraaortic lymph nodes, the fat/lymph node containing tissue lateral to the aorta between the bifurcation of the left common iliac artery and the left renal vein is removed. Although it is rarely necessary, the inferior mesenteric artery can be ligated to accomplish a high paraaortic dissection. Because the lymph nodes rest on top of the lumbar vertebral bodies great care must be taken not to injure the lumbar veins. Other complications of the surgery include vascular and ureteral injuries and lymphocele formation. Some authors recommend a more extensive lymph node dissection behind the vessels and posterior to the obturator nerve (28), but there is little evidence that this more extensive dissection is of diagnostic or therapeutic benefit.

Several retrospective studies have indicated that the rate of positive lymph nodes in patients, of all FIGO stages, who undergo a systematic pelvic and paraaortic lymph node dissection is 25% to 53%, with most of the positive lymph nodes found in the high paraaortic and interaortocaval regions (114–117). Because imaging and intraoperative palpation of lymph node beds have a low sensitivity and specificity for the detection of lymph node metastasis, several studies have investigated the role of a systematic pelvic and paraaortic lymph node dissection. In a prospective trial, Maggioni and colleagues randomized 310 patients with early, FIGO stage I and II ovarian cancer who had undergone optimal surgical debulking to receive either a systematic lymph node dissection or lymph node sampling (118). Patients with all major histologic subtypes were represented in the study: serous (39%), endometrioid (21%), mucinous (13%), and clear cell tumors (13%). Positive lymph nodes (which upstage a patient to stage IIIC) were found in 9% of patients in the sampling group, and in 22% of the systematic lymph node dissection group ($p < 0.05$), suggesting that 13% were upstaged because of the lymph node dissection. Of all patients in the study with negative lymph nodes, 66% of the patients in the control arm and 51% in the systematic lymphadenectomy arm received chemotherapy ($p < 0.03$), suggesting that in an unstaged patient, physicians tend to err on the side of over-treatment. The patients in the systematic lymph node dissection arm spent an average of 90 minutes longer in surgery, lost 300 mL more blood, and received significantly more blood transfusions (22% vs. 36%, $p < 0.05$). Both groups had similar rates of postoperative complications. There was no difference in progression-free survival (PFS) or overall survival (OS) between the 2 groups, but the study was underpowered for the detection of a small benefit.

Of note, patients with initial clinical stage I/II ovarian cancer upstaged to FIGO stage IIIC disease only by retroperitoneal lymph node involvement have much better 5-year PFS and OS than stage IIIC patients with intraperitoneal disease (165). Review of the large GOG #182 trial analyzed patients who underwent cytoreduction to microscopic disease. The median PFS was 21 months for patients with positive lymph nodes and intraperitoneal disease greater than 2 cm before surgery, 29 months with negative lymph nodes and disease greater than 2 cm, and 48 months for patients who had positive lymph nodes but preoperative intraperitoneal disease less than 2 cm (166). The rate of positive lymph nodes is very low in mucinous ovarian cancer. A lymph node dissection probably can be omitted in these cancers (114,167).

In summary, systematic lymph node dissection provides important prognostic and staging information for patients with suspected early-stage ovarian cancer, which assists with decisions about adjuvant chemotherapy.

Advanced Epithelial Ovarian Cancer

Rationale for Surgical Debulking in Advanced Ovarian Cancer

Surgical debulking is central to the initial management of advanced FIGO stage III/IV ovarian cancer, and extent of residual disease after surgery is the only prognostic factor under the control of the operating surgeon. The concept of removing widely disseminated tumors within the abdominal cavity is specific to epithelial ovarian/fallopian/peritoneal, and appendiceal cancers. It is very unusual to attempt tumor debulking in patients with metastatic colon, breast, or gastric cancer. One reason that the surgical debulking of ovarian cancer is technically feasible is that serous ovarian cancer is usually confined within the peritoneal borders of the abdominal cavity. It spreads along the peritoneal, diaphragmatic surfaces without deep invasion (16) into abdominal organs, and this allows dissection along a surgical plane between an organ and the attached tumor. For example, while the omental tumor is very large and often densely attached to the transverse colon, it is rarely necessary to perform a transverse colon resection and it is almost always possible to sharply dissect the tumor off without injuring the colon muscularis (Fig. 24.11). The omental tumor often reaches the splenic hilum and distal pancreas but rarely invades these organs. While ovarian tumors can occlude the pelvis completely and transform the pelvic peritoneum into thick tumor plaques, the pelvis can usually be completely cleared of tumors with a modified posterior exenteration (97). Serous ovarian cancer tumors never extend via direct invasion beyond the lining of the peritoneal surfaces, and a retroperitoneal dissection allows the entire tumor-covered peritoneal reflection to be removed (Figs. 24.13 and 24.14). In contrast, colon and

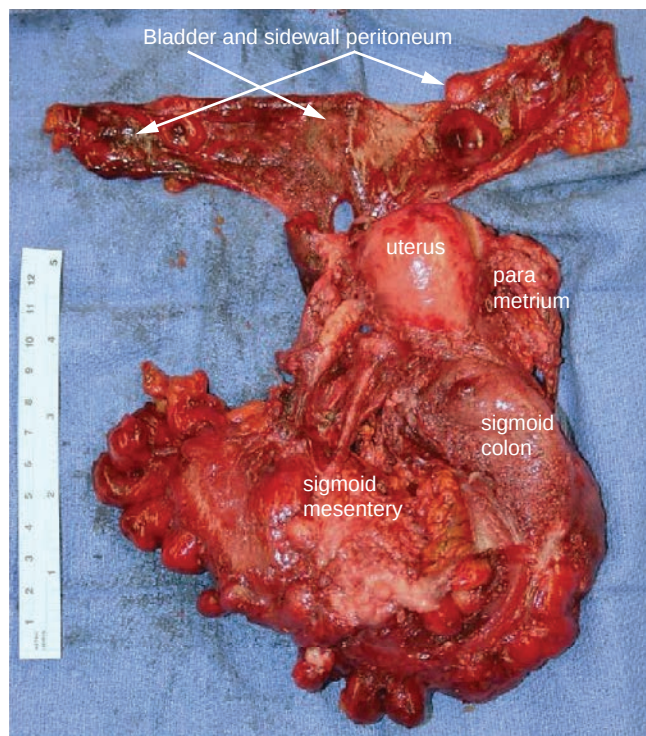


FIGURE 24.13. Specimen from a modified posterior pelvic exenteration. *En bloc* resection of sigmoid colon and its mesentery, uterus, parametrium, and tumor-covered pelvic peritoneum (cul-de-sac, pelvic sidewall, bladder).

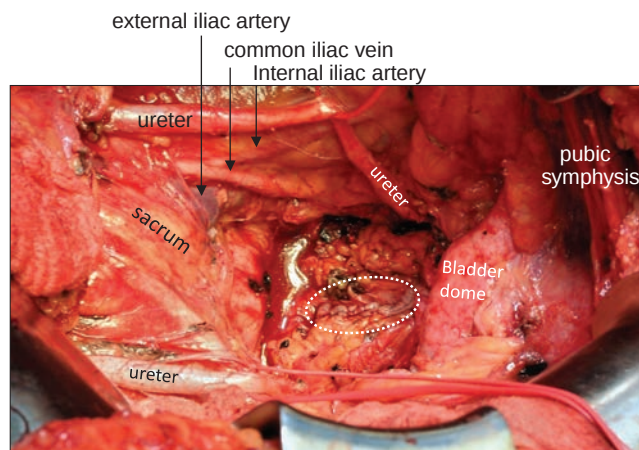


FIGURE 24.14. Pelvic floor after a modified posterior exenteration with *en bloc* resection of bilateral ovarian tumors, tubes, sigmoid colon, uterus, and pelvic peritoneum including the cul-de-sac and pelvic sidewall peritoneum, as well as the inferior bladder peritoneum. Red vessel loops are on both ureters. The stapled rectum is outlined with a white circle. View prior to primary end-to-end stapled anastomosis.

breast cancers often grow retroperitoneally, making a complete resection much more challenging.

Several theories have been put forward to explain the strong association of surgical debulking with patient survival. Large bulky tumors may contain necrotic or hypoxic areas that have a low growth fraction and are resistant to chemotherapy. Optimal debulking could then theoretically drive remaining microscopic cells into the cell cycle and into becoming more susceptible to cytotoxic chemotherapy. Smaller postoperative tumor volume may decrease the chance of acquiring more mutations which promote chemoresistance.

In a patient who has an incidentally discovered “low tumor volume” ovarian cancer after an oophorectomy or a “simple” TAH/BSO, restaging (reoperation to accomplish complete surgical staging) and debulking is almost always recommended to evaluate the true extent of the disease and determine whether it is advisable to withhold chemotherapy.

In advanced “high tumor volume” ovarian cancer staging takes place as part of the initial debulking surgery, with the goal of removing all visible disease and, possibly, implanting a port for intraperitoneal chemotherapy (122). In patients with extensive tumor dissemination combined with a chronic bowel obstruction the cancer leads to tumor associated cachexia with a catabolic metabolic status causing adverse metabolic consequences and limiting the patient’s ability to maintain a reasonable nutritional status. In patients with extensive tumor dissemination, removal of tumor masses (“debulking”) accomplishes significant symptom relief from tumors externally pressing on organs in the pelvis or the upper abdomen. Surgical tumor debulking will also reduce ascites production and improve the nutritional and functional status of the patient, resulting in a higher quality of life and improved immunocompetence.

Overall, there is no uniform surgical approach to the treatment of advanced ovarian cancer. Patient (age, nutritional status, comorbidities) and intraoperative factors (disease location, adhesions from previous surgeries, intraoperative stability/anesthesia, blood loss) will determine the extent of surgical resection in the individual patient. It requires significant surgical training and experience to successfully remove pelvic and upper abdominal disease with a low complication rate. In Europe a gynecologist generally collaborates closely with a general surgeon who usually performs the bowel resections and upper

abdominal debulking (e.g., diaphragm stripping, splenectomy). In North America, the majority of debulking, including gastrointestinal procedures, is performed by a gynecologic oncologist with the consultation of a hepatobiliary surgeon should extensive mobilization of the liver or a liver resection be necessary. While the comparative efficacy of these 2 approaches has never been studied, studies on both sides of the Atlantic have shown that high volume centers have a higher rate of optimal surgical debulking in advanced ovarian cancer. The resectability of extensive disease with acceptable morbidity is likely to reflect a combination of surgical experience, technique, anesthesia care, critical and postoperative care, and nursing. Optimal debulking rates of up to 70% to 80% have been reported in various centers (103,104,168,169) but 50% is an accepted quality measure (157). Several centers have shown that a dedicated surgical team and a multidisciplinary effort can improve a program's complete and optimal cytoreduction rates over time. Size and tumor distribution at the beginning and end of surgery should be carefully documented in the operative report in order to define the 2 most important prognostic factors (stage and residual disease).

While surgical debulking plays a very important role in the management of ovarian cancer, patients with very extensive carcinomatosis and extensive upper abdominal disease and/or mesenteric involvement tend to obtain limited benefit from primary debulking procedures as many will be suboptimally debulked. Surgery alone is never curative in advanced cancer, and therefore should only be attempted as part of a treatment concept including postoperative chemotherapy. As discussed below, it is not possible to predict with high accuracy the patients who can be optimally debulked. Neither CT nor PET has a high enough specificity, to predict which patients can be optimally debulked (144), and sometimes only the direct visualization of tumor distribution by laparoscopy provides the necessary information. Moreover, heroic attempts to remove unresectable tumors will not benefit patients.

The characterization of surgical outcome based on the amount of residual disease at the end of surgery is an accepted measure of surgical success, with the caveat that tumor measurements have a high degree of interobserver variability (170).

While many surgeons had previously recommended a maximal debulking effort for patients with advanced ovarian cancer (e.g., Meigs 1934), it was a retrospective study by Griffiths (171) in 1975 that showed an inverse relationship between residual tumor size and survival. Primary surgery, which attempts maximal tumor debulking has never been subjected to a rigorous randomized trial. However, several retrospective studies and meta-analyses have reported the prognostic value of residual disease for both PFS and OS (90,106,107,120,168,172–174). In 1992, Hoskins and colleagues (173,174) reviewed survival and surgical results in 2 GOG studies which enrolled patients with FIGO stage III and IV disease (GOG 52, 97). Defining 3 different groups (microscopic vs. <2 cm vs. >2 cm residual disease), the authors found that survival is inversely related to the volume of residual disease at the end of surgery. At least as important was their finding that, in patients with residual disease greater than 2 cm, size of residual disease was not correlated with survival.

In the largest (4312 women) phase III ovarian cancer trial ever performed to date (GOG 182), the Gynecological Cancer InterGroup studied the addition of a third chemotherapy group to the standard carboplatin and taxol regimen in stage III/IV cancer (395). While the addition of a third drug did not show any benefit, the extent of cytoreductive surgery was significantly correlated with PFS and OS. Patients with FIGO stage III and IV who had no macroscopic disease at the end of surgery, minimal residual (<1 cm), or gross residual disease had a median PFS of 29, 16, and 13 months, respectively, and a median OS of 68,

44, 30 months, respectively. Breakdown by stage is shown in Figure 24.15.

The improved survival seen with benefit of complete tumor resection also applies to the subgroup of patients with FIGO stage IV disease. Winter, reviewing the experience of the GOG #111, #132, #152, #162, showed that patients with residual disease greater than 5 cm, multiple stage IV defining sites of metastasis (parenchymal liver disease, pleural effusion), and clear cell/mucinous ovarian cancer had a significantly worse survival (106) (Fig. 24.16). The median PFS and OS for stage IV patients whose tumor was reduced to microscopic disease was better than that for patients with any amount of residual disease. Patients with residual disease of 0.1 to 1.0 cm and 1.1 to 5.0 cm had comparable survival, and patients with residual tumor bigger than 5 cm had the worst prognosis. These data have been interpreted to suggest that, even in patients with FIGO stage IV disease, cytoreduction to microscopic disease should be the primary goal at initial surgery. A positive association of largest residual disease with survival was confirmed upon review of 3 prospective phase III AGO trials (AGO-OVAR #3, #5, #7) (107).

An important question is whether every patient benefits from surgical debulking independent of the extent of disease at the beginning of surgery. In GOG #52, patients with a large-volume disease at the beginning of surgery, who were optimally debulked using an aggressive upper abdominal procedure still had a worse survival than patients who had low-volume disease to begin with, even if the surgical outcome was similar (174). On the other hand, in a Mayo clinic review of 194 patients with stage IIIC ovarian cancer, those who required aggressive surgical procedures to achieve an optimal debulking result had a disease-specific 5-year OS similar (46% vs. 47%; $p = 0.8$) to that of patients who underwent less aggressive surgical resections to achieve an optimal result (104). Du Bois and colleagues, summarizing the AGO experience from 3 prospective phase III trials (AGO-OVAR #3, #5, #7) with identical inclusion criteria, concluded that complete surgical debulking improves prognosis in any FIGO substage but cannot completely overcome the prognostic impact of preoperative disease load (120). In summary, both the preoperative tumor burden, including the extent of upper abdominal disease, and the amount of surgical resection and subsequent residual disease appear to influence the PFS and OS of patients with advanced ovarian cancer.

Consistent with the smaller studies discussed above, Bristow and colleagues (168) confirmed, in a meta-analysis of 81 studies, that survival is associated with the amount of residual disease, with a median OS of 22.7 months for patient cohorts with 25% or less maximum cytoreduction and 33.9 months for patient cohorts with 75% or greater rates of maximal cytoreduction. Each 10% increase in the proportion of patients who had undergone maximal cytoreduction was associated with a 5.5% increase in median cohort survival time. In summary, complete resection of all visible tumors at primary debulking surgery is, together with disease stage, the most important independent prognostic factor in epithelial ovarian cancer. Therefore, the goal of cytoreductive surgery for patients with advanced-stage FIGO III/IV ovarian cancer should be, whenever feasible, the complete cytoreduction of all visible disease.

The demonstration of improved outcome with radical debulking suggests that patients should be counseled regarding this option. However, it is important to remember that while we justify surgical debulking because it provides symptom relief and it has been shown, in numerous retrospective reviews, to be associated with improved survival, the clinical benefits of radical surgery in ovarian cancer have never been studied in a prospective randomized trial.

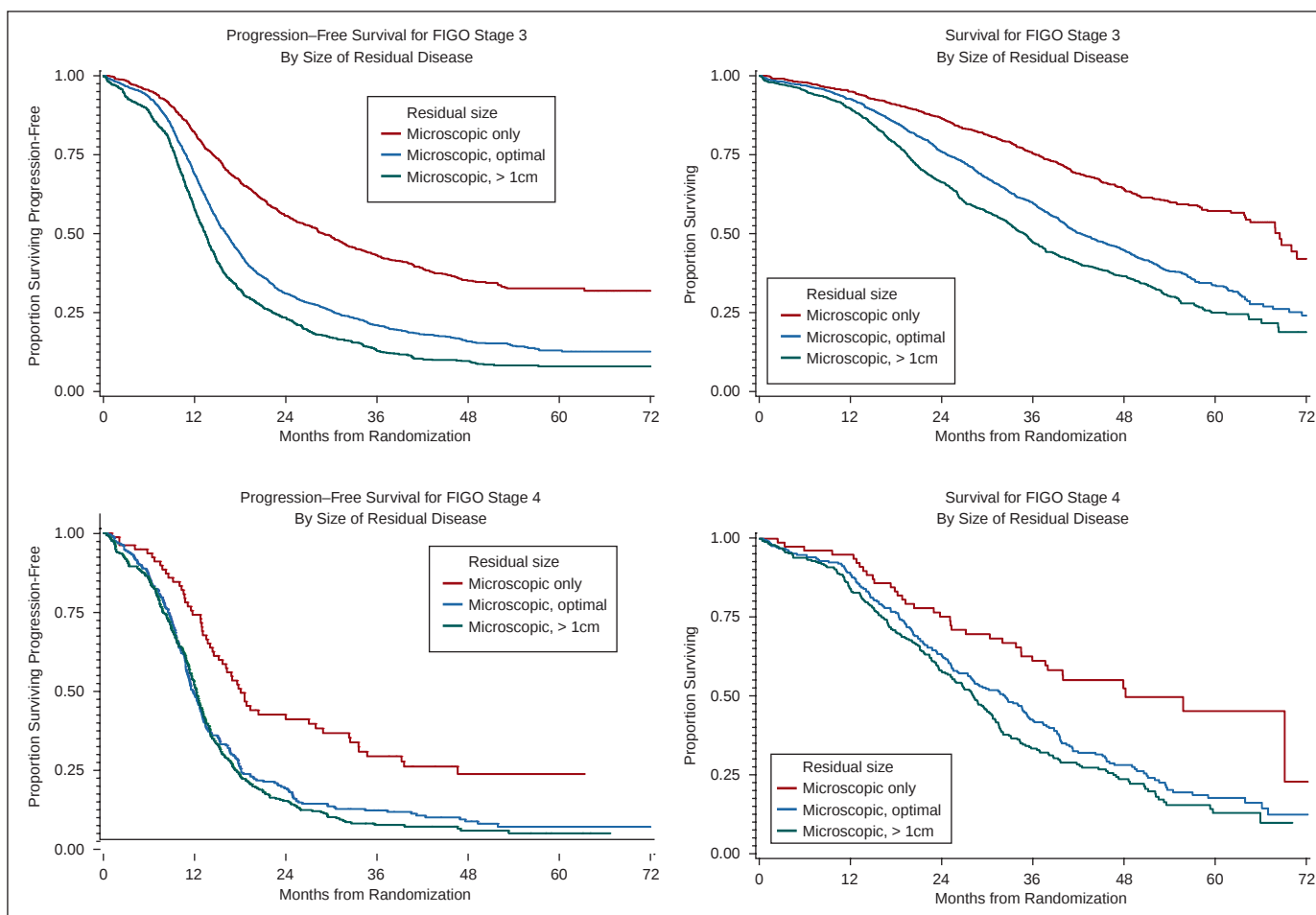


FIGURE 24.15. Outcomes by residual disease in GOG #182. Figure courtesy of Drs Bookman, Brady, and Lengyel of the Gynecologic Oncology Group.

Surgical Debulking—Pelvic and Upper Abdominal Procedures

The surgery of patients with advanced ovarian cancer should start with a vertical midline incision from the pubic symphysis to above the umbilicus. This allows visualization of the entire abdominal cavity, including the diaphragms and permits the safe resection of upper abdominal disease. With a careful exploration of the abdominal cavity the surgeon will be able to evaluate the extent of the disease. Particularly careful attention should be paid to the upper abdomen, since the disease distribution in that region will often determine if a patient can be optimally debulked. It is almost always possible to completely remove even the most extensive disease in the pelvis (97). Pelvic and diaphragmatic washings and biopsies of suspicious peritoneal surfaces (e.g., paracolic gutters) should be performed. Patients with advanced ovarian cancer but low-volume disease should have comprehensive staging including a total abdominal hysterectomy, bilateral-salpingo-oophorectomy, and infragastric omentectomy between the hepatic flexure and the splenic hilum. If the patient can be rendered macroscopically disease-free a pelvic and high paraaortic lymph node dissection is reasonable (116), but this procedure remains controversial (see below).

Patients with advanced ovarian cancer and high volume disease usually have extensive tumor burden in the pelvis with encasement of the reproductive organs and sigmoid colon (Fig. 24.10). This requires a modified posterior exenteration,

an *en bloc* resection of the tumor-studded bladder, peritoneum, uterus, sigmoid colon, and proximal rectum, as well as ovarian/fallopian tube masses, cul-de-sac tumors, and possibly the appendix (Figs. 24.13 and 24.14). Low colorectal anastomosis (97), a procedure some gynecologic oncologists call a modified posterior exenteration, should follow; a colostomy is rarely required in patients with serous cancers. Performing a rectosigmoid colectomy as part of the pelvic debulking is often the only option if complete cytoreduction is to be achieved, and is a superior alternative to peritoneal stripping (98). The possible complications of an extensive radical pelvic dissection include pelvic abscess, sepsis, and an anastomotic leak. Patients with serous ovarian cancer who require a modified posterior exenteration often require one or more upper abdominal procedures as well (e.g., a splenectomy, diaphragm peritonectomy/resection, liver resection, and dissection of the porta hepatis) if a complete surgical debulking is to be accomplished (101–104).

The decision to perform extensive upper abdominal surgery often depends on the philosophy of the surgeon in regard to the specific value of upper abdominal surgery and the general value of debulking surgery for ovarian cancer. Centers that are very aggressive surgically report that they perform at least 1 extensive upper abdominal procedure in about 50% of FIGO stage IIIC ovarian cancer cases, as part of their attempt to render as many patients as possible tumor free. This may include a splenectomy with or without a distal pancreatectomy,

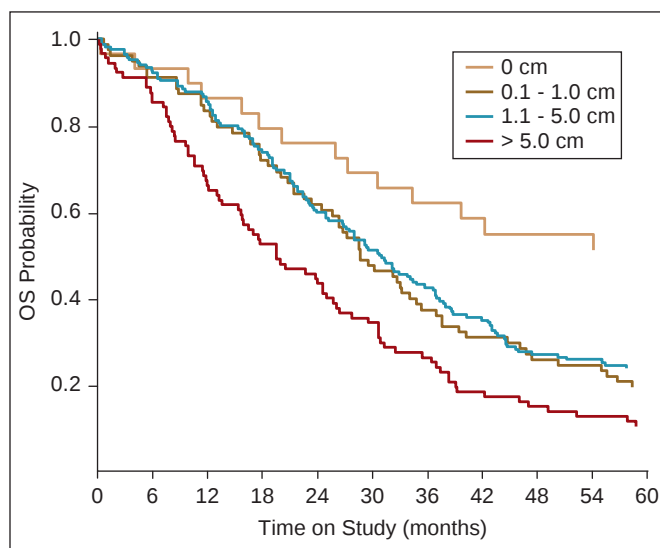


FIGURE 24.16. Kaplan-Meier estimate of overall survival (OS) by residual tumor size in patients with FIGO stage IV disease.

Source: Reprinted with permission from Winter WE 3rd, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2008;26:83–89.

diaphragm peritonectomy/resection, liver resection, and dissection of the porta hepatis (101–104). Still, extensive involvement of the upper abdomen with disease may preclude an optimal debulking.

Magtibay and colleagues reported on 112 patients operated at the Mayo clinic who underwent a splenectomy as part of the ovarian cancer debulking effort (175). The most common indication was metastatic involvement (46%), perisplenic involvement from an omental tumor that reached the splenic hilum (42%), and intraoperative trauma (13%). In this large series complications included wound infections (6%), postoperative pneumonitis (4.5%), thromboembolic events (8%), and sepsis (4.5%). The overall perioperative mortality was 5%. Patients undergoing splenectomy should be vaccinated 2 weeks before or after surgery to reduce the risk of overwhelming postsplenectomy infection that can develop into septic shock. Pneumococcal, hemophilus B, and meningococcal vaccinations are recommended.

Role of Lymph Node Dissection in Advanced Ovarian Cancer Surgery

A prospective randomized Italian trial of 427 patients with advanced ovarian cancer (stages IIIB–IV) compared an extensive systematic lymph node dissection with resection of enlarged (“bulky”) lymph nodes and concluded that positive lymph nodes are a negative prognostic marker but that systematic lymph node dissection did not contribute to the benefit of optimal tumor debulking. Systematic lymph node dissection improved PFS (median PFS, 22 vs. 29 months), but not OS (median OS, 59 vs. 56 months) (116). The addition of systematic lymph node dissection resulted in a greater blood loss, more transfusions, and added operative time. The perioperative and late morbidity of a systematic lymph node dissection was 28%, while it was 18% in the control arm. Most of the morbidity was caused by lymphocyst formation and lymphedema. Therefore, even in experienced hands a systematic lymph node dissection carries significant morbidity, which should be factored into decision making. The study took over 12 years to recruit patients from 13 centers and 63% had residual tumor at the end of surgery.

However, it is worth noting that 63% of the patients in the study had residual tumor after their debulking surgery. The German AGO retrospectively reviewed data (AGO-OVAR #3,5,7) from 3 large phase III trials, which studied chemotherapy in advanced epithelial ovarian cancer (117). They found that in the subgroup of patients with no residual disease and no enlarged lymph nodes, a systematic lymph node dissection was associated with a significant survival benefit (median OS, 108 vs. 83 months) (Fig. 24.17) (117).

At this time, however, there is no convincing data that lymph node dissection has a therapeutic survival benefit in advanced ovarian cancer. The current literature suggests that in advanced ovarian cancer, enlarged/suspicious lymph nodes should be removed as part of tumor debulking, and that a systematic pelvic and paraaortic lymph node dissection might therapeutically benefit patients who previously had been optimally debulked to microscopic residual disease. The results of an ongoing large international phase III trial in patients with advanced ovarian cancer who were debulked to microscopic disease and randomized to a systematic lymph node dissection or sampling, should be able to clarify the role of a lymph node dissection.

Neo-Adjuvant Chemotherapy

The EORTC-GCG and NCIC performed a phase III trial randomizing 718 patients with FIGO IIIC or IV ovarian cancer to neo-adjuvant platinum-containing chemotherapy, followed by interval debulking or primary debulking surgery, followed by platinum-based chemotherapy (152). The largest residual tumor was less than 1 cm in 80% of patients treated with the neo-adjuvant approach while this was only accomplished in 42% of all patients with upfront debulking. There was a trend towards less blood loss, and fewer postoperative infections and thromboembolic complications in the neo-adjuvant treatment group and the patients undergoing neo-adjuvant chemotherapy had a shorter operative time. Most importantly, there was no difference in PFS and OS between the 2 groups, and this was independent of the rate of optimal debulking accomplished in a specific center (Figure 24.18). This study started a heated discussion on the role of neo-adjuvant chemotherapy and the best timing of radical debulking in the upfront treatment of ovarian cancer (176,177). The study was criticized for its low PFS and OS results, but most patients had an adverse prognosis to begin

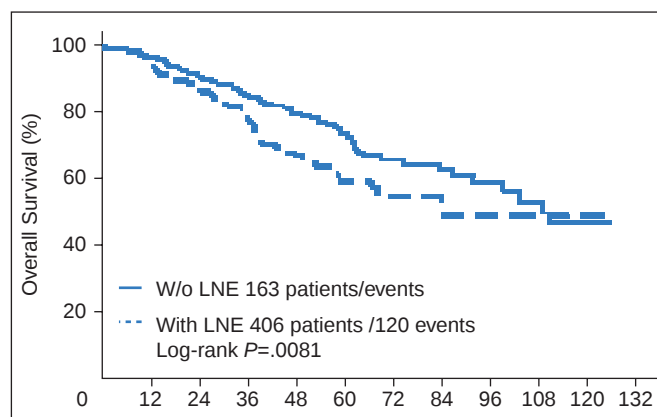


FIGURE 24.17. OS after lymphadenectomy (LNE) or no LNE in patients with no gross residual tumor and without preoperative/intraoperative clinically suspect lymph nodes.

Source: Reprinted with permission from du Bois A, Reuss A, Harter P, et al. Potential role of lymphadenectomy in advanced ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase III multicenter trials. *J Clin Oncol.* 2010;28:1733–1739.

with: 74% had tumors larger greater than 5 cm (61% >10 cm) in size, indicating that study participants had widely metastatic, very advanced disease. Another criticism was the low rate of optimal debulking. There are no preoperative factors or imaging studies (144) that could be used to predict the success of interval cytoreduction. In patients with extensive tumor burden, ascites, and several comorbidities, neo-adjuvant chemotherapy is a very reasonable choice, while a healthier younger patient with disease that appears resectable should be offered initial surgery with the goal to accomplish a complete tumor debulking with no visible residual disease.

Summary of Primary Debulking Surgery for Ovarian Cancer

Many factors contribute to how long a given patient with advanced ovarian cancer survives. Inherent genetic characteristics of the tumor may play a more important role in overall survival than stage or cytoreductive surgical debulking. However, the study of genetic factors in relation to surgical treatment is in its infancy. At present, the degree of surgical debulking is the only prognostic factor that can be influenced by the surgeon, and we know that among patients with advanced-stage III/IV ovarian cancer, a woman who has undergone a complete debulking has the most favorable prognosis. Whether a complete resection is performed is, at least in part, determined by the surgeon's skill and willingness to engage in a maximal surgical effort. Once the decision has been made to proceed, the goal of every surgery in patients with advanced-stage III/IV ovarian cancer should be a complete resection of all visible tumors.

However, ultraradical surgery, involving the addition of upper abdominal procedures to pelvic tumor debulking, will increase morbidity and not every patient is a good candidate for such an aggressive approach (178). Large-volume involvement of the upper abdomen, extended small and large bowel surface and mesentery involvement, and multiple liver metastases, will preclude an optimal debulking. Wright and colleagues, reviewing a

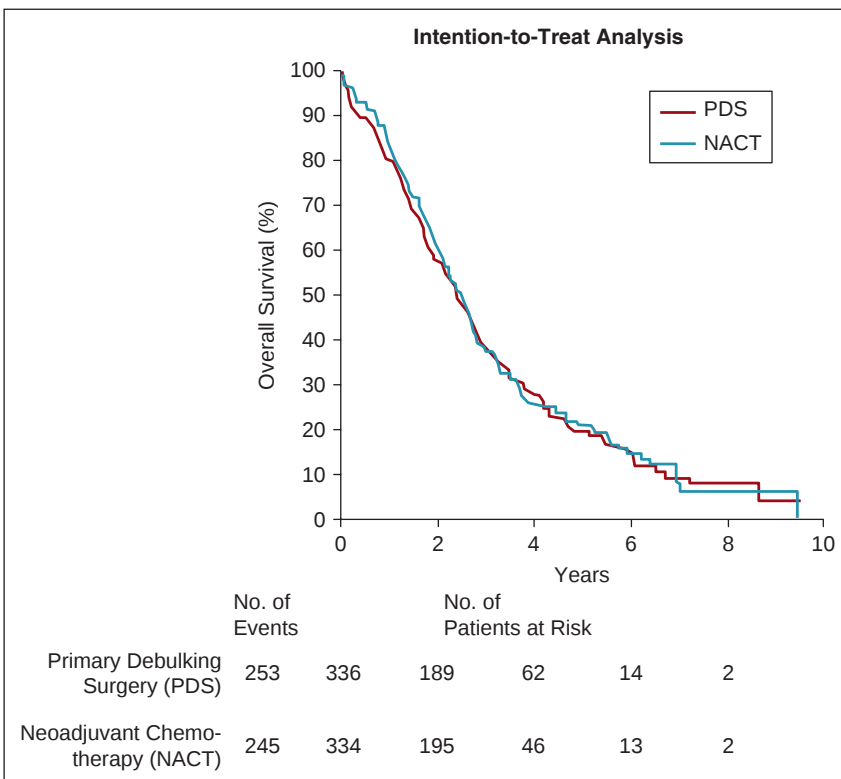
large administrative database with over 28,000 patients, showed that the complication rate of extensive ovarian cancer debulking increases with age. Women younger than 50 years, 70 to 80 years, and those older than 80 years have a 17.1%, 29.7%, and 31.5%, complication rate respectively (178).

Two groups of factors will contribute to the decision to take a patient to surgery and perform a radical debulking procedure (146): (a) A careful preoperative evaluation of patient-related risk factors: Patients with significant comorbidities and low performance status (American Society of Anesthesiology [ASA] preoperative scores 3 or 4, poor nutritional status, low albumin < 3 g/dL) have a low likelihood of optimal debulking to microscopic disease and are at risk of significant peri- and postoperative morbidity; (b) A critical evaluation of the extent of disease with particular attention to upper abdominal tumor burden, ascites, and upper abdominal tumor distribution. Patients with 1 or more of these risk factors often have a prolonged postoperative recovery, since they have limited ability to withstand a long operation. Furthermore, once a complication occurs, the patient may not receive chemotherapy, and is more likely to succumb to disease within 3-months (146,179). For these patients, neo-adjuvant chemotherapy is a well-studied alternative to a debulking surgery that has a similar outcome (Fig. 24.18) and less morbidity (152). Sometimes it is not possible to preoperatively decide if radical debulking surgery is feasible because of the limited ability of CT scans to predict success (144). In these difficult cases a laparoscopy or mini-laparotomy will give a better impression of disease extent than any imaging modality, and should be performed with the plan to forego a more extensive surgery if extensive disease is found. In one small prospective study, a laparoscopic procedure was able to predict whether optimal debulking was possibly in 96% of patients (180).

In summary, the extent of surgical cytoreduction in patients with advanced ovarian cancer and multiple comorbidities should be determined for every patient individually. If in doubt, and until more data becomes available, it is reasonable to treat these patients with neo-adjuvant chemotherapy followed by

FIGURE 24.18. Neo-adjuvant chemotherapy versus upfront debulking.

Source: Reprinted with permission from Vergote I, Troupe CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med*. 2010;363:943–953. Set as source information.



debulking surgery. Surgical debulking is only one component of the treatment that women with ovarian cancer require.

Second-Look Surgery

Second-look laparotomy was often performed in the 1980s after primary surgery and adjuvant cisplatin-based therapy for prognostic information and as an effort to improve survival by continuing chemotherapy for those found to have residual small volume disease. Second-look surgery is no longer generally performed, because no therapy instituted as a result of disease found at second-look surgery was found to alter prognosis. Reoperation following chemotherapy also introduces unnecessary morbidity. About one-third of such patients with advanced ovarian cancer were free of disease at a second-look laparotomy, yet even after a negative second look, over half of these patients eventually recurred.

Interval Debulking for Suboptimally Debulked Patients

The term interval debulking surgery refers to a surgical procedure in a patient with persistent abdominal disease after an initial surgical debulking effort and 3 cycles of chemotherapy.

There is conflicting evidence from 2 large prospective, randomized trials whether secondary cytoreductive surgery can improve survival in these patients (181,182). In a multicenter trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) (181), patients with suboptimal (>1 cm) disease remaining after primary cytoreduction were treated with 3 cycles of cyclophosphamide and cisplatin. Those without progression were randomized to interval debulking surgery and additional chemotherapy *versus* additional chemotherapy alone. With approximately 140 patients randomized to each arm, patients undergoing the interval debulking showed a statistically significant improvement in both progression-free interval and median survival (Fig. 24.19A). The survival of patients with residual lesions of more than 1 cm after the interval debulking surgery was similar to that of patients who did not undergo the surgery.

The GOG has reported the results of a prospective, randomized trial of interval secondary cytoreduction in patients with advanced FIGO stage III/IV ovarian cancer with suboptimal (> 1 cm) residual disease (GOG#152) (182). Five hundred fifty patients were enrolled in this study within 6 weeks of initial surgery. After 3 cycles of paclitaxel and cisplatin, patients without evidence of tumor progression were randomized to receive either secondary cytoreduction and 3 additional cycles of chemotherapy or chemotherapy alone. At the time of the report (2004), median PFS and OS (Fig. 24.19B) for the interval cytoreduction group were 10.5 months and 33.9 months, respectively, compared to 10.7 months and 33.7 months for the chemotherapy-alone group. A consistent lack of effect was seen in all patients independent of the residual tumor size at the end of the interval debulking surgery.

Several theories have been advanced to explain the difference in outcomes between the GOG and European studies, both large prospective, randomized trials. In the GOG trials, both the initial and interval cytoreductive operations were clearly defined and were performed almost exclusively by trained gynecologic oncologists, whereas in the EORTC trial the extent of the initial surgery was not clearly defined and surgery was most often performed by general gynecologists. As a result, residual disease following primary surgery measured less than 5 cm in about two-thirds of the GOG patients, compared to one-third of the patients in the EORTC trial. Following chemotherapy, residual disease greater than 1 cm was found in 56% of the GOG patients *versus* 65% of the European patients. This resulted in a higher likelihood of

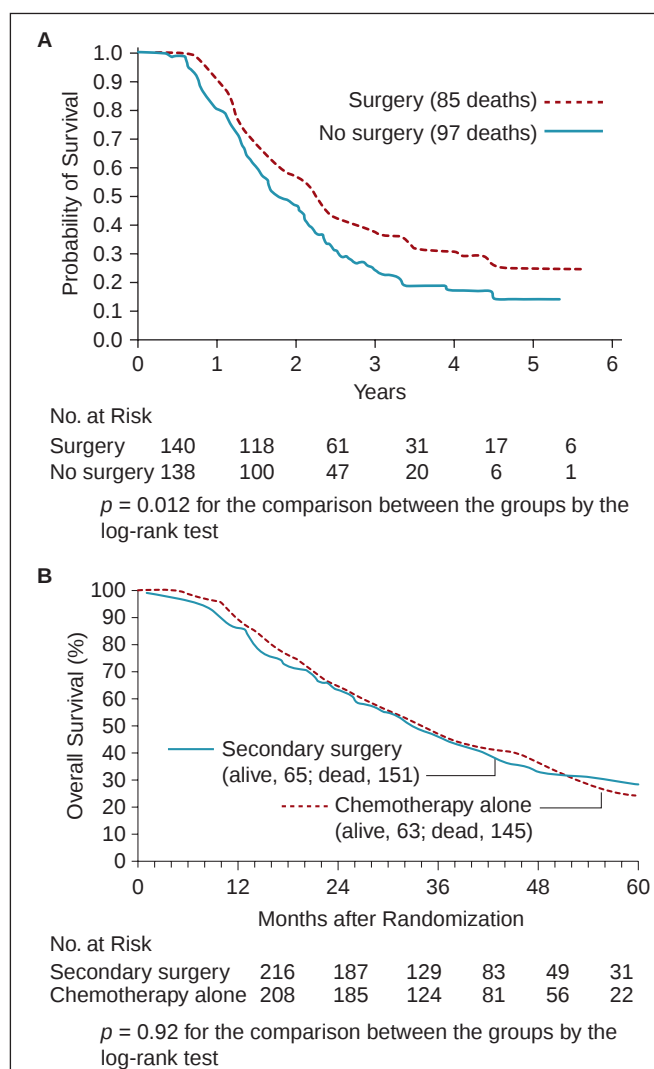


FIGURE 24.19. A: Overall survival of patients with advanced ovarian cancer who underwent interval debulking surgery compared to treatment with chemotherapy only. EORTC trial.

Source: van de Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecologic Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med*. 1995;332:629–634. With permission.

B: Overall survival of patients with advanced ovarian cancer who underwent interval debulking surgery compared to treatment with chemotherapy only. GOG trial.

Source: Rose PG, Nerenstone S, Brady M, et al. A phase III randomized study of interval secondary cytoreduction in patients with advanced stage ovarian carcinoma with suboptimal residual disease: a Gynecologic Oncology Group study. *Proc Am Soc Clin Oncol*. 2002;21:201a. With permission.

successful cytoreduction in the EORTC trial, with conversion from suboptimal to optimal residual tumor in 45% of patients as compared to 36% in the GOG trial.

Additionally, the chemotherapeutic regimen used in the GOG trial, paclitaxel and platinum, may have reduced the benefit of interval cytoreduction relative to the EORTC trial, which used a platinum and cyclophosphamide combination. Differences in outcome may also be related to differing posttreatment surveillance and to the availability of more effective second-line therapies since the EORTC trial completed accrual in May 1993. It is of interest to note that the similar median and overall survival in both arms of the GOG trial were substantially longer than those reported in the best (interval cytoreduction) arm of the EORTC trial.

In conclusion, it is probable that patients who had an initial maximal effort at cytoreduction resulting in suboptimal

debulking will not benefit from interval cytoreduction (182). Selected patients who previously only had a biopsy, removal of the ovary, or partial removal of ovarian tumors will benefit from one attempt at maximally debulking advanced ovarian cancer (181).

Secondary Cytoreductive Surgery for Recurrent Disease

Despite improvements in adjuvant chemotherapy for ovarian cancer (intraperitoneal chemotherapy [183], dose-intense chemotherapy [184], Bevacizumab [185]) and aggressive primary debulking (including upper abdominal procedures), the majority (70%) of patients with advanced epithelial ovarian cancer will have a recurrence (90). Since there is currently no chemotherapy that can cure recurrent ovarian cancer, surgical resection of recurrent disease is an option for a select group of patients.

An early retrospective study of secondary cytoreduction for recurrent disease from investigators in Munich showed an overall survival time of 29 months for patients cytoreduced to microscopic residual disease, while patients with any visible disease had a median survival of only 9 months (186). Chi and colleagues reviewed the Memorial Sloan-Kettering experience of 157 patients who had undergone secondary cytoreduction (187). For patients with a disease-free interval from completion of their primary adjuvant chemotherapy between 6 to 12 months, 13 to 30 months, and longer than 30 months, the median survival rates were 30, 39, and 51 months, respectively ($p = 0.005$). Median survival was 60 months for patients with a single site of recurrence, while patients with carcinomatosis had a median survival of 28 months ($p < 0.001$). In patients whose residual disease at the completion of surgery was larger than 0.5 cm, the median survival was 27 months, compared to 56 months in patients with residual disease lesser than 0.5 cm. Based on this study, disease-free interval, number of sites of recurrence, and residual disease at the end of surgery are independent prognostic factors for OS in patients considered for secondary cytoreduction.

Eisenkop and colleagues prospectively followed patients who underwent secondary cytoreductive surgery, and showed that patients with microscopic residual disease had a median survival of 44.4 months compared to 19.3 months if any visible disease was left (188). Therefore, as is the case with primary cytoreductive surgery, the disease burden at the end of surgery seems to be the most important prognostic factor. The German/Swiss DESKTOP I trial (189) enrolled 267 patients with recurrent ovarian cancer who had secondary cytoreductive surgery and found that patients with carcinomatosis had a 19.9 months median survival *versus* 45.3 months for patients without disseminated disease ($p < 0.0001$). In this trial, a score ("AGO score") was developed to predict optimal operability in this recurrent patient group, using criteria that includes performance status, complete debulking at first surgery, and less than 500 cc of ascites. The score was then tested in the DESKTOP II prospectively: 76% of the patients who fulfilled all 3 criteria had an optimal debulking (190). Another study, however, should serve to caution against too much surgical enthusiasm. Güngör (191) reviewing patients with recurrent ovarian cancer after optimal debulking and with a disease-free interval greater than 6 months showed that patients who had suboptimal secondary cytoreduction surgery had a worse prognosis when compared to a nonsurgery group who only underwent chemotherapy.

A small subset of patients (4% to 5%) will present with isolated recurrences in retroperitoneal lymph nodes. Several small retrospective studies found that complete resection of lymph nodes limited to one anatomic region (60% are high paraaortic) is associated with significantly improved survival (165,166). If this is the only site of disease, postoperative radiation of the lymph node bed might reduce the risk of recurrence.

All studies reporting on secondary cytoreductive surgery are retrospective or prospective nonrandomized studies, which have an inherent bias for the selection of patients in a favorable prognostic group to receive surgery. However, based on the consistent findings of these studies the following selection criteria for secondary debulking seem reasonable: Patients with (a) a disease-free interval longer than 12 months, (b) platinum sensitive disease with additional chemotherapy options, (c) oligometastatic or localized disease with the absence of ascites and carcinomatosis, and (d) a good performance status (192). For all other patients, the potential morbidity and limited benefit associated with suboptimal secondary cytoreduction should be carefully weighed against the possible benefit of surgery. In cases where radiologic studies do not provide a clear preoperative picture of disease extent a diagnostic laparoscopy to assess resectability might assist with the decision (180). In appropriately selected patients secondary cytoreduction is associated with an improved patient outcome with the largest benefit in patients from whom all visible disease could be removed.

Two prospective randomized trials will hopefully clarify the impact of secondary cytoreductive surgery on survival. The DESKTOP III trial and the GOG #213 trial both randomize patients with platinum-sensitive disease to secondary cytoreduction or no surgery with chemotherapy required in the GOG trial and recommended in the DESKTOP III trial.

Palliative Surgery Including Surgery for Malignant Bowel Obstruction

The primary goal of palliative surgery is to relieve symptoms and improve the quality of life, rather than prolonging survival. Bowel obstruction is one of the main causes of death from ovarian cancer. Others are extensive ascites, intractable pleural effusions, sepsis from a bowel perforation, and tumor cachexia (193).

In patients with ovarian cancer, a malignant bowel obstruction is the most common reason for a hospital admission during the last year of life. The median survival of patients admitted with a bowel obstruction is around 3 months. The tumor, while it does not deeply invade the bowel, connects and then kinks bowel loops and/or encases the bowel mesentery, limiting bowel mobility, blood supply, and causing a combination of mechanic bowel obstruction and adynamic ileus. Other etiologies can be extrinsic compression of the bowel lumen by intra-abdominal tumors or retroperitoneal lymph nodes pushing on the pyloric antrum or the duodenum. In patients without evidence of disease recurrence and who underwent an extensive debulking procedure or received postoperative radiation, adhesions, an old hematoma or a new incisional hernia may be the cause of a bowel obstruction.

Patients with advanced disease tend to present to the emergency room with one of the following signs and symptoms: tachypnea/dyspnea because of cranial displacement of the diaphragm/atelectasis of lower lung lobes or a pleural effusion, tachycardia from dehydration and pain, a low-grade fever from the dehydration and the chronic inflammation associated with a long-standing obstruction. Symptoms of a bowel obstruction include nausea and vomiting, periumbilical cramping and a combination of dull and sharp abdominal pain, and abdominal distension.

Instant nausea and vomiting after oral intake or projectile vomiting, is an indication of a very proximal obstruction of the stomach or duodenum which cannot not be relieved by surgery. If the patient has an adynamic ileus from carcinomatosis the auscultation will show absence of bowel sounds, yet if there is a complete small bowel obstruction bowel sounds will be high pitched. The proximal bowel obstruction might be caused either by an extensive upper abdominal tumor load or by enlarged

high paraaortic lymph nodes causing extrinsic compression of the duodenum or jejunum. The abdomen of patients with a proximal bowel obstruction is often not distended, which can give the mistaken impression of a limited problem. Laboratory analysis often shows hemoconcentration, low albumin, and a hypokalemic, hypochloremic metabolic alkalosis, which is sign of repeated vomiting or longstanding NG tube drainage. Patients with a volvulus or chronic bowel ischemia may have a metabolic acidosis, leukocytosis, and increase in lactate. While bowel obstruction is really a clinical diagnosis, an upright abdominal x-ray will show air fluid levels. A contrast CT scan of the abdomen and pelvis or a small bowel follow-through will allow for the evaluation of the small/large bowel over its entire length and will help determine whether a patient has multiple, partial, or complete bowel obstructions, or if there is a single transition point. The bowel is often dilated proximal to the transition point and collapsed after the transition.

Treatment options at this point include palliative care with symptom control, a percutaneous endoscopic gastrostomy (PEG) tube, parenteral nutrition, palliative chemotherapy, and palliative surgery. Initial treatment for a malignant bowel obstruction should be conservative and may include bowel rest and hydration to correct metabolic abnormalities, which are signs of a longstanding obstruction. Additional supportive measures are treatment with octreotide to reduce secretions, antiemetics, corticosteroids to reduce inflammation and as an antiemetic, and adequate pain management that will require narcotics.

In selected patients it is possible to accomplish a temporary surgical correction and relieve the blockage by either removing tumors obstructing the bowel or by performing a diversion that may be a colostomy, ileostomy, or a limited bowel resection with intestinal bypass. Preoperative contraindications to an attempted surgical correction of a malignant bowel obstruction include an adynamic ileus caused by carcinomatosis or extensive ascites, diffusely metastatic cancer with bowel obstructions on multiple levels, and involvement of the proximal ileum, duodenum or stomach. Relative contraindications to palliative surgery for a malignant bowel obstruction are a long-standing obstruction, significant deconditioning and tumor cachexia (low serum albumin), multiple previous abdominal surgeries, and rapidly progressing, chemotherapy resistant disease. A very proximal obstruction of the stomach or duodenum can rarely be relieved by surgery.

Since the purpose of palliative surgery is to improve the quality of life, the procedure must be short and limited, with the lowest possible complication rate. In experienced hands and with appropriately selected patients, a surgical correction is possible in 84% of all patients and successful palliation, defined as the ability to tolerate oral intake for at least 60 days after surgery, in 71% of patients (194). In 16% of patients, a gastrostomy tube was placed and most of the other patients received an ileostomy, a colostomy, or the obstructed area was bypassed. The rate of major surgical complications was 22% and included enterocutaneous fistula formation, abscess formation, bacterial peritonitis, thromboembolic events, and death. The median survival for patients who were able to receive chemotherapy (70%) was 9.7 months, while it was 2.4 months for the other patients (194).

Excessive ascites production is also often encountered in patients with progressive disease. Ultrasound guided intraperitoneal catheter placement is safe and can be performed intermittently as an outpatient procedure. Visceral injury followed by peritonitis is very rare with this procedure, but with repeated paracentesis the ascites may become loculated and drainage incomplete. Often repeated paracenteses are necessary, and should this be the case, a permanent indwelling catheter can be placed in the patient's abdomen and the patient or her family instructed on how to drain the ascites. Potassium-sparing diuretics (Triamterene, Spironolactone) or anti-angiogenesis therapy (e.g. aflibercept) may also reduce ascites production. (558)

PATHOLOGY

Classification

The WHO classification of surface epithelial tumors is summarized in Table 24.9. Epithelial tumors comprise about half of all ovarian tumors, and account for 40% of benign tumors and 90% of malignant tumors. Over 1,200 consecutive ovarian surface epithelial tumors accessioned at the Washington Hospital Center from 1999 to 2011 were recently reviewed using uniform pathologic review with current criteria (Table 24.10). Although not population-based, these data on carcinomas are very similar to population-based data from Canada (195) and Sweden (196).

The apparent cell type distribution of ovarian cancer has changed significantly in the past 2 decades as metastatic mucinous carcinomas have been recognized and properly categorized (197). Primary invasive mucinous carcinoma now appears to be quite uncommon, comprising only 3% of ovarian carcinomas and less than 1% of advanced-stage carcinomas (Table 24.11). Carcinosarcoma (malignant mixed müllerian tumor), previously regarded as a rare primary ovarian tumor, now appears to comprise over 6% of ovarian carcinomas in the United States. This apparent increase in frequency may be due to more thorough sampling with the identification of small sarcomatous components in otherwise typical high-grade serous carcinomas.

Abbreviations used in this section

AGUS	Atypical glandular cells of undetermined significance
APCCT	Atypical proliferative clear cell tumor
APET	Atypical proliferative endometrioid tumor
APMT	Atypical proliferative mucinous tumor
APST	Atypical proliferative serous tumor
DPAM	Disseminated peritoneal adenomucinosis
ESS	Endometrioid stromal sarcoma
MMMT	Malignant mixed mesodermal tumor
MPSC	Micropapillary serous carcinoma
MBT	Mucinous borderline tumor
PMP	Pseudomyxoma peritonei
SBT	Serous borderline tumor
STIC	Serous tubal intraepithelial carcinoma
TCC	Transitional cell carcinoma

Pathogenesis

Dualistic Model of Ovarian Cancer Pathogenesis

Advances in molecular biology correlated with morphologic studies have shed new light on the pathogenesis of ovarian carcinoma and have challenged many of the time-honored concepts of ovarian neoplasia. These studies have led to the proposal of a new model of carcinogenesis (198). Concomitantly, recent studies have provided evidence that the origin of ovarian carcinoma, previously regarded to be the ovarian surface epithelium, may be the fallopian tube in many or possibly even most cases (199,200). The view that ovarian cancer begins in the ovary and spreads systematically to the pelvis, abdomen and then distant sites is now less favored and the concept that ovarian carcinoma, over time, progresses from well to poorly differentiated also appears to be incorrect for the vast majority of cases.

Accumulating clinicopathologic and molecular genetic data have led to the proposal of a new model of ovarian

Table 24.9 Histologic Classification of Common Epithelial Tumors of the Ovary**Serous Tumors**

Benign

- Cystadenoma and papillary cystadenoma
- Surface papilloma
- Adenofibroma and cystadenofibroma
- Borderline tumor (atypical proliferative tumor)

Malignant

- Adenocarcinoma
- Surface papillary adenocarcinoma

Mucinous Tumors

Benign

- Cystadenoma
- Adenofibroma and cystadenofibroma
- Borderline tumor (atypical proliferative tumor)
 - Intestinal type
 - Endocervical-like

Malignant

- Adenocarcinoma
- Malignant adenofibroma
- Mural nodule arising in mucinous cystic tumor

Endometrioid Tumors

Benign

- Adenoma and cystadenoma
- Adenofibroma and cystadenofibroma
- Borderline tumor (atypical proliferative tumor)

Malignant

- Adenocarcinoma
- Adenosquamous carcinoma
- Adenosarcoma
- Endometrial stromal sarcoma (low grade)
- Malignant Mixed Mullerian Tumors (Carcinosarcoma, homologous and heterologous)
- Undifferentiated sarcoma

Clear Cell Tumors

Benign

- Borderline tumor (atypical proliferative tumor)

Malignant

- Adenocarcinoma

Transitional Cell Tumors

Brenner's tumor

Proliferating Brenner's tumor

Malignant Brenner's tumor

Transitional cell carcinoma (non-Brenner type)

Squamous Cell Carcinoma Mixed Epithelial Tumors (Specify Types)

Benign

- Borderline tumor (atypical proliferative tumor)

Malignant

Undifferentiated carcinoma

Source: Modified with permission from Tavassoli FA, Devilee P. *Tumours of the Breast and Female Genital Organs*. World Health Organization Classification of Tumors. Lyon, France: IARC Press; 2003:114.

carcinogenesis that reconciles the differing relationships of borderline and malignant tumors among the different cell types. This model divides surface epithelial tumors into 2 categories,

Table 24.10 Distribution of 1,247 Ovarian Epithelial Tumors by Cell Type, Washington Hospital Center, 1999 to 2011

	Benign (%)	Atypical proliferative/ borderline (%)	Malignant (%)	Total (%)
Serous	48.6	1.8	17.8	68.2
Endometrioid	0.8	0.2	1.9	2.9
Clear cell	0	0.2	2.2	2.4
Mucinous	7.6	1.0	0.8	9.4
Seromucinous	1.8	0.3	0.2	2.3
Transitional	9.9	0.2	0.3	10.4
Mixed	0.6	0	0.7	1.3
Undifferentiated	–	–	0.1	0.1
Carcinosarcoma	–	–	1.6	1.6
Squamous	1.3	–	0.1	1.4
Totals	70.6	3.7	25.7	100

Seidman, unpublished data.

Type I and Type II, based on their clinicopathologic features and characteristic molecular genetic changes (198).

Type I tumors are low-grade, relatively indolent neoplasms that arise from well-characterized precursor lesions (atypical proliferative [borderline] tumors and endometriosis) and usually present as large stage I neoplasms. This group includes low-grade serous (invasive micropapillary serous carcinoma [MPSC]), low-grade endometrioid, mucinous, and probably clear cell carcinomas. Clear cell carcinoma, although it exhibits most of the features of the Type I tumors such as association with a well-established precursor (endometriosis) and frequent large size and presentation in stage I, is typically high-grade unlike the other Type I tumors. Nonetheless, preliminary molecular genetic data show a greater similarity of clear cell carcinoma to Type I as compared to Type II tumors.

Type I tumors often harbor mutations of genes encoding protein kinases including *KRAS*, *BRAF*, *PIK3CA*, and *ERBB2*, as well as other signaling molecules including *PTEN* and *CTNNB1* (β -catenin). The atypical proliferative or borderline serous and mucinous tumors appear to develop from cystadenomas, while the atypical proliferative endometrioid and clear cell tumors arise from endometriosis. Type I carcinomas are heterogeneous and often display areas identical to their benign and atypical proliferative counterparts. Similar mutations have been identified in the different components of each tumor cell type, providing supportive evidence of the neoplastic sequence of benign to atypical proliferative to invasive carcinoma.

In contrast, Type II tumors, of which the vast majority are high-grade serous carcinomas and its variants, are aggressive, high-grade neoplasms from the outset; in the past they have been said to arise “de novo.” Recent data suggest that high-grade serous carcinomas arise from intraepithelial carcinomas, the majority of which have been detected in the tubal mucosa, usually the fimbriae (serous tubal intraepithelial carcinoma, or STIC). It is currently not clear what proportion of high-grade serous carcinomas arise from the tube. A large majority of Type II carcinomas have *TP53* mutations. *TP53* mutations have been found in tubal intraepithelial carcinomas and in a recently described putative precursor lesion of tubal intraepithelial carcinoma designated “p53 signature”. This latter lesion appears

morphologically normal but overexpresses p53 and can harbor a p53 mutation. These findings highlight the importance of p53 mutation in the early development of high-grade serous carcinoma (198,201). The dualistic model is supported by findings from many investigators (202).

The anatomical progression of ovarian carcinoma is poorly understood. It is generally assumed that carcinoma originates in the ovary, is confined to the ovary for a period of time and then disseminates to the pelvis, followed by the abdominal cavity before spreading to distant sites. This view underlies the basis of the FIGO staging system (see Table 24.6) in which, tumors confined to the ovary are stage I, those involving the pelvic organs stage II, with involvement of abdominal organs stage III, and distant sites stage IV. This view also has been used to justify the attempts to develop a screening test. There are, however, significant problems with this assumption. Clinicopathologic comparison of stage I with stage III carcinomas shows that stage I tumors are predominantly Type I and nonserous while stage III tumors are predominantly Type II and most often high-grade serous (203).

It is important to appreciate that Type II ovarian carcinomas account for the vast majority of ovarian cancer deaths (204). Most Type II tumors are high-grade serous carcinomas and at the time of diagnosis, most are widely disseminated throughout the peritoneum with the largest volume of tumor outside the ovaries. Serous carcinoma and its variants (peritoneal serous carcinoma, carcinosarcoma, undifferentiated carcinoma and mixed carcinomas with a high-grade serous component) account for 87% of cases of peritoneal carcinomatosis from ovarian carcinoma (Table 24.11; 197) and accordingly the vast majority of ovarian cancer deaths. These data that analyze stage distribution by histologic type suggest that early and advanced-stage tumors are often fundamentally different diseases, and provide further support for the dualistic model (203).

Putative Histopathologic Precursor Lesions

The study of precursors of ovarian carcinoma is very difficult because the ovaries are not readily accessible for screening, and ovarian carcinomas typically present in advanced stage,

obliterating or rendering unrecognizable any possible precursor lesions. Furthermore, identification of a putative precursor lesion is based on microscopic examination of a complete oophorectomy specimen, and therefore the natural history of the lesion cannot be observed. Studies on ovaries removed prophylactically from high-risk women, and normal-appearing ovaries contralateral to stage I carcinomas, have generated conflicting data.

Surface Epithelial Dysplasia

Investigators have studied ovarian surface epithelium in the vicinity of carcinomas in an attempt to define the putative entity of “ovarian dysplasia,” and have reported atypical cellular and nuclear features that appear more frequently in ovarian surface epithelium near or contralateral to carcinomas in comparison to control ovaries. These findings, however, have not been widely corroborated.

Surface Epithelial Inclusions

The superficial ovarian cortex usually contains simple glands and cysts lined by a single layer of flat, cuboidal epithelium or ciliated tubal-type epithelium (Fig. 24.20). These are termed surface epithelial or cortical (formerly “germinal”) inclusions, and their presence directly correlates with age. Historically, they have been considered to arise after postovulatory repair of the damaged ovarian surface; however, the evidence for this is weak. It has been stated that they arise when invaginations or clefts of the ovarian cortex lined by surface epithelium lose their connection to the surface. However, this circumstantial observation may be based on confusion of tangentially sectioned clefts with inclusions (205). It has recently been suggested that the origin of inclusions could be the fimbrial epithelium, which is in close apposition with the ovarian surface epithelium (201). In this model, the postovulatory disruption of the ovarian surface allows fimbrial epithelium access to the superficial cortical stroma. At present, this is the most compelling hypothesis as it explains the tubal morphology of inclusions and their age distribution, but the evidence is largely circumstantial. Nonetheless, there is no more than circumstantial evidence for the previously “well-established” surface epithelial origin of these inclusions. Furthermore, the ovarian surface epithelium is not müllerian in origin; it is mesothelial, and metaplasia of the peritoneal mesothelium

Table 24.11 Distribution of 530 Invasive Ovarian Carcinomas by Cell Type, Washington Hospital Center, 1991 to 2011

	Stage I	Stage II	Stage III	Stage IV	Totals (%)
High-grade serous	11	12	227	92	342 (64.5)
Low-grade serous	2	0	20	4	26 (4.9)
Endometrioid	20	7	9	2	38 (7.2)
Clear cell	21	9	11	4	45 (8.5)
Mucinous	15	0	2	0	17 (3.2)
Transitional	7	0	0	0	7 (1.3)
Carcinosarcoma	1	5	21	7	34 (6.4)
Seromucinous	3	1	0	0	4 (0.8)
Mixed	4	3	5	2	14 (2.6)
Undifferentiated	0	0	1	0	1 (0.2)
Squamous	0	0	0	2	2 (0.4)
Totals	84	37	296	113	530

High-grade serous includes those of peritoneal and tubal origin. Transitional cell carcinomas (other than malignant Brenner tumors) are classified as high-grade serous carcinoma (see text).

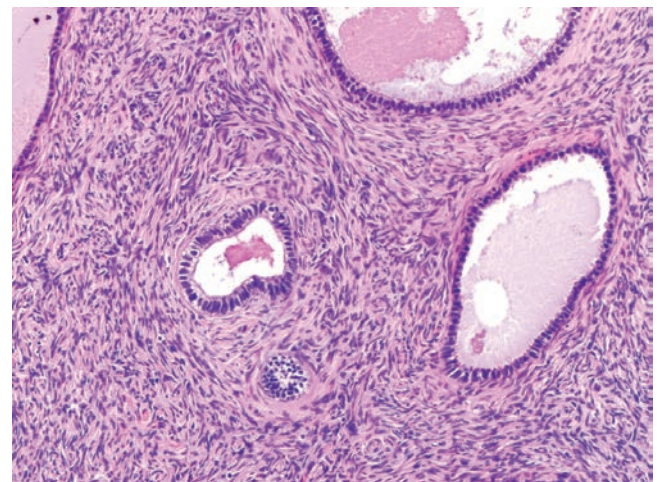


FIGURE 24.20. Cortical inclusions are lined by ciliated columnar tubal-type epithelium within the ovarian cortical stroma. The ovarian surface is seen at the top left.

to tubal-type epithelium, though widely believed to occur, is another widely held assumption that has not been convincingly demonstrated.

Some studies on prophylactic oophorectomy specimens in high-risk women and normal-appearing ovaries contralateral to stage I carcinomas have shown a higher number of these cortical inclusions in comparison to controls, but others have not confirmed these findings. These studies have also evaluated a variety of other features including cortical invaginations (clefts) and surface papillomatosis and some have found the latter 2 to be more common in cancer-prone ovaries than in controls, but these findings have not been confirmed by other investigators either. Many of these studies have significant drawbacks. For example, the method of quantitation of cortical inclusions and clefts is variable among studies (206).

Endometriosis

Although the precursors of ovarian carcinoma are for the most part unknown, endometriosis is a well-documented and easily recognized precursor lesion. This is because carcinomas arising in endometriosis are Type I tumors, grow slowly, and therefore allow a greater window of opportunity for discovery prior to obliteration of the precursor lesion by the carcinoma. Endometriosis is common and found in about 10% of reproductive-age women, but the risk of malignant transformation in an individual patient is very low. Nonetheless, endometriosis is associated with up to about 20% of ovarian cancers and is acknowledged to be the precursor of many endometrioid and clear cell carcinomas and an occasional mucinous carcinoma. Serous carcinomas may be found coincidentally in women with endometriosis but do not appear to be histogenetically related.

The plausibility of endometriosis as an ovarian cancer precursor is supported by our understanding of endometrial cancer precursors. Atypical endometrial hyperplasia in the uterus is a well-defined precursor of endometrial adenocarcinoma, and changes similar to this lesion are occasionally observed in endometriosis. In addition, atypical changes are also seen in endometriosis in the vicinity of endometrioid adenocarcinomas of the ovary and even more frequently in association with clear cell carcinoma. On occasion, the full morphologic spectrum from endometriosis with hyperplasia, to atypical hyperplasia and well-differentiated endometrioid adenocarcinoma can be observed. Further support for the premalignant potential of endometriosis comes from molecular biologic studies, which have demonstrated molecular alterations including LOH in the *PTEN* gene and microsatellite instability, as well as chromosomal aberrations including trisomies and monosomies, all indicative of a neoplastic process.

It has been estimated that carcinoma develops in 0.3% to 3% of cases of endometriosis, but this is likely an overestimate since a large number of cases of endometriosis never come to biopsy. The true figure is probably closer to 0.3%. Ovarian endometriosis appears to be significantly more likely to undergo malignant transformation than extraovarian endometriosis (207).

Further evidence that endometriosis is a precursor of ovarian carcinoma is provided by large studies from Sweden and Japan. In a Swedish study of over 20,000 women hospitalized with endometriosis, after a mean follow-up of 11.4 years, the relative risk of ovarian cancer in comparison to the control population was 1.9. Patients with a long-standing history of endometriosis (10 years or longer) had a relative risk of 4.2 (208). In a study in Japan of 6,398 women with endometriosis, the standardized incidence ratio was 9.0 after 17 years of follow-up, with a risk of 13.2 in women diagnosed after age 50 (209). In the latter study, the mean age at diagnosis of ovarian carcinoma was 51, a reflection of the significantly younger age of women with endometriosis-associated cancers.

Benign and Atypical Proliferative (Borderline) Neoplasms

Although the natural history of benign ovarian tumors cannot be observed since they must be completely removed for accurate diagnosis, the observation of morphologically benign areas within carcinomas, and recent molecular data, strongly suggest that atypical proliferative/borderline tumors are precursors of low-grade serous, endometrioid and mucinous carcinomas (Type I tumors in the dualistic model). Invasive low-grade serous carcinomas (invasive MPSC) usually display large areas of atypical proliferative serous tumor (APST), also known as serous borderline tumor (SBT). Similarly, atypical proliferative mucinous tumors (APMT), also known as mucinous borderline tumors (MBT), are heterogeneous and usually display large areas of mucinous cystadenoma and APMT as well as morphologically intermediate forms, which include mucinous cystadenoma with focal atypia, and APMT with intraepithelial carcinoma (210). The progression of APST to low-grade serous carcinoma and APMT to mucinous carcinoma is supported by similar molecular changes in the separate components of these neoplasms.

Tubal Intraepithelial Carcinoma

It has recently been proposed that the origin of some serous carcinomas is the tubal fimbriae (198,200). The fimbriae are normally in close contact with the ovarian surface. Reported associations of chronic salpingitis with both ovarian serous tumors and tubal carcinomas (31,211,212) suggest the possibility of incorporation of fimbrial epithelium into the ovarian cortex via adhesions or a role of salpingitis in tubal carcinogenesis (213).

The typical fallopian tube carcinoma is a high-grade serous carcinoma and, until recently, was felt to be characterized by a dilated tubal lumen with the tubal mucosa displaying grossly obvious papillary tumor. In fact, a luminal tumorous mass has generally been required to assign the primary site to the fallopian tube (214). However, a fimbrial carcinoma seems unlikely to cause luminal dilatation except possibly in a short distal segment, and could be misinterpreted as ovarian in origin, particularly because the fimbriae normally reside on the ovarian surface. Epithelial atypia, intraepithelial carcinoma (STIC) and small high-grade serous tubal carcinomas have been found in prophylactic specimens from women with *BRCA* mutations (214). In addition, it is frequently impossible to completely separate the ovary and tube for evaluation in serous carcinoma. All of these observations suggest the possibility that some apparent ovarian cancers are in fact tubal in origin (198,200). Carcinoma involving the tubal mucosa has generally been regarded as secondary when there is also tumor in the ovary, peritoneum and/or endometrium, however this is an assumption. Many of the dominant tumorous adnexal masses appear to be paraovarian and/or extensively involve the fallopian tube in a manner consistent with peritoneal or tubal origin. The identification of *TP53* mutations in STICs as well as in high-grade serous carcinomas provide further support for the tubal origin of many high-grade serous carcinomas.

Meticulous examination of risk-reducing salpingo-oophorectomy (RRSO) specimens has disclosed occult invasive carcinomas in 3% of cases: 53% ovarian, 39% tubal, and 8% peritoneal (205), and it has been suggested that some apparent primary peritoneal carcinomas after RRSO reflect undetected microscopic ovarian carcinomas. It has also been suggested that some apparent peritoneal carcinomas in women who have undergone oophorectomy but not salpingectomy may reflect metastases from primary tubal carcinomas. Foci of STIC and atypical hyperplasia have been reported in RRSO specimens and the tubal fimbria is by far the most common site (78,79,85,200,215,216,217). As noted earlier, the reported frequency of occult invasive carcinomas in prophylactic specimens from high-risk women is 3% but varies widely; 0% to 12% in a compilation of 16 series, which

included 1,750 patients (205). In an additional 1%, STIC has been identified, making intraepithelial or invasive tubal carcinoma the majority of occult carcinomas. The wide range among studies could reflect differing thresholds for the diagnosis of tubal carcinoma, particularly intraepithelial carcinoma. In addition, there are several potential sources of bias in these types of studies (218). The interobserver reproducibility of the diagnosis of STIC has not been optimal, but recent data suggest that using p53 and Ki67 immunostaining in conjunction with morphology markedly improves reproducibility (219).

STICs have been identified in association with a high proportion of high-grade serous carcinomas. STICs contain *TP53* mutations and are cytologically malignant but are confined to the tubal epithelium. More recently, it has been found that there are small foci of morphologically normal tubal epithelium that are immunohistochemically positive for p53, and that have a Ki-67 proliferation index higher than normal tubal epithelium but lower than that found in STICs. A minimum of 12 tubal secretory epithelial cells that are p53 positive has been proposed as a definition for a “p53 signature” that is a candidate for a STIC precursor (220). Such p53 signatures have been associated with STICs as well as apparent ovarian serous carcinoma, but are also not uncommonly found in the general population. *TP53* mutations have been found in a majority of p53 signatures. These findings have led to the proposal that the p53 signature is the long sought precursor of a subset of ovarian high-grade serous carcinomas. Much of these data derives from Crum and associates (220) and awaits confirmation in larger series and by other investigators.

In and around the fimbriae, there is a junction between the tubal epithelium and the mesothelium which has been designated the tubal-peritoneal junction (Figs. 24.21 and 24.22). This is an extensive and highly tortuous zone and had escaped notice until a recent comprehensive characterization (221). Because junctions between different types of epithelium, such as the gastroesophageal junction and the cervical transformation zone, are often hot spots for carcinogenesis, this region is now of great interest. We have often observed STIC within 1 to 2 mm of this junction, and on occasion STIC can be found precisely at this junction. Further characterization of the relationship of STIC to the tubal-peritoneal junction will be of great interest.

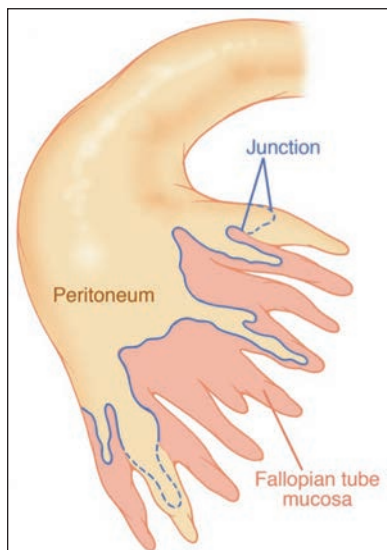


FIGURE 24.21. Schematic diagram of the fimbrial region showing the tubal-peritoneal junction as a tortuous blue line in and around the fimbriae.
Source: Reproduced from *Int J Gynecol Pathol*. 2011;30:4–11, with permission.

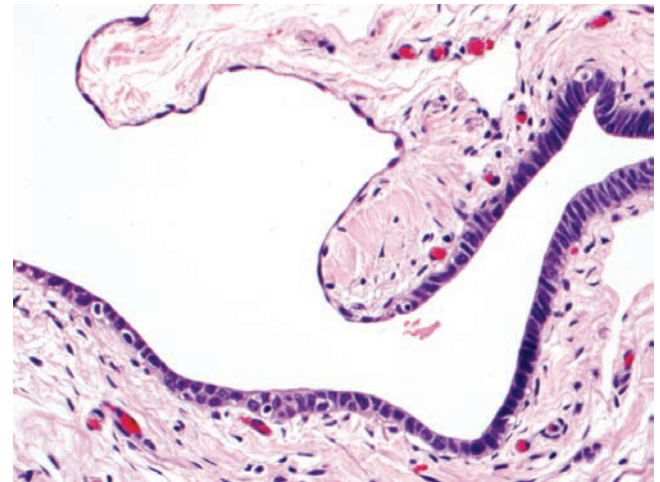


FIGURE 24.22. Histology of the tubal-peritoneal junction showing a flattened mesothelial lining at top left and the columnar tubal epithelium at bottom and right.

Intraoperative Consultation (Frozen Section)

Getting the most out of a frozen section requires open lines of communication between the surgeon and the pathologist. The value of clinical information and operative findings to the pathologist should not be underestimated. A frozen section should be requested only when information is needed to determine what surgical procedure will be performed. Unnecessary frozen sections waste valuable resources and introduce opportunities for error (222).

The main purpose of intraoperative consultation for an ovarian mass is to determine whether a malignancy is present so that staging can proceed. However, a simple diagnosis of “malignant” is not enough since metastatic neoplasms to the ovary are not infrequent and may present prior to the diagnosis of the primary lesion. Because 5% to 10% of malignant ovarian masses are metastases from extraovarian primaries, the pathologist should attempt to make as specific a diagnosis as can reasonably be rendered given the limitations of frozen section. The benign versus malignant distinction in most cases is easily made, and the accuracy in most hospitals is over 95% (223). More difficult and hence less accurate is the distinction of a primary from a metastatic tumor, and atypical proliferative/borderline tumor from invasive carcinoma, both of which will affect the surgical approach.

Atypical proliferative (borderline) tumors present a unique intraoperative problem. Low-grade serous neoplasms are heterogeneous, and low-grade serous carcinomas nearly always have benign appearing areas resembling a cystadenoma or an APST/SBT. The amount of tissue that can be examined intraoperatively is limited. Consequently, approximately 20% to 30% of ovarian tumors diagnosed as atypical proliferative (“borderline”) at the time of frozen section examination prove to be carcinomas on further sampling. Accordingly, it is important that the surgeon perform a thorough exploration when the frozen section is diagnosed as an APST/SBT. Whether a complete staging with its attendant morbidity should be undertaken depends on the findings at exploration, the level of suspicion for carcinoma on the part of both the pathologist and surgeon, and the patient’s preferences (222). Also of note is that the distinction of benign from atypical proliferative/borderline is not always reliable, with a tendency to overdiagnose borderline tumors intraoperatively (223). The likelihood of a tumor interpreted as borderline at frozen section proving to be a carcinoma increases with tumor size. One recent study showed that invasion was

found in 22.4% of tumors interpreted as borderline that were larger than 8 cm as compared to 3.2% of smaller tumors (224).

Discrepancy rates for frozen sections of ovarian mucinous tumors can exceed 1 in 3 (225). When a mucinous tumor is diagnosed intraoperatively, it is important for the surgeon to do a complete abdominal exploration. The likelihood of a mucinous tumor being an extraovarian primary increases with the degree of atypia, gross and microscopic complexity, and the presence of extraovarian disease. Simple unilocular mucinous cysts or cystadenomas are nearly always benign primary ovarian tumors. Once any degree of atypia is present, even if mild, an extraovarian primary should be considered in addition to a primary ovarian APMT/MBT. If peritoneal disease in the form of pseudomyxoma peritonei (see pseudomyxoma peritonei later in this chapter) or metastatic adenocarcinoma is present, the likelihood of an extraovarian primary is very high, as most true primary ovarian mucinous carcinomas are stage I. If clear-cut evidence of mucinous carcinoma is present within the ovary, the likelihood of an extraovarian primary is about 80%. This latter figure can be refined based on other findings including bilateral ovarian involvement, which is nearly always metastatic, or unilateral involvement with tumor size smaller than 10 to 13 cm, which is usually but not always metastatic (226). Nearly all primary ovarian mucinous carcinomas are large and unilateral. One study on the accuracy of frozen sections for ovarian mucinous tumors showed that a tumor size of greater than 13 cm was associated with a significantly increased discrepancy rate (227).

When an extraovarian primary is considered likely, the surgeon should perform a complete abdominal exploration with particular attention to the gastrointestinal and hepatobiliary tracts and pancreas, as most metastatic mucinous carcinomas to the ovaries arise in these sites. The appendix should be removed even if it appears normal, as small appendiceal neoplasms can disseminate, and appendectomy is a low-risk procedure.

CAP Checklist Reporting

The College of American Pathologists (CAP) has issued guidelines for the reporting of ovarian cancer (228). Complete reporting with the CAP cancer checklist requires assessment of ovarian surface involvement and tumor rupture for stage I and II disease. It is therefore important that the pathologist communicate with the surgeon or review the operative report to provide these data. For advanced-stage disease, the size of the largest peritoneal nodule needs to be assessed, and although this is often evident from the gross pathologic examination, input from the surgeon may be required since the tumor may be incompletely resected. In apparent stage III disease, clinical or pathologic information may be needed to determine whether distant metastases have been diagnosed (stage IV). Required elements of the checklist include specimen type, procedure, specimen integrity, primary site, tumor size, histologic type, grade and TNM stage.

Cytopathology

There are 2 types of cytopathologic specimens typically used in evaluation of ovarian epithelial neoplasms: fine-needle aspirates (FNA) of ovarian cysts and peritoneal fluids (obtained by peritoneal washing or by aspiration of ascitic fluid). FNA specimens or effusions from sites of distant metastasis may also be examined. Rarely, the presence of psammoma bodies in a Pap smear will be the first sign of primary or recurrent ovarian or peritoneal serous carcinoma, more commonly when associated with atypical glandular cells of undetermined significance (AGUS) or in older women with symptoms and signs suggesting malignancy. In a review of over 200,000 Pap smears, psammoma

bodies were found in 6 patients, 2 of whom proved to have ovarian carcinoma. In a review of 138 cases of AGUS, 5 (3.6%) proved to have ovarian cancers (229).

FNA may be useful in patients who appear to have inoperable ovarian cancer or who cannot undergo surgery for other reasons. Unsatisfactory specimens from ovarian cyst aspirates are common and limit the usefulness of the procedure. FNA specimens from most ovarian carcinomas are cellular and contain cytologically malignant cells, but accurate subclassification is often difficult and may be impossible based solely on cytologic material.

Cytologic samples of peritoneal fluid and diaphragmatic scrapings are routinely obtained during staging procedures for ovarian cancer. Cytologic findings are important in substaging early (FIGO I and II) ovarian cancer; malignant cells in peritoneal washings or ascites warrants assignment of tumors to stage IC or IIC. Malignant cells are more often present in ascites than in washings, and their presence correlates positively with volume of ascites, serous histology, stage and positive lymph nodes (230). The cytologic features of tumor cells generally resemble those in FNA specimens but may be more degenerate.

Peritoneal lavage is often performed at the time of RRSO in high-risk women. Occult carcinomas can be identified in these cytology specimens. Colgan and associates found malignant cells in 3 of 35 such specimens in the absence of other evidence of malignancy. Endosalpingiosis, manifested by morphologically benign tubal-type epithelium, was found in 22% (231). In 2 studies, malignant cells reported in washings at RRSO led to the discovery of early-stage tubal carcinomas (216,232).

Atypical epithelial cells resembling the ovarian tumor can occasionally be found in peritoneal cytology specimens associated with atypical proliferative (borderline) tumors. This finding has not been associated with adverse outcome and can be ignored except in the small proportion of patients who have bona fide carcinomas (patients with invasive MPSCs or APSTs with invasive implants), who can be substaged based on the presence or absence of epithelial cells resembling the primary ovarian tumor in the cytology specimens. This situation is rarely encountered since most MPSCs or APSTs with invasive implants are stage III.

Endometriosis and endosalpingiosis involving peritoneal surfaces may shed epithelial fragments into peritoneal washings or ascites. In addition, benign fallopian tube epithelium (particularly if salpingitis is present) and benign eutopic endometrial tissue may also be shed into the fluid via expulsion through the fallopian tubes. If the cells in the fluid are not obviously malignant, comparison of the cytologic features of the epithelium in the fluid with those of the tissue sections is essential. It is also important to note that cytologic abnormalities mimicking malignancy may be caused by chemotherapy as well as radiation.

Borderline Tumors

The borderline category of ovarian epithelial tumors was introduced in the early 1970s in order to describe a group of tumors that did not display invasion, but that occasionally appeared to behave in a malignant fashion. Their behavior appeared to be intermediate between benign cystadenomas and frank serous carcinomas. The classification was intended as provisional, but with its continued use over the past 3 decades, the borderline category has become entrenched. Recent studies have documented a wide histologic spectrum encompassed by the borderline category, which correlates with behavior. Some experts believe that the borderline group has been sufficiently resolved into benign and malignant types such that the category is no longer needed. However, most prefer to retain the borderline category with some modifications in terminology.

Serous Borderline Tumors

Tumors at the lower end of the morphologic spectrum of proliferating serous tumors behave in a benign fashion and display a papillary architecture in which papillae have a hierarchical branching pattern. These tumors are termed APSTs or serous borderline tumors (SBT). Tumors at the upper end of the morphologic spectrum behave like low-grade carcinomas and display a more complex nonhierarchical branching pattern characterized by delicate micropapillae and are classified as “noninvasive micropapillary serous carcinomas” (MPSC). APSTs comprise about 50% of atypical proliferative (borderline) ovarian tumors of all histologic types (Table 24.10). The atypical proliferative terminology has been accepted as synonymous with “borderline” while “low malignant potential” is currently not favored by most experts (233).

The most confusing aspect of serous borderline tumors is their association with peritoneal implants in the absence of invasive disease. There are 2 types of so called “peritoneal implants”: noninvasive and invasive. It is now clear, however, that patients with noninvasive implants have a survival that approaches 100%, while those with invasive implants have a prognosis similar to that of patients with invasive low-grade serous carcinoma, with 5- and 10-year survival rates of approximately 70% and 40%, respectively (233). Invasive implants are therefore believed to represent metastatic low-grade serous carcinomas. The finding of invasive implants with APST is very unusual and warrants further sampling of the ovarian tumor to identify occult areas of MPSC or invasion. The nature of noninvasive implants is unclear and there are conflicting data as to whether they arise from the ovarian tumor or are independent peritoneal proliferations. In either case, the prognosis is excellent and no therapy is needed, although patients may develop complications due to adhesions.

Microinvasion and associated lymph node lesions are found in a minority of cases. Different types of such lesions have been described (see below), and although their origin and significance are not entirely clear, the survival with microinvasion and/or lymph node lesions in the absence of MPSC or invasive implants is virtually 100%.

To summarize, APST/SBT can now be subclassified into those for which survival is close to 100% and those with a malignant, though indolent, behavior. APST with or without microinvasion, with or without lymph node lesions, and with or without noninvasive implants, can, for practical purposes, be considered benign. MPSC and APST/SBT with invasive implants, in contrast, have recurrence and mortality rates similar to those of low-grade serous carcinoma. Many authorities prefer the term “micropapillary serous borderline tumor” over MPSC.

Nonserous Borderline Tumors

The vast majority of nonserous borderline tumors are of the mucinous type. Endometrioid, clear cell and transitional cell types are rare and have never been convincingly demonstrated to be anything but completely benign.

APMT/MBT are not associated with peritoneal implants, and, like APST/SBT, have virtually 100% survival. Microinvasion (less than 5 mm) is occasionally seen and is not an adverse prognostic factor (210). Intraepithelial carcinoma may also occur in APMTs and although this is usually benign, there are occasional reports of malignant behavior (234). Since mucinous tumors are usually very large, malignant behavior is generally regarded as a manifestation of occult undetected invasion. Aggressive behavior of APMTs in the older literature is virtually always confined to patients with pseudomyxoma peritonei (PMP), and it is now clear that nearly all cases of PMP are of gastrointestinal origin (see below).

Primary versus Metastatic Ovarian Carcinomas

Metastatic carcinomas involving the ovaries often have unusual and deceptive features. The ovarian metastases may be the first manifestation of malignancy and may be much larger than the associated primary tumor. They are often cystic and accordingly grossly mimic primary ovarian carcinomas. They occasionally present prior to the identification of the primary tumor. The most common and problematic type of carcinoma metastatic to the ovary is mucinous carcinoma. Metastatic carcinomas are typically bilateral, small (typically less than 10 to 12 cm), display ovarian surface and superficial cortical involvement, a nodular pattern of ovarian involvement, and a haphazard infiltrative pattern of stromal invasion. However, some metastatic carcinomas, especially mucinous carcinomas derived from the colorectum, pancreaticobiliary tract, appendix, and endocervix, can exhibit gross and microscopic features simulating a primary ovarian mucinous or endometrioid tumor. In particular, metastases can be large, unilateral, and multicystic and can display deceptive patterns of ovarian involvement. If these patterns are not recognized, these metastatic carcinomas can be misinterpreted as primary ovarian APMT with intraepithelial carcinoma or well-differentiated mucinous or endometrioid carcinoma. Not infrequently, some of these metastases display highly differentiated areas adjacent to invasive areas, simulating benign and APMT precursor lesions.

When mucinous carcinomas in the ovaries are rigorously classified based on refined criteria and awareness of deceptive patterns, metastatic mucinous carcinomas are much more commonly encountered than primary ovarian mucinous carcinomas. In general, the presence of a mucinous carcinoma in the ovary, particularly if extraovarian disease is present, should always prompt the pathologist and surgeon to consider the possibility of metastatic mucinous carcinoma. Immunohistochemical analysis can be useful for identifying some metastatic mucinous carcinomas that simulate primary ovarian mucinous tumors; however the value of currently available markers is limited due to overlapping immunoprofiles of primary tumors and certain metastases (see Metastatic mucinous carcinoma, later in this chapter). Clinical evaluation is usually required to exclude metastatic mucinous carcinoma in the ovary derived from a clinically occult extraovarian source. Many investigators find it a safe and useful practice to consider mucinous carcinoma in the ovary metastatic until proven otherwise (205).

Serous Tumors

Serous Cystadenoma and Adenofibroma

Benign serous tumors including cystadenomas, adenofibromas and cystadenofibromas are common and account for two-thirds of benign ovarian epithelial tumors and the majority of ovarian serous tumors. Benign serous tumors are equally distributed among unilocular cysts, multilocular cysts and cystadenofibromas. The vast majority of lesions classified as serous cystadenoma display a serous epithelial lining lacking proliferation, suggesting that this tumor is not neoplastic. In a recent study, only 7% of serous cystadenomas had greater than 1 mm of epithelial proliferation (235). In support of this concept is the finding of polyclonality in the epithelium of most serous cystadenomas (236). Furthermore, another study confirmed these findings and found genetic abnormalities in the stroma of serous cystadenofibromas (237). Accordingly, not only are most serous cystadenomas probably not true epithelial neoplasms, the epithelium reflecting cystically dilated inclusions, but also the stroma may be the only neoplastic component. Accordingly, and most surprisingly, these may in fact, turn out to be benign stromal tumors, a finding which will eventually lead to reassessment of the distribution of ovarian neoplasms and the place of serous cystadenomas, if any, in the neoplastic sequence.

Cystadenomas are lined by pseudostratified, tubal type epithelium, with the characteristic elongated (secretory cell) and rounded (ciliated cell) nuclei. A single layer of flattened to cuboidal cells with uniform basal nuclei is also common. Mitoses and atypia are generally absent. Psammoma bodies are present in the stroma in 15% of cystadenomas. There is a broad spectrum of epithelial proliferation in benign serous tumors, which is manifested by variation in the prominence and complexity of the papillae, from a simple, single layer and blunt papillae to focal epithelial stratification and detachment of cell clusters approaching the degree of proliferation seen in APST/SBT. Identification of these features in 10% of the tumor separates serous cystadenoma from APST/SBT. If these features are focal (<10%), a diagnosis of serous cystadenoma with focal atypia is used (233).

Atypical Proliferative Serous Tumor; Serous Borderline Tumor (SBT)

The conceptual issues regarding the borderline category are discussed earlier in this chapter.

Clinical and Operative Findings

The clinical features of patients with APSTs are similar to those for serous cystadenomas; the mean age at diagnosis is 42 years. The risk factors are similar to those for ovarian cancer with notable exceptions of a higher frequency of infertility and a lower frequency of *BRCA* mutations.

APST are bilateral in 37% of cases in the older literature; the recent Stanford series showed a 55% bilaterality rate (238). This difference probably reflects more diligent examination of normal-sized ovaries with the identification of small serous proliferations contralateral to obviously tumorous ovaries. Exophytic papillae reflecting ovarian surface involvement are common, and are more often found in patients who also have peritoneal implants. Tumors with an exophytic component are associated with implants in up to two-thirds of cases as compared to 10% to 20% of tumors that are completely intracystic.

Gross Findings

APSTs have fine, friable, and exuberant papillary projections in contrast to the smooth walled cysts of serous cystadenoma. Papillae are nearly always present on the internal surfaces of the cyst, and are present on the external surfaces in up to 70% of cases.

Peritoneal endosalpingiosis in patients with APST is grossly inconspicuous. Noninvasive desmoplastic implants are firm and fibrotic, and are covered by an inflammatory exudate in 20% of cases. Invasive implants (metastatic low-grade serous carcinoma) resemble typical serous carcinoma but are often less bulky and more calcified.

Thorough sampling of the primary tumor for histologic examination is needed to rule out invasion. Previous recommendations of 1 section per cm of maximum tumor diameter (233) will not identify invasion in a significant minority of cases in which invasion is actually present. Recent data suggest that at least 2 sections per cm are needed to confidently exclude invasion (239) (see below, Microinvasion).

Microscopic Findings

APSTs display extensive epithelial stratification, tufting (budding) and detachment of individual cells and cell clusters in addition to hierarchical branching with successively smaller papillae emanating from the larger, more centrally located papillae. Stratification and budding in at least 10% of the tumor warrants a diagnosis of APST (Fig. 24.23). Focal areas of fusion of the epithelial buds may create a Roman bridge or cribriform

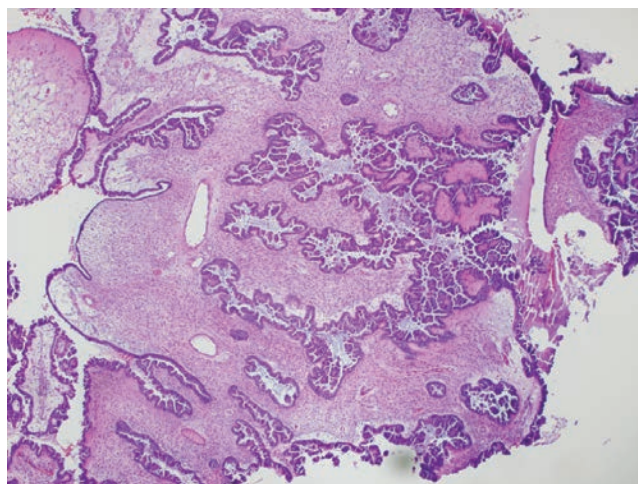


FIGURE 24.23. Atypical proliferative serous tumor (serous borderline tumor) displaying a complex papillary pattern with detachment of atypical cell clusters at the tips of the papillae.

pattern. Similarly, foci of nonhierarchical branching with fine elongated micropapillae emanating directly from large central papillae are seen not infrequently. When cribriform and/or micropapillary patterns constitute either a 5 mm or greater confluent area, or 10% or greater proportion, the tumor warrants classification as noninvasive MPSC (see below). Ciliated cells resembling fallopian tube epithelium are present in about one-third of tumors. The nuclei of APSTs resemble those in cystadenomas but tend to display slightly more atypia. Nuclei tend to be ovoid or rounded and nucleoli may be prominent. Mitoses are not common. Psammoma bodies are present in up to half of APSTs.

Microinvasion

Two distinct types of lesions have been designated “microinvasion” in APSTs. In most published reports, the 2 types have not been specifically distinguished or correlated with outcome. The usual type of microinvasion (eosinophilic type) accounts for the vast majority of reported cases. It is characterized by isolated cells and small cell clusters with abundant eosinophilic cytoplasm that appear to be budding from the epithelium into the superficial stromal cores of the papillae (Fig. 24.24). The lesion must be smaller than 5 mm, and can be multiple. When carefully sought, 10% of reported APSTs contain microinvasion; however, microinvasion was specifically noted in only 1.3% of reported APSTs up to 1999 (240). More recent series suggest that microinvasion is quite common and may be found in 25% or more of APSTs (241).

The second type of microinvasion occurs less commonly and is characterized by a haphazard infiltrative pattern of small solid nests of cells and micropapillae, often surrounded by a clear space and associated with an identifiable stromal response. This second pattern of invasion closely resembles primary ovarian invasive low-grade serous carcinomas (invasive MPSC) as well as “invasive implants” and may be referred to as “microinvasive carcinoma,” because the evidence, albeit limited, indicates that it is a manifestation of true invasive carcinoma. To qualify as microinvasive carcinoma, the lesion must be smaller than 5 mm. Multiple foci are permitted.

Microinvasion has been associated with a higher frequency of bilaterality, exophytic growth and peritoneal implants. Recent evidence suggests that the identification of microinvasion or microinvasive carcinoma is a clue that further sampling might disclose more extensive invasion. A minimum of 2 sections per

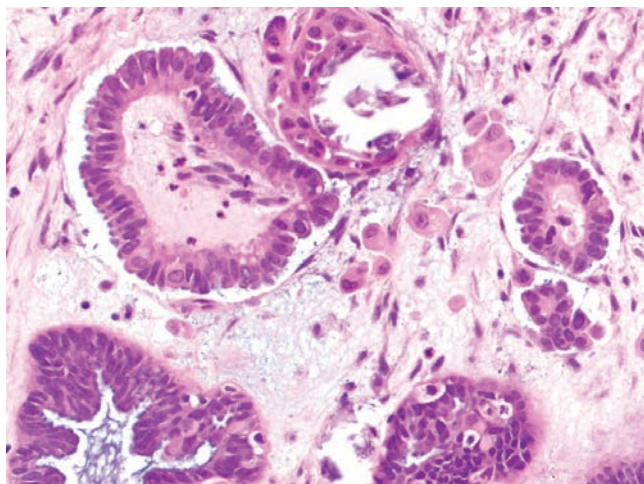


FIGURE 24.24. Microinvasion in an atypical proliferative serous tumor: The individual cells in the center with abundant eosinophilic cytoplasm reflect the more common type of microinvasion. Two papillae at left and right center are surrounded by a clear space reflecting the less common type of microinvasion (“microinvasive carcinoma”).

cm of maximum tumor diameter are needed to maximize detection of occult invasion (239).

A review of 94 patients with microinvasion reported up to 1999, the vast majority of which were not associated with peritoneal implants, showed 100% survival (240). More recently, the Stanford group found that microinvasion was a significant predictor of survival on univariate but not multivariate analysis (242). Although more data are needed, from the standpoint of prognosis and management, microinvasion does not appear to have clinical relevance. Whether or not staging is needed for a woman with microinvasive carcinoma is unclear. There are no data at present suggesting that follow-up or any treatment will influence recurrence or survival.

Associated Peritoneal Lesions: Endosalpingiosis and “Implants”

APSTs are often associated with serous lesions involving the peritoneum. Endosalpingiosis, or benign glandular inclusions, are found in 40% of patients. At present, 40% of reported APSTs are associated with peritoneal implants in contrast to 25% in the pre-1980 literature (240). However, in population-based and hospital-based material, the figure is closer to 10% to 15%, indicating a significant referral bias to large specialized centers in favor of tumors with implants. In the Stanford series, 59% had implants (243). Among those with implants, about three-fourths were noninvasive and one-fourth were invasive.

Endosalpingiosis, or benign glandular inclusions, may involve the peritoneal surfaces in patients with or without benign or malignant serous ovarian tumors. These glands typically are lined by simple columnar epithelium, which displays tubal differentiation. The epithelium may display minor degrees of atypia and form simple papillary structures; psammoma bodies are often present and may persist after degeneration of the epithelium.

Among women with APSTs, 31% (78% of all patients with implants) have peritoneal epithelial lesions that display a degree of proliferation beyond that usually seen in endosalpingiosis, but that lack features of invasion. These have been designated “noninvasive implants” and have 2 morphological forms: epithelial and desmoplastic.

Noninvasive epithelial implants are papillary and resemble the ovarian APST to some extent (Fig. 24.25). The cores of the papillae have fibrovascular support, and the epithelial cells

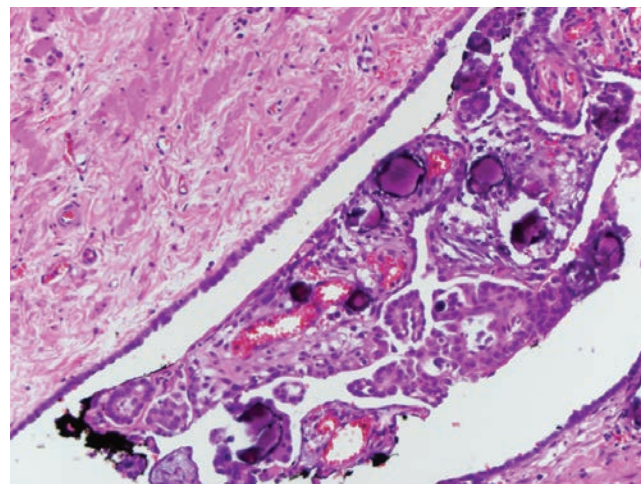


FIGURE 24.25. Noninvasive epithelial peritoneal implant associated with atypical proliferative serous tumor/serous borderline tumor. The implant displays a papillary architecture with psammomatous calcification. Note there is no invasion of adjacent peritoneum at top right and bottom left.

resemble those in endosalpingiosis. Thus, mild atypia is often present, but mitoses are usually absent. Calcification in the form of psammoma bodies is common and frequently is extensive.

The desmoplastic noninvasive implant is a plaque-like thickening overlying peritoneal surfaces and may extend into the septae that separate omental lobules creating a low-power appearance that suggests invasion (Fig. 24.26). These implants display an exuberant fibroblastic proliferation in which gland-like or papillary structures lined by epithelial cells are present. Psammoma bodies are usually present. The epithelium typically shows minimal cytologic atypia (Fig. 24.26). The fibroblastic proliferation often has a granulation tissue-like appearance characterized by edematous fascicles of plump fibroblasts, often with interspersed small vascular channels. Mitotic figures are usually absent, and psammoma bodies are present in over 90% of cases. This type of implant can be very difficult to interpret for pathologists who may be unfamiliar with these lesions. The rarity of advanced-stage APST/SBT results in most general pathologists seeing fewer than 1 case per year of the desmoplastic noninvasive implant and therefore most pathologists do not have experience with these lesions. Since the invasiveness of the

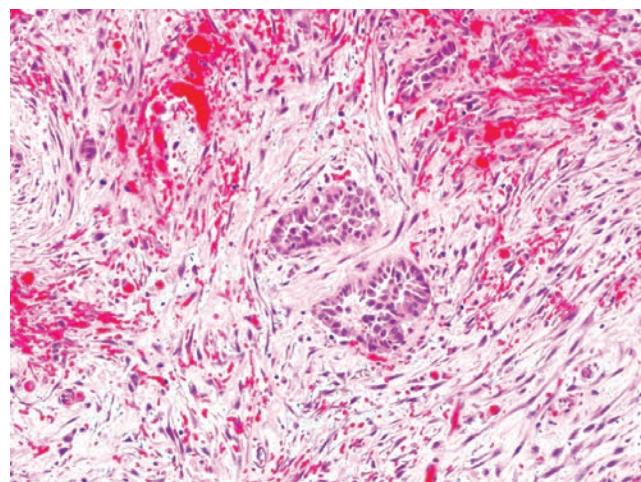


FIGURE 24.26. Noninvasive desmoplastic peritoneal implant displays an abundant granulation tissue-like spindle cell stroma with rare scattered glands lined by minimally atypical epithelium.

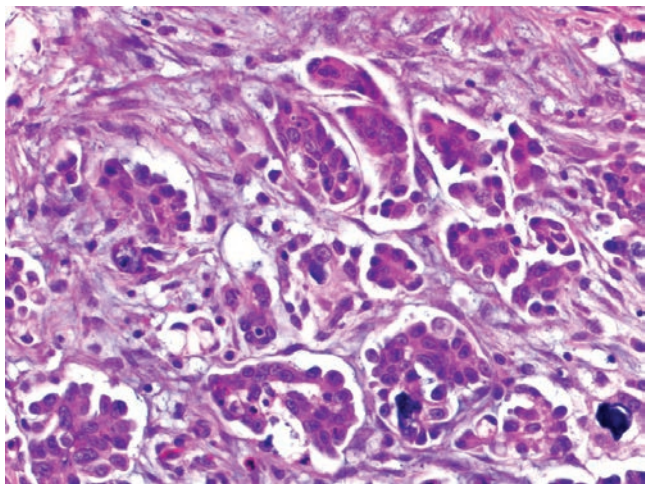


FIGURE 24.27. Invasive low-grade serous carcinoma/invasive peritoneal implant, characterized by small papillae lined by epithelium with mild atypia and surrounded by clear spaces.

implant is the determinant of benign versus malignant behavior in these tumors (see below), expert pathology consultation should be obtained if there is doubt about the diagnosis.

Among patients with APST or noninvasive MPSC, 9% (22% of those with implants) have invasive implants. In a population-based study from Canada, 12% of stage III patients had invasive implants (244). About three-fourths of patients with invasive implants have noninvasive MPSC; the finding of invasive implants with APST is very unusual and warrants further sampling of the ovarian tumor to identify occult areas of MPSC or invasion.

The characteristic architectural feature of an invasive implant is a haphazard infiltrative growth pattern (Fig. 24.27). A confluent or cribriform glandular pattern may be present. An exophytic pattern is not uncommon and usually displays a micropapillary pattern. Typically, micropapillae are haphazardly arranged and small solid nests of cells embedded in fibrous stroma and surrounded by a clear space or cleft are present (Fig. 24.27) (245). Invasive implants often display only mild cytologic atypia, but occasionally atypia is moderate. If severe atypia is present, high-grade serous carcinoma should be diagnosed.

Invasive implants are rare, and bonafide invasive implants reflect peritoneal metastases of MPSCs (some with undetected occult invasion) or, less likely, independent primary peritoneal serous carcinomas. Since MPSCs are often exophytic, malignant cells can theoretically be shed from the surface of the tumor and implant on peritoneal surfaces even when the primary tumor is not invasive. Invasive implants are associated with a poor prognosis and are considered invasive carcinomas.

Lymph Nodes

Nodal endosalpingiosis, or benign glandular inclusions, are found in 45% of patients with APST/noninvasive MPSC in whom lymph nodes are examined, in comparison to about 10% of women who have nodes removed for other reasons. Up to 42% of these patients have nodes containing serous lesions with proliferative features beyond endosalpingiosis. There is a strong association with invasive peritoneal implants and micropapillary architecture. In the Stanford series, 42% of patients with APST and lymph node resection had lymph node lesions, but this is likely an overestimate due to consultation bias and may also be related to the higher frequency of node sampling in patients with peritoneal implants (246).

Proliferative serous lesions in lymph nodes have been reported in over 100 cases of APST. Although these lesions have been referred

to as “metastases,” it is preferable to refer to them as “associated serous lesions in lymph nodes” or “lymph node involvement” as they may or may not be related to the ovarian tumor.

Lymph node lesions apart from endosalpingiosis can be divided into 2 types. One is characterized by individual cells and clusters of cells with abundant eosinophilic cytoplasm in the sinuses, predominantly subcapsular sinuses. The nature of these cells is unclear. When associated with simple papillae with serous features, they correspond to “individual cells, cell clusters and simple papillae,” as described in the Stanford series (246).

The second type of lymph node lesion is characterized by glandular inclusions and papillary serous structures, usually within or just beneath the capsule of the lymph node, that resemble the ovarian APST. The majority of these papillary serous lesions are also associated with endosalpingiosis in the same lymph node. Cytologic atypia is mild or moderate and mitotic figures are rarely seen. The observation of papillary proliferations arising within endosalpingiosis, and the rare reports of APSTs and carcinomas arising within lymph nodes from endosalpingiosis, suggest an independent origin of this second type of lymph node lesion.

In the 2006 Stanford series, 8 of 31 patients (26%) with lymph node involvement had invasive peritoneal implants. Among 22 patients with follow-up, 4 were alive with disease and there were 2 deaths, one in a patient with indeterminate peritoneal implants (246).

Clinical Behavior

In 6 prospective randomized trials including 373 patients with SBTs followed for a mean of 6.7 years, the survival was 100% (240), and large studies, some population-based, in the United States, Korea and Sweden show a 10-year survival of 96% to 100% (247,248,249). The disease-specific survival rate of patients with SBTs (APSTs and noninvasive MPSCs) confined to the ovaries after a mean of approximately 6.7 years, based on over 2000 reported cases, exceeds 99.5%. Essentially none of the allegedly fatal cases have been shown to have been comprehensively staged or sufficiently sampled. If patients with invasive implants (carcinoma) or indeterminate implants are excluded, then the overall survival for patients with lymph node lesions other than endosalpingiosis is 98% to 99%. The survival for patients with microinvasion or microinvasive carcinoma unassociated with invasive implants is 100%.

The behavior of SBTs with extraovarian lesions is based on the type of implants that are present. In the older literature, survival for SBTs with peritoneal implants ranged from 70% to 90%. Now, after excluding noninvasive MPSCs, nontumor deaths and invasive peritoneal implants, it is clear that the survival rate of patients with APSTs with noninvasive implants approaches 100% after a mean follow-up of 7.4 years (240). Recurrences and deaths reported in the literature are poorly documented in the majority of cases. When carefully documented, most deaths are either treatment-related or are the result of complications from adhesions and bowel obstruction rather than carcinoma (250). A literature review of over 18,000 borderline tumors which included over 4000 SBTs with clinical follow-up, failed to identify a single well-documented case of an SBT with noninvasive peritoneal implants, whose primary ovarian tumor had been adequately sampled to exclude invasion (at that time, 1 section per cm of maximum tumor diameter), that had progressed to documented invasive carcinoma. Based on a literature review of 467 noninvasive serous tumors, which included both invasive and noninvasive implants, the survival rate for patients with invasive implants was 66% after a mean follow-up of 7.4 years, compared to 95% for patients with noninvasive implants ($p < 0.0001$) (240). The survival rate for patients with invasive implants is similar to that for patients with invasive low-grade (micropapillary) serous carcinoma (251).

Low-Grade Malignant Serous Tumors

Low-grade serous carcinoma; micropapillary serous carcinoma (MPSC), invasive and noninvasive types; micropapillary serous borderline tumor; psammocarcinoma.

Low-grade serous carcinoma is synonymous with invasive MPSC and is a distinctive invasive carcinoma that is currently believed to arise from APSTs (see Pathogenesis, earlier in this chapter). It is not simply a low-grade version of the usual serous carcinoma, as accumulating evidence strongly indicates that this is a distinctively different cell type of ovarian carcinoma. It therefore should not be lumped with high-grade serous carcinoma, the usual fatal type of ovarian cancer.

A characteristic micropapillary and cribriform pattern in SBTs has been associated with invasive implants and a worse prognosis than typical SBTs (205). Despite the lack of demonstrable invasion, these tumors behave like low-grade carcinomas in contrast to the other tumors in this group (APSTs) which had nearly 100% survival. It was therefore proposed that they be designated noninvasive micropapillary serous carcinomas. Others have preferred the term “micropapillary serous borderline tumor”.

Unfortunately, the term MPSC has been used for 2 morphologically distinct, albeit related, entities and this has caused some confusion. The noninvasive form of MPSC is a variant of serous borderline tumor. The invasive form of MPSC is classified as well-differentiated serous carcinoma. It is likely that noninvasive MPSC is a form of *in situ* or intraepithelial carcinoma.

Noninvasive MPSCs comprise 14% of SBTs in consultation-based material; 10% in stage I, and 19% in advanced stage. In a population-based study from Canada, Gilks et al. found that 26% of advanced-stage SBTs were noninvasive MPSC (252). Invasive MPSCs are quite uncommon and comprise only 5% of ovarian carcinomas and 7% of serous carcinomas (Table 24.11). Advanced-stage serous carcinomas are invasive MPSC in 6% to 9% of cases.

Clinical and Operative Findings

The mean age of patients with the noninvasive form of MPSC is 42 years, the invasive form, 45 years, and the psammomatous variant (psammocarcinoma), 54 years. For noninvasive MPSC, two-thirds are bilateral as compared to only one-third with APST. Half of patients are stage I and the remainder are stages II and III. For invasive MPSC, 80% to 90% are bilateral and 94% are advanced stage. Bilateral tumors and those with an exophytic component are more likely to be associated with advanced-stage disease.

Gross Findings

The mean tumor size for the noninvasive form is about 8 cm, and for the invasive form, about 11 cm. Surface involvement is present in 54% of cases. As these tumors are very well differentiated, they tend to have a more papillary and cystic gross appearance like APSTs, and little if any necrosis, in contrast to many typical high-grade serous carcinomas that often have solid areas and extensive necrosis. Bilaterality, exophytic growth, and peritoneal implants are more common with noninvasive MPSC as compared to APST (253,254).

Microscopic Findings

Noninvasive MPSC is a proliferating serous neoplasm, which displays a high degree of epithelial proliferation and complexity but is noninvasive. The tumor displays a characteristic pattern of papillary branching. The distal papillary branches are thin and delicate with minimal fibrovascular support, and emanate abruptly from thick, more centrally located papillae without intervening branches of successive intermediate sizes, unlike

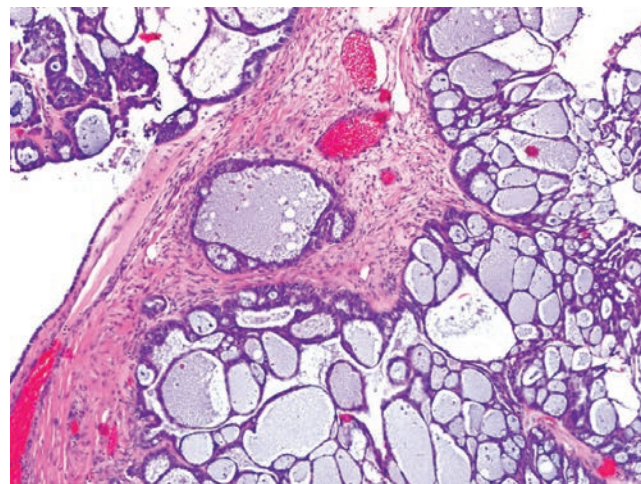


FIGURE 24.28. Noninvasive micropapillary serous carcinoma/micropapillary serous borderline tumor displays a cribriform or complex glandular pattern without invasion of underlying stroma.

the hierarchical branching pattern of APSTs. When the papillae fuse, a cribriform pattern or a Roman bridge-like pattern results on the surfaces of the large papillae (Fig. 24.28). Both micropapillary and cribriform patterns may be present. A 5 mm in diameter area of a confluent micropapillary pattern or 10% of the tumor occupied by the micropapillary pattern is required for the diagnosis. The majority of noninvasive MPSCs have areas of typical APST, in contrast to only 2% of high-grade serous carcinoma. In cases associated with metastases (invasive implants), invasion has been found in the primary tumor after exhaustive histologic sampling (239).

Noninvasive MPSC displays no invasion of the stromal cores of the papillae. Invasion in MPSC is recognized by haphazard infiltrative growth composed of solid nests or complex gland-like structures displaying micropapillae (Fig. 24.27). The nests and gland-like structures are often surrounded by a clear space or cleft. Psammoma bodies are common. The psammomatous variant of invasive MPSC, so-called “psammocarcinoma,” is characterized by a myriad of psammoma bodies occupying greater than 75% of the papillae.

MPSCs with or without invasion display similar cytologic features. Cells tend to be rounded with scant cytoplasm, and there is mild or moderate nuclear atypia, often with prominent small nucleoli. The cells in APSTs tend to be columnar, are often ciliated, and have less nuclear atypia. Mitotic activity tends to be low. Severe nuclear atypia warrants a designation of high-grade serous carcinoma even in the absence of overt invasion. In this latter situation, which is quite uncommon, further histological sampling of the tumor is likely to identify invasion.

The peritoneal implants associated with MPSC are frequently invasive (i.e., carcinoma). Among 157 reported cases of advanced-stage noninvasive MPSC, 45% of the implants were invasive, in comparison to 7% of the implants associated with APSTs ($p < 0.0001$). Noninvasive MPSCs also are more likely to be associated with serous lesions in lymph nodes that replace the node parenchyma, supporting the view that these are invasive carcinomas with metastatic potential.

Clinical Behavior

Despite the absence of obvious invasion in the noninvasive variant of MPSC, the data indicate that it behaves as a low-grade serous carcinoma. Stage I noninvasive MPSC has virtually 100% survival. In contrast to noninvasive MPSCs, invasive MPSCs are rarely stage I. The 5-year and 10-year survival rates for patients with advanced-stage noninvasive MPSC are approximately

70% to 85% and 40% to 60%, respectively. After recurrence as invasive carcinoma, the outcome of noninvasive MPSC is similar to that of invasive MPSC, with a progression-free survival of about 2 years and a median survival of 6 years to 7 years (255,256,257).

Invasive MPSC is synonymous with invasive low-grade serous carcinoma. Although the patterns of spread are similar to ordinary high-grade serous carcinoma, low-grade serous carcinoma has a significantly better prognosis (258). Stage III low-grade serous carcinoma is more likely to be stage IIIA as compared to high-grade serous carcinoma, which is nearly always stage IIIC. The natural history of low-grade serous carcinoma is characterized by indolent growth that is resistant to chemotherapy, and recurrences that maintain the well-differentiated histological appearance of the primary tumor, even decades later. Rare exceptions show transformation to high-grade serous carcinoma. The strong association of noninvasive MPSC with invasive implants is a highly significant difference from APSTs. These findings indicate that noninvasive MPSCs are in fact carcinomas, although this view is not shared by all experts.

High-Grade Serous Carcinoma of Ovarian, Tubal, and Peritoneal Origin

High-grade serous carcinoma is the most common type of ovarian cancer and accounts for approximately 50% of ovarian carcinomas. If the clinically and pathologically identical peritoneal and tubal serous carcinomas are included, in addition to carcinosarcoma and undifferentiated carcinoma which are variants, the frequency is over 70% (Table 24.11). In nearly one-third of women with advanced-stage high-grade serous carcinoma, the ovaries are small and display predominantly surface involvement. In the past, these findings have justified a diagnosis of primary peritoneal serous carcinoma.

It has been suggested recently that many or even most serous carcinomas classified as ovarian or peritoneal may actually be tubal carcinomas of fimbrial origin. This is discussed further earlier in this chapter (see Pathogenesis). For practical purposes, the clinical and pathological features of tubal, ovarian and peritoneal high-grade serous carcinomas are identical as described below.

Clinical and Operative Findings

Serous carcinoma most often occurs in the sixth and seventh decades, and the mean age is 63 years for advanced-stage high-grade tumors. Nearly all comprehensively staged patients present in advanced stage with tumor usually disseminated throughout the abdominal and pelvic cavities. Although most advanced-stage cases involve both ovaries microscopically, grossly the ovaries are of normal size in one-third to one-half of cases (includes all cases formerly classified as of peritoneal origin). The vast majority of advanced-stage ovarian carcinomas involve peritoneal surfaces, including the pelvic peritoneum and the surfaces of the bowel and other abdominal organs. Both pelvic and abdominal spread can be by direct extension or metastasis. For example, direct extension to the rectosigmoid, broad ligament, or uterus can occur by contiguous growth, or by exfoliation of malignant cells resulting in seeding of the peritoneal surfaces of the bowel or pelvic peritoneum.

Gross Findings

Serous carcinomas range from microscopic to about 20 cm in greatest dimension. They are typically multilocular, cystic and solid, with soft, friable papillae filling the cyst cavities, and occasionally are completely solid. The cysts contain serous, turbid, or bloody fluid. The external surfaces often display papillae. Solid areas on cut surface are pink to gray. Hemorrhage and necrosis are often present.

When the ovaries are normal in size, the ovarian surfaces often display papillary excrescences of variable size. The appearance of the fallopian tubes is variable. Sometimes they appear normal and may be adherent to the ovarian tumor. Sometimes they cannot be clearly identified. When the fimbriae are identified and carefully examined, they may appear hyperplastic and splayed over the ovarian or tumor surface. In occasional cases, a tumorous papillary outgrowth of the fimbriae constitutes the largest pelvic tumor. Rarely, the fallopian tube is dilated and filled with tumor; in the past, these were the only cases classified as being of tubal origin.

Omental and other peritoneal metastases are characterized by firm nodules with white or gray cut surfaces, which may coalesce to form an omental cake or large masses adherent to bowel and other structures. A grossly normal omentum contains microscopic tumor in 22% of cases.

Microscopic Findings

High-grade serous carcinomas display complex papillary and solid patterns and marked cytologic atypia (Fig. 24.29). Frequently they display a lace-like or labyrinthine pattern characterized by extensive bridging and coalescence of papillae resulting in slit-like spaces. Areas of solid growth, glandular and cribriform patterns are common (Fig. 24.29). Cytoplasmic clear cell change may occur, but characteristic architectural patterns of clear cell carcinoma are not present. Nearly all cases display areas of large, pleomorphic nuclei. Multinucleated tumor giant cells may be present (Fig. 24.29). Bizarre nuclei greater than 50 microns in diameter are characteristic and occur in 86% of advanced-stage tumors (Fig. 24.29). Mitoses, including abnormal mitoses, are numerous and necrosis is often pronounced. There are always at least focal areas with papillary or glandular architecture that permit the diagnosis of a serous carcinoma rather than undifferentiated carcinoma. Psammoma bodies are present in a majority of cases. Rarely, a completely solid carcinoma without any evidence of glands, papillae or other recognizable patterns occurs; this is probably a variant of high-grade serous carcinoma but is designated undifferentiated carcinoma (see below, Undifferentiated Carcinoma).

The fallopian tube mucosa displays intraepithelial carcinoma (STIC) in a substantial proportion of cases (Fig. 24.30). Depending on both interobserver diagnostic reproducibility and on whether the fallopian tubes were entirely embedded for examination, reports of STIC associated with high-grade

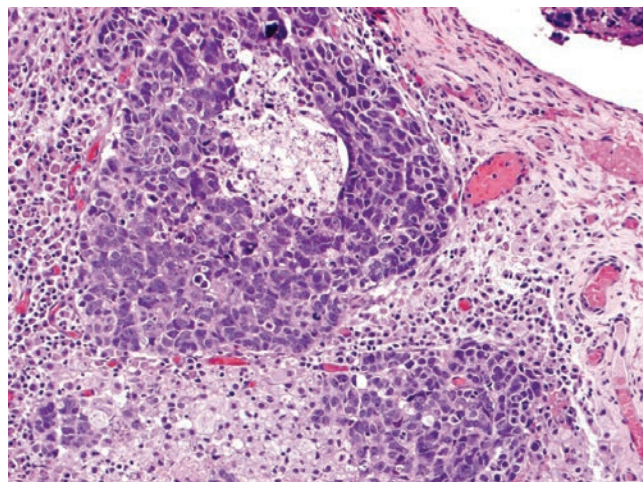


FIGURE 24.29. High-grade serous carcinoma displaying solid growth of markedly atypical epithelium with very large hyperchromatic nuclei. Necrosis is present.

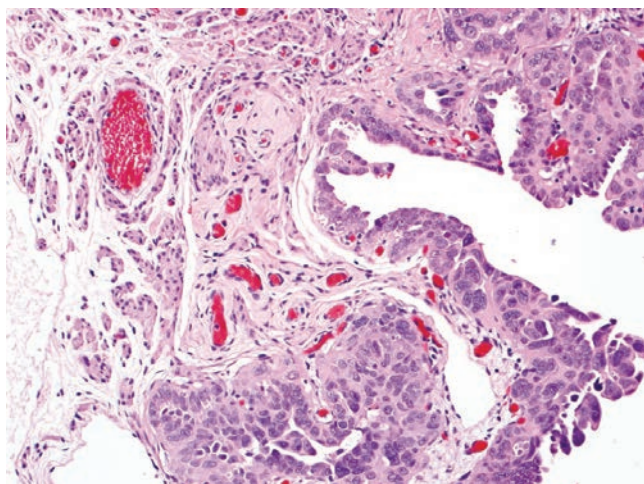


FIGURE 24.30. Serous tubal intraepithelial carcinoma displays a stratified layer of markedly atypical tubal epithelium without invasion of the underlying lamina propria of the fallopian tube mucosa.

serous carcinoma vary from 19% to 53% in tumors classified as ovarian and from 29% to 56% in tumors classified as peritoneal (217,259,260,261,262). STIC is usually, but not always, confined to the fimbriae. Complete embedding of the tube increases the yield of STIC. Accordingly, the fallopian tubes should be meticulously examined and entirely embedded for microscopic examination in all high-grade extrauterine serous carcinomas.

Grade

There is a bimodal distribution that separates serous carcinomas into a small group of low-grade carcinomas and a much larger group of high-grade serous carcinomas (263,291,301). These findings along with the distinctly different molecular genetic profile that distinguish low- from high-grade serous carcinoma support the use of a two-tier grading system instead of the traditional three-tier systems of well, moderate and poorly differentiated serous carcinomas. Unlike the two-tier system proposed by Malpica and colleagues from MD Anderson (MDACC), the three-tier system as advocated by Shimizu and associates does not have a histological or molecular basis to separate grades II and III (559). Besides the morphometric and molecular underpinning that support the binary grading system, this division reveals distinctive epidemiologic differences (264), more consistently separates prognostic groups, and has been validated to be reproducible among generalists and specialists (265). Low-grade serous carcinoma is characterized by uniform cells with mild to moderate nuclear atypia, whereas high-grade tumors have pleomorphic cells with marked nuclear atypia. Low-grade tumors have a mitotic index less than 12 per 10 HPF, and usually much lower, while high-grade tumors usually display greater than 12 per 10 HPF.

Mucinous Tumors

Primary ovarian mucinous tumors include cystadenomas, APMT, and carcinomas (intraepithelial and invasive). Cystadenomas and APMT are noninvasive and are distinguished from each another primarily by their degree of complexity and epithelial proliferation. The invasive carcinomas are distinguished by the presence of stromal invasion. There is a morphologic spectrum of epithelial proliferation in mucinous tumors that includes cystadenomas with focal epithelial proliferation, and APMT with intraepithelial carcinoma and/or microinvasion,

providing evidence that these tumors comprise a biologic spectrum with individual types representing steps in the sequence of ovarian mucinous carcinogenesis.

The other types of mucinous tumors seen in the ovary include metastatic mucinous carcinomas, most commonly from the gastrointestinal tract, and low-grade mucinous tumors of appendiceal origin, secondarily involving the ovary in association with the clinical syndrome of pseudomyxoma peritonei. Both metastatic mucinous carcinomas and low-grade mucinous tumors of appendiceal origin can simulate primary ovarian mucinous tumors, usually APMT and primary ovarian mucinous carcinoma (210). It is now clear that primary ovarian mucinous carcinomas are much less common than previously believed. Furthermore, most mucinous carcinomas within the ovary prove to be metastatic (197).

Benign Mucinous Tumors, Intestinal and Mullerian (Seromucinous, Endocervical-Like) Types

Mucinous cystadenomas (including the mullerian type; see below) comprise 15% of benign ovarian epithelial neoplasms (Table 24.10). About 80% are of the intestinal type. The mean patient age is about 50 years. Intestinal-type mucinous cystadenomas are unilocular or multilocular tumors of variable size, ranging from a few centimeters to over 30 cm, with a mean of about 10 cm. They are typically unilateral (95%). The capsule is typically thick and white with a smooth outer surface. The cysts contain thick gelatinous material. They are composed of glands and cysts lined by simple nonstratified mucinous epithelium (Fig. 24.31). When epithelial atypia or proliferation resembling APMT is present, this feature must be limited. Tumors composed predominantly of cystadenoma with less than 10% of APMT are diagnosed as mucinous cystadenoma with focal proliferation or focal atypia (210). Up to 18% of mucinous cystadenomas contain transitional cell nests, also referred to as a Brenner tumor component, often in a discrete nodule, which is usually interpreted as a concurrent Brenner tumor (Fig. 24.32) (285). Occasionally, cystadenomas have endocervical-type mucinous epithelium. These are referred to as mullerian type mucinous, endocervical-like mucinous, or seromucinous cystadenoma. They usually have a papillary architecture in contrast to the pure glandular pattern of the intestinal-type.

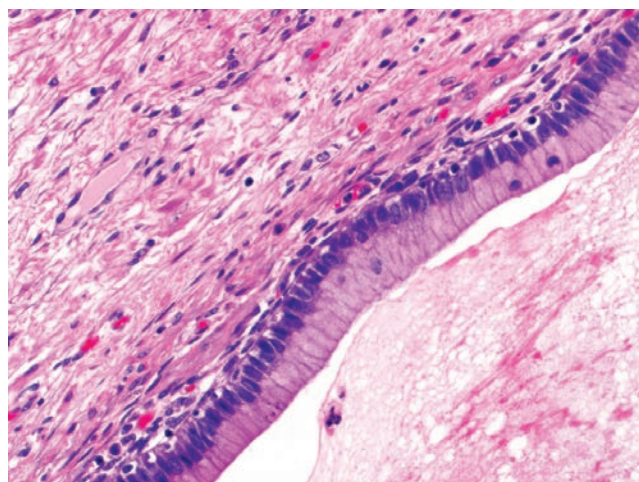


FIGURE 24.31. Mucinous cystadenoma shows a single layer of columnar epithelium with small basal nuclei and abundant mucin-rich cytoplasm.

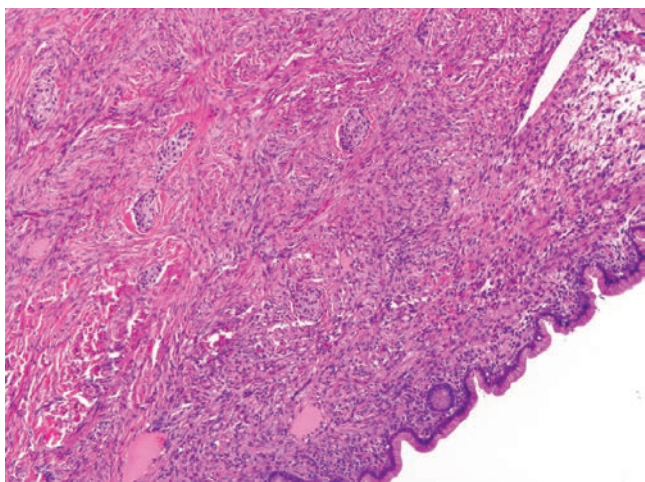


FIGURE 24.32. Mixed mucinous-Brenner tumor with several Brenner-type (transitional) nests within the stroma toward the top left, and a single layer of mucinous epithelium at bottom right.

Atypical Proliferative Mucinous Tumor (Mucinous Borderline Tumor, Intestinal Type)

Although the borderline category was intended mainly for serous tumors, the concept was also extended to mucinous tumors since they also appeared to have intermediate forms. These were most often characterized by pseudomyxoma peritonei and were felt to be analogous to serous borderline tumors with peritoneal implants. There are 2 types of APMT/MBT corresponding to the 2 types of mucinous cystadenoma: the gastrointestinal type, and the endocervical-like (mullerian, or seromucinous) type. The gastrointestinal type of APMT is typically a large, multicystic tumor with a smooth capsule, and is usually unilateral (>95%) with median size of about 20 cm to 22 cm (210,266). The locules of the tumor are usually filled with mucinous material and the lining appears smooth, without grossly evident papillations. Microscopically, the cysts are lined by stratified, proliferative gastrointestinal-type mucinous epithelium exhibiting tufted and villoglandular or papillary intraglandular growth and displaying mild to moderate nuclear atypia; stromal invasion is absent (Fig. 24.33).

Review of the literature on tumors meeting the diagnostic criteria for APMT, gastrointestinal type, reveals a benign behavior. Over 600 stage I tumors have been reported and fewer than

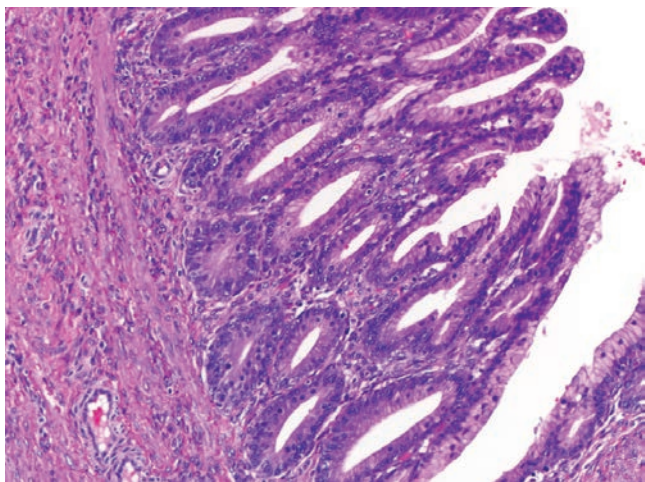


FIGURE 24.33. Atypical proliferative mucinous tumor shows glandular proliferation, cellular stratification, and mild cytologic atypia.

1% of patients have died of disease. Most fatal tumors had an unknown degree of sampling and are reported in the older literature; most recent studies report 100% survival (210). Approximately 100 “advanced-stage MBTs” have been reported, with nearly 50% mortality. Of these, about 85% have been associated with pseudomyxoma peritonei. More recent studies have established that virtually all cases of pseudomyxoma peritonei are of gastrointestinal (usually appendiceal), not ovarian, origin (see pseudomyxoma peritonei, below) (210). The remaining 15% of advanced-stage APMTs reported are probably metastatic mucinous carcinomas that masquerade as MBTs. Therefore, there is no clear pathologic description of peritoneal implants associated with true primary ovarian APMT, and therefore, for practical purpose, advanced-stage APMT does not even exist. When these latter tumors are removed from the APMT category, the remainder consist of stage I tumors with benign behavior.

Atypical Proliferative Mucinous Tumors, Seromucinous (Endocervical-Like or Mullerian) Type

The seromucinous type of APMT (atypical proliferative seromucinous tumor, APSMT) is grossly, microscopically and immunophenotypically distinct from the gastrointestinal-type tumor. The seromucinous tumors are much less common, smaller, more frequently bilateral, architecturally resemble APST, and are much more often associated with endometriosis (over one-third of cases). In addition, they frequently display acute inflammation of the stroma, and a combination of endocervical mucinous and serous (ciliated) type epithelium, often admixed with minor components (<10%) of other cell types. Based on a small number of studies, these tumors appear to exhibit benign behavior (210).

Atypical Proliferative Mucinous Tumors with Intraepithelial Carcinoma

Noninvasive mucinous tumors with marked nuclear atypia are classified as APMT with intraepithelial carcinoma. Intraepithelial carcinomas confined to the ovaries have an excellent prognosis (about 95% survival, with most recent studies reporting 100% survival). A small number of so-called “advanced-stage intraepithelial mucinous carcinomas” have been reported, with a few tumor deaths. In view of the ability of metastatic mucinous carcinomas to simulate APMT with intraepithelial carcinoma, it is likely that some of these apparent advanced-stage intraepithelial carcinomas with adverse outcomes represent metastases from occult extraovarian primary tumors. It is also possible that some of these represent true primary ovarian mucinous carcinomas with foci of destructive invasion in unsampled tissue.

Atypical Proliferative Mucinous Tumors with Microinvasion

Microinvasion in APMT has been defined as either small foci of stromal invasion characterized by single cells, glands or small clusters or nests of mucinous epithelial cells within the stroma, or as small foci of confluent glandular or cribriform growth within the stroma. The size criterion for each focus has varied from 2 mm to 5 mm, with no requirement regarding the number of foci allowed. Some tumors with microinvasion also have intraepithelial carcinoma. Based on the relatively small number of microinvasive tumors with follow-up that have been reported, no well-documented recurrences or deaths due to disease have been reported.

Mucinous Tumors Associated with Pseudomyxoma Peritonei

Pseudomyxoma peritonei has historically referred to the presence of mucinous ascites or mucoid nodules adherent to peritoneal surfaces and has not had a consistently applied histopathologic definition. Recent studies have clarified that pseudomyxoma peritonei is a clinicopathologic syndrome in which mucoid peritoneal nodules and/or mucinous ascites are accompanied by low-grade neoplastic mucinous epithelium associated with pools of extracellular mucin. Morphologic, immunohistochemical, and molecular genetic studies have provided compelling evidence that virtually all cases of pseudomyxoma peritonei are derived from low-grade mucinous adenomas, usually of the appendix, and that the ovarian involvement is secondary (210). When intraoperative consultation with frozen section leads to a diagnosis of a mucinous ovarian tumor in the setting of pseudomyxoma peritonei, appendectomy and thorough examination of the gastrointestinal and pancreaticobiliary tracts should be performed. The pathologist should examine the entire appendix microscopically. The rare exception to the gastrointestinal origin of pseudomyxoma peritonei is the occurrence of mucinous tumors arising in ovarian mature cystic teratomas associated with mucinous ascites (267). The terms “disseminated peritoneal adenomucinosis” (DPAM) and “involvement by low-grade appendiceal mucinous neoplasm” are now preferred as specific pathologic diagnostic terms for these low-grade peritoneal and ovarian mucinous tumors, respectively.

Invasive Mucinous Carcinomas

Clinical and Operative Findings

Mucinous carcinomas of the intestinal type are rare and comprise 3% of ovarian carcinomas (Table 24.11). Primary ovarian mucinous carcinomas, like APMT, most often present as large unilateral ovarian masses without evidence of ovarian surface involvement or extraovarian disease. The vast majority present in FIGO stage I.

Gross Findings

The gross findings are similar to APMT in that the tumors are typically large, unilateral, multicystic mucus-containing tumors with smooth white capsules and have mean and median sizes of 18 cm to 22 cm. They may contain solid areas and foci of necrosis and hemorrhage.

Microscopic Findings

Mucinous carcinomas of intestinal type typically are architecturally well-differentiated and display a variety of glandular patterns, with most tumors containing areas of APMT adjacent to areas of carcinoma. In addition to destructive stromal invasion, there is a second pattern of invasion termed the “confluent glandular” or “expansile” pattern. In this pattern, the glandular epithelium is markedly crowded and interconnected with little intervening stroma (268) (Fig. 24.34). Primary ovarian mucinous carcinomas commonly exhibit this pattern of invasion, and the presence of an infiltrative pattern of stromal invasion should raise concern for metastatic mucinous carcinoma. For tumors composed predominantly of APMT, the foci of confluent growth should measure more than the upper size limit allowed for microinvasion (5 mm) to qualify for the diagnosis of invasive carcinoma. Mucinous carcinomas of the seromucinous (mullerian or endocervical-like) type are quite uncommon. They are clinically and grossly similar to the atypical proliferative tumors of this type. Microscopically, they also resemble APMT but exhibit destructive stromal invasion or sufficient complex or confluent growth to be classified as carcinoma. Like their

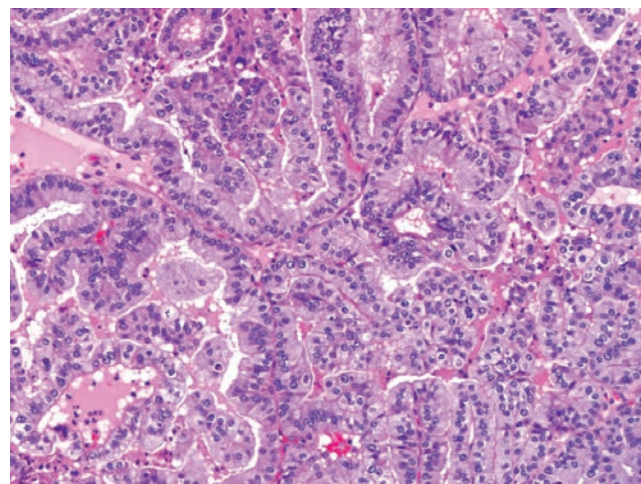


FIGURE 24.34. Mucinous carcinoma with confluent glandular pattern of invasion manifested by complex and interconnected epithelial proliferation lacking stroma.

noninvasive counterparts, they have a strong association with endometriosis.

As discussed above, it is critical when evaluating a mucinous carcinoma involving the ovary to consider the possibility of an extraovarian primary. Metastatic mucinous carcinomas are usually readily recognized as such when the ovarian tumors exhibit at least 2 of the following features: bilaterality, smaller size (typically less than 10 cm to 12 cm), ovarian surface involvement, a nodular pattern of ovarian involvement and a haphazard infiltrative pattern of stromal invasion. Immunohistochemistry can be of great value in this distinction. In general, primary ovarian mucinous tumors are positive for CK7 and variably positive for CK20. Most gastrointestinal carcinomas are negative for CK7 and positive for CK20. HPV and p16 staining can help assess for a cervical primary. Mammaglobin and GCDFP-15 are positive in most breast carcinomas and negative in ovarian mucinous tumors. DPC4 is positive in ovarian mucinous carcinoma and often negative in pancreatic carcinoma. ER and PR are generally not helpful markers as they are usually negative in primary ovarian mucinous tumors. An algorithm has been proposed to assist in the distinction of primary versus metastatic mucinous carcinoma, particularly at the time of intraoperative evaluation when only limited histologic material can be examined. As originally proposed, bilateral mucinous carcinomas and unilateral ones smaller than 10 cm are metastatic, and unilateral ones larger than 10 cm are primary (197). This algorithm correctly classified 90% of mucinous carcinomas. Subsequent studies have confirmed and refined the algorithm, also with close to 90% accuracy, and suggest that 13 cm is a better cutoff than 10 cm (226). Because these size measurements are often not extremely precise and may be taken after the tumor has been partially deflated and emptied of its mucinous contents, the 10 cm to 15 cm size range is of lesser predictive value (269).

Clinical Behavior

Patients with stage I mucinous carcinomas have a survival of about 90%, similar to comprehensively staged FIGO stage I patients with the other cell types of ovarian carcinoma. For patients with APMT with microinvasion and/or intraepithelial carcinoma, a staging procedure is unlikely to yield positive findings, but no data are available to address its value. Bona fide advanced-stage mucinous carcinomas have a poor prognosis, and limited data based on a recent GOG study suggests that the survival is significantly worse than that for serous carcinomas (270).

Metastatic Mucinous Carcinomas

It is now clear that the historical canon that mucinous carcinoma is a common type of primary ovarian cancer is incorrect. As noted earlier, 80% of mucinous carcinomas that involve the ovaries are metastatic from other sites. Metastatic mucinous carcinomas are typically bilateral, small (typically less than 10 to 12 cm), display ovarian surface and superficial cortical involvement, a nodular pattern of ovarian involvement, and a haphazard infiltrative pattern of stromal invasion. However, some metastatic mucinous carcinomas can exhibit gross and microscopic features simulating a primary ovarian mucinous tumor. In particular, metastases can be large, unilateral (thus misclassified by the algorithm discussed earlier), and multicystic and can display deceptive patterns of ovarian involvement. Recognizing metastases is especially problematic when the ovarian tumor is the initial manifestation of disease and an extraovarian primary mucinous carcinoma is occult. When mucinous carcinomas in the ovaries are rigorously classified based on refined criteria and awareness of the deceptive patterns, metastatic mucinous carcinomas are much more commonly encountered than primary ovarian mucinous carcinomas (197). In general, the presence of a mucinous carcinoma in the ovary, particularly if extraovarian disease is present, should always prompt the surgeon and pathologist to consider the possibility of metastatic mucinous carcinoma. Immunohistochemical analysis can be useful for identifying some metastatic mucinous carcinoma, but clinical evaluation is essential to exclude a clinically occult extraovarian source.

Endometrioid Tumors

The vast majority of endometrioid ovarian neoplasms are carcinomas. Endometrioid adenofibromas and atypical proliferative endometrioid tumors (APET) are quite uncommon. However, endometriosis is quite common and now regarded as neoplastic. Consequently, endometriomas and endometriotic cysts are the true benign endometrioid ovarian neoplasms, notwithstanding the likelihood that their ultimate origin is from the endometrium via tubal reflux. Molecular biological studies have shown that endometrioid ovarian carcinomas have similarities with and differences from their uterine counterparts.

Endometrioid Adenofibromas

Endometrioid adenofibromas are uncommon benign tumors that comprise less than 1% of ovarian epithelial neoplasms, and are unilateral 83% of the time. The median age at diagnosis is 57 years. The mean diameter is about 10 cm. The external surface is smooth and the cut surface is densely fibrous, often with intermixed cystic areas creating a honeycomb appearance. Microscopically, the dominant pattern is that of an adenofibroma or cystadenofibroma. The epithelial elements are arranged in branching tubular glands and cysts, and usually resemble those of proliferative or mildly hyperplastic endometrium. Endometrioid adenofibromas are frequently associated with endometriosis.

Atypical Proliferative Endometrioid Tumors

There is a spectrum of epithelial proliferation, glandular crowding, and cytologic atypia in benign endometrioid neoplasms ranging from mild atypia, mild glandular crowding, and epithelial stratification slightly beyond that seen in endometrioid adenofibromas, to confluent epithelial proliferation lacking stromal support in areas up to 5 mm in diameter resembling atypical hyperplasia and well-differentiated adenocarcinoma of the endometrium. A variety of terms have been employed for

these tumors, including proliferating or proliferative endometrioid tumor, atypical endometrioid adenofibroma, endometrioid tumor of low malignant potential, endometrioid borderline tumor and APET. APET with microinvasion (<5 mm), which is very rare, constitutes the upper end of this spectrum after which a diagnosis of low-grade endometrioid carcinoma is used. The behavior of all of the tumors up to and including those with microinvasion, has been benign.

Clinical and Operative Findings

APET comprise only 0.2% of ovarian epithelial neoplasms. Among 5 series, there were 134 patients with a mean age of about 51 years. Six patients (4%) had bilateral tumors, and all but 2 were confined to the ovaries. The mean tumor size was about 9 cm. The characteristic gross appearance is cystic in two-thirds and solid and cystic in the rest; the cyst fluid is usually hemorrhagic, brown or green. Many patients have had endometriosis and some have also had endometrial hyperplasia.

The 2 characteristic microscopic architectural appearances of APET are adenofibromatous and glandular/papillary. The glandular/papillary proliferation can show varying degrees of glandular complexity and crowding. When the glandular proliferation becomes confluent, this is considered evidence of invasion and is classified as microinvasion if the confluent area is less than 5 mm. Some investigators prefer to classify these as APET with intraepithelial carcinoma. A confluent epithelial proliferation or invasion that exceeds 5 mm in diameter warrants a diagnosis of carcinoma (268). The glands show crowding, mild or moderate cytologic atypia, epithelial stratification, and often display tufting and bridging. Severe cytologic atypia warrants a diagnosis of intraepithelial carcinoma, but this is quite rare. Among 134 reported APETs, all of those with clinical follow-up have had a benign behavior after a mean follow-up period of approximately 5 years (205,271). Rarely, an endometriotic cyst is lined by markedly atypical epithelial cells that have cytologic features of malignancy. If the lesion is well-sampled and invasion is not found, a designation of APET with intraepithelial carcinoma should be used.

Endometrioid Adenocarcinoma

In the older literature, about 15% to 20% of reported ovarian carcinomas are endometrioid, up to 25% in some reports (272), but when strict criteria are applied, the figure is lower and probably in the range of 10% to 15%. When very strict criteria are used, requiring a readily recognized resemblance to uterine endometrioid carcinoma and classifying nonspecific high-grade adenocarcinomas as serous carcinoma as is currently preferred (273,274), the figure is about 7.2% (Table 24.11).

Clinical and Operative Findings

These tumors are most common in the fifth and sixth decades, and the mean patient age at diagnosis is 55 years to 58 years. Tumor size ranges from 12 cm to 20 cm with a mean of about 15 cm. The stage distribution differs significantly from serous carcinoma. A high proportion of endometrioid carcinomas are diagnosed in stage I: 43% in a review of 874 cases from 19 series, and 53% at the Washington Hospital Center (Table 24.11). About 13% of early-stage (FIGO I–II) cases are bilateral. Endometriosis, which may be extraovarian, in the ipsilateral or contralateral ovary or within the tumor itself, is found in at least 15% to 20% of patients.

Gross Findings

Endometrioid carcinomas have a smooth outer surface. On cut section, they are solid and cystic, with the cysts containing friable soft masses and bloody fluid. Cysts occasionally contain

mucus or greenish fluid. Less commonly, the tumor is solid with extensive hemorrhage and necrosis. Tumors arising in endometriosis may display gross findings of an endometriotic cyst containing chocolate-colored fluid, with one or more solid nodules or papillary excrescences protruding from the wall and containing carcinoma.

Microscopic Findings

Destructive infiltrative growth characterizes one pattern of endometrioid carcinoma. This pattern is characterized by angulated glands with an infiltrative pattern, jagged irregularly spaced and unevenly shaped nests and solid sheets with jagged edges. More commonly, a confluent glandular epithelial proliferation exceeding 5 mm (the limit for microinvasion) is present. This pattern is characterized by extensive glandular branching, budding, true cribriform architecture and highly complex papillary proliferations (Fig. 24.35). Confluent or expansile invasion is the predominant pattern in most endometrioid carcinomas (268).

Architecturally well-differentiated endometrioid adenocarcinoma accounts for the majority of cases and is characterized by a confluent or cribriform proliferation of glands lined by tall, stratified columnar epithelium with sharp luminal margins (Fig. 24.36). A villoglandular growth pattern also occurs. Despite the low-grade architecture, high-grade nuclear features can be observed, at least focally. Mitotic figures are common. Squamous differentiation is present in up to 50% of cases. Focal secretory changes are seen in up to a third of cases. In the majority of cases, a component of endometriosis, endometrioid adenofibroma or APET can be identified.

Moderately and poorly differentiated endometrioid carcinomas show solid growth, complex glandular and microglandular patterns with marked nuclear pleomorphism and mitotic activity, however the majority of high-grade carcinomas with these features are usually classified as serous. It has been suggested that solid areas in some endometrioid adenocarcinomas may reflect an undifferentiated component (275).

At present, clinicopathologic and molecular data indicate that it is important to be strict about classifying an adenocarcinoma as endometrioid type. Most predominantly glandular non-clear cell, nonmucinous high-grade ovarian carcinomas should be classified as serous carcinoma. Glandular, cribriform, and solid patterns are common in serous carcinoma (273,274). A bonafide endometrioid adenocarcinoma should resemble eutopic endometrial carcinomas. Foci of squamous differentiation, secretory change, endometriosis, or endometrioid

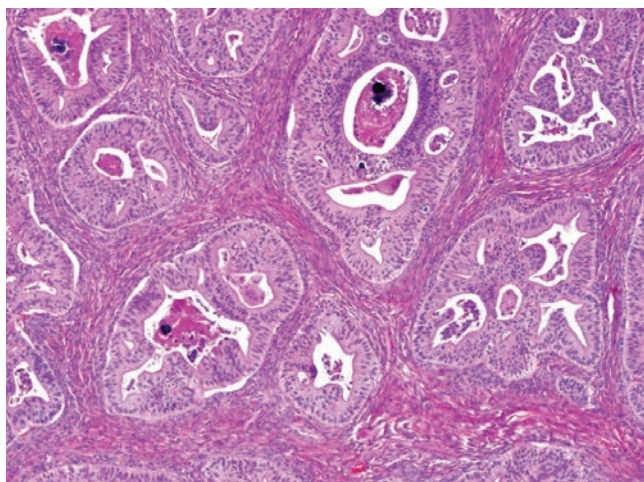


FIGURE 24.35. Endometrioid adenocarcinoma displaying an infiltrative pattern of cellular islands containing endometrioid-type epithelium with a cribriform pattern.

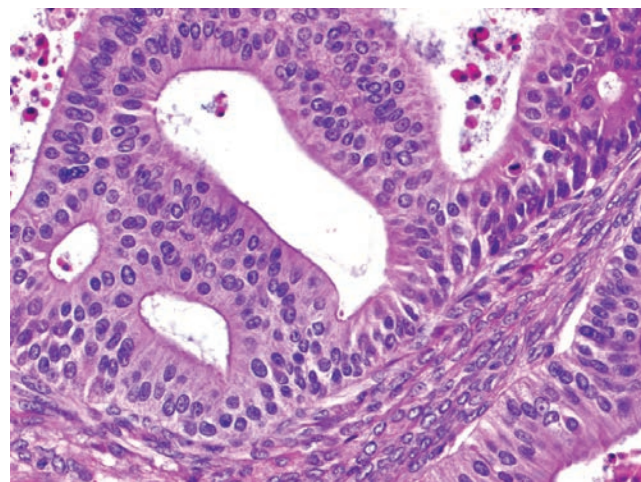


FIGURE 24.36. Endometrioid adenocarcinoma, high magnification (same case as Fig. 24.35) showing tall columnar epithelium with sharply punched out glandular spaces and mild to moderate cytologic atypia.

adenofibroma can be of value in supporting the diagnosis of endometrioid carcinoma.

Peritoneal keratin granulomas may be found in women with endometrioid ovarian carcinomas, presumably as a result of rupture of the neoplasm or exfoliation of squamous cells. Follow-up of a limited number of these patients reveals that these lesions have no prognostic significance and therefore should not be considered evidence of advanced-stage disease.

Clinical Behavior

Overall, endometrioid carcinomas of the ovary have a better prognosis than typical serous carcinomas due to the high proportion of stage I cases. The favorable prognosis may also result, in part, from the young age of most women diagnosed with endometrioid carcinoma and the high frequency of low-grade tumors. However, data on the influence of grade on prognosis are less clear because grade and stage are mutually confounding factors (see below, Prognostic factors). One recent large prospective series found that in stages II and III, the prognosis was significantly better for endometrioid as compared to serous carcinoma. In that series, however, endometrioid carcinomas were significantly more likely to be optimally debulked as compared to serous carcinomas, and occurred in younger women. In addition, neither substage nor grade was considered (272).

Endometrioid Carcinoma Associated with Uterine Endometrial Carcinoma

Approximately 14% of women with endometrioid ovarian carcinoma also have endometrial cancer of the uterine corpus. Endometrial hyperplasia is also commonly present. As both tumors are usually well-differentiated endometrioid adenocarcinomas, they resemble each other, and excluding the possibility that the ovarian tumor is metastatic can be a problem. Usually this can be determined based on a careful evaluation of the clinicopathologic features (276). If the uterine endometrial tumor is low-grade with no or only inner half myometrial invasion, its metastatic potential is very low and the ovarian tumor can confidently be regarded as independent. If the endometrial tumor is high-grade and/or deeply myoinvasive, the features of the ovarian tumors come into play. Bilaterality and a multinodular pattern, as well as other patterns characteristic of metastatic disease indicate metastatic tumor. Close association of the ovarian tumors with either an underlying adenofibroma or endometriosis, if present, can provide evidence that the ovarian tumor is independent.

The median age of women who present with simultaneous uterine and endometrioid ovarian cancer is about 50 years, significantly lower than that the median age of presentation for high-grade serous carcinomas (about 63 yr), and close to that for all women with endometrioid carcinomas (55 to 58 yr). The median ovarian tumor size is about 9 cm. The majority of tumors in both sites are well differentiated. The 5-year survival is 70% to 92%, and the median survival is 10 years or longer (277).

Over the last few years, investigators have employed several different molecular strategies to assess the likelihood that simultaneously detected endometrioid adenocarcinomas in the ovary and endometrium represent a single versus 2 independent primaries. Most of these have relied upon the presence or absence of shared genetic alterations in the ovarian and endometrial adenocarcinomas. The difficulty of correctly classifying some of these cases is highlighted by the fact that virtually every published series of synchronous ovarian and uterine endometrioid adenocarcinomas includes cases that, after being diagnosed using standard histologic criteria, would be reclassified based on molecular analysis (278).

Endometrioid Carcinoma Arising in Endometriosis

On average, 15% to 20% of endometrioid carcinomas of the ovary are associated with endometriosis which may occur within the tumor, the ipsilateral or contralateral ovary, or elsewhere. The frequency can be as high as 42%. It is likely that when strict criteria are applied to diagnose endometrioid carcinoma (see above), some cases would be reclassified as high-grade serous carcinomas and therefore the percentage of endometrioid carcinomas associated with endometriosis would be higher. The majority of bona fide endometrioid carcinomas can be shown to be associated with endometriosis when extensive histologic sampling and meticulous searching for the histologic features of endometriosis are performed, and strict diagnostic criteria are used. In only a minority of cases, however, can direct continuity from endometriosis to atypical hyperplasia to carcinoma be demonstrated. This is most commonly seen in the lining of an endometriotic cyst, which may display a thickening of the cyst wall, papillary excrescences, or a nodule protruding into the cyst. The mean age of women with endometrioid carcinoma associated with endometriosis is 5 to 10 years younger than for women whose endometrioid tumors are unassociated with endometriosis. Tumors associated with endometriosis, and particularly those arising in an endometriotic cyst, are usually architecturally well-differentiated and stage I, and therefore the prognosis is excellent. On rare occasions, a limited atypical epithelial proliferation in an endometriotic cyst will raise the differential diagnosis of atypical hyperplasia similar to the type seen in the uterine corpus, versus well-differentiated endometrioid adenocarcinoma. In such cases, criteria for this distinction used in the uterine corpus have been applied with minor modifications.

The identification of genetic alterations in endometriotic lesions and the observation of a morphological transition from endometriosis to carcinoma in over one-third of cases indicates that endometriosis is a precursor of endometrioid carcinoma. Progression from endometriosis to benign endometrioid neoplasm to well-differentiated endometrioid carcinoma is analogous to that proposed for progression of low-grade serous carcinoma from serous borderline tumor. Hence, low-grade (well-differentiated) endometrioid carcinomas are classified as Type I tumors in the dualistic model of ovarian cancer pathogenesis (see Pathogenesis, earlier in this chapter). Classification of high-grade endometrioid carcinomas is less clear. Overlap of both morphological and molecular features between high-grade endometrioid and high-grade serous carcinomas has led most authorities to classify the vast majority of gland forming

or near-solid cytologically high-grade ovarian carcinomas to the serous category, to the degree that “true” high-grade endometrioid carcinomas are considered to be very uncommon (273,274).

Clear cell Tumors

The vast majority of clear cell neoplasms of the ovaries are carcinomas and they comprise 8.5% of ovarian carcinomas (Table 24.11). Clear cell adenofibromas and atypical proliferative clear cell neoplasms are vanishingly rare (Table 24.10).

Clear cell Adenofibromas

These are among the rarest of the ovarian epithelial tumors; no cases were found among 1,247 consecutive epithelial tumors (Table 24.10). Among 12 reported cases of benign clear cell tumors, the mean age was 45 years. One tumor was bilateral. The median diameter was 12 cm. The tumors display a smooth lobulated external surface and the cut surfaces have a fine honeycomb appearance with minute cysts embedded in firm rubbery stroma. The cyst fluid is clear. Microscopically, the tumor is characterized by tubular glands lined by one or 2 layers of peg-like or hobnail cells that may bulge into the lumen or are flattened. The cytoplasm is either scanty, often in the hobnail cells, or abundant clear, granular or eosinophilic in the large polyhedral cells. Nuclear atypia and mitotic activity are minimal. The clinical behavior appears benign, although data are very limited.

Atypical Proliferative Clear Cell Tumors

Atypical proliferative clear cell tumors (APCCT) comprise 0.2% of ovarian epithelial tumors (Table 24.10). Among approximately 30 cases of APCCT (clear cell adenofibroma of borderline malignancy) in the literature, the mean age is 60 to 70 years. The mean tumor diameter is about 15 cm. The gross appearance is similar to that of the clear cell adenofibroma, but in addition there are softer and fleshier areas. Microscopically, the architecture is similar to the clear cell adenofibroma, but glands are more crowded. The tumor has greater epithelial proliferation and atypia than the adenofibroma and lacks stromal invasion. The cell types lining the glands and cystic spaces are similar to those in benign tumors but display significant nuclear atypia with coarse chromatin clumping, prominent nucleoli, and mitotic activity up to 3 per 10 hpf. The epithelium may display stratification and budding; true papillary structures are uncommon. Small solid nests of clear cells, significant gland crowding or papillary growth should raise the suspicion of stromal invasion. Distinction of an APCCT from clear cell carcinoma is one of the most difficult distinctions in gynecologic pathology. Some clear cell carcinomas lack an obviously infiltrative pattern and are characterized solely by crowded glands. The point at which gland crowding in a clear cell neoplasm reflects invasion is not well defined. The vast majority of tumors in which this differential is considered are best classified as clear cell carcinoma.

Occasionally, an endometriotic cyst is lined by atypical epithelial cells with clear cytoplasm. This has been designated “atypical endometriosis”. Rarely, cytologic features of malignancy are present in this setting. If the lesion is well-sampled and invasion is not found, the lesion is classified as APCCT with intraepithelial carcinoma. Microinvasion should be diagnosed if invasive areas measure less than 5 mm, but this finding should prompt additional sampling to look for diagnostic features of carcinoma. There are virtually no published data on clear cell tumors with microinvasion or intraepithelial carcinoma, both of which are exceedingly rare. Peritoneal “implants” have not been described associated with these tumors. Among the limited reported APCCTs, there is one alleged recurrence and no tumor deaths.

Clear cell Carcinomas

The accurate and reproducible diagnosis of ovarian clear cell carcinoma now relies heavily on recent data indicating that serous carcinomas can have areas of clear cells, and that such tumors have the other pathologic and immunohistochemical features of serous carcinoma and should be diagnosed as such (279). Old literature on clear cell carcinomas may therefore be inaccurate due to this recently emphasized classification problem.

Clinical and Operative Findings

The mean age of patients with clear cell carcinoma is 50 to 53 years. Symptoms usually relate to a pelvic or abdominal mass. Clear cell carcinoma is the most common epithelial ovarian neoplasm to be associated with vascular thrombotic events (18% to 46% of patients) and paraneoplastic hypercalcemia (2% to 10%).

The relationship with endometriosis is strongest for clear cell carcinoma among all cell types of ovarian carcinoma. Accordingly, endometriotic implants are commonly present in close proximity to the tumor or elsewhere in the pelvis or abdomen. About 45% to 60% of clear cell carcinomas present in FIGO stage I, and 10% to 20% in stage II (280) (Table 24.11). Eight percent are bilateral; 4% of stage I cases are bilateral (281). Several recent studies have shown that stage I clear cell carcinoma is more likely to be stage IC (50% to 74%) as compared to the other cell types (282,283,284). The reason for this is not clear, but it seems to be correlated with a higher risk of tumor rupture; this may be due to the extent and inherent difficulty in dissecting adhesions due to endometriosis.

Gross Findings

Tumors range up to 30 cm with a mean diameter of about 13 cm to 15 cm. Although they may be solid and fibrous with a honeycomb cut surface resembling benign and atypical proliferative clear cell tumors, more commonly the cut surfaces reveal a thick-walled unilocular cyst with multiple yellow-beige fleshy nodules protruding into the lumen, or a multiloculated cystic mass with cysts containing watery or mucinous fluid. Most tumors arise in endometriosis and often display features of an endometriotic cyst that typically contains chocolate-brown fluid, and a thickened, polypoid, or nodular area in the wall, or a larger solid area reflecting the focus of malignant transformation.

Microscopic Findings

Clear cell carcinomas display several different patterns, which often occur together (Figs. 24.37, 24.38, and 24.39). These include papillary, tubulocystic and solid. In a minority of cases, there is a prominent adenofibromatous component. Recently, some investigators have subdivided clear cell carcinomas into those arising in a cyst and those that are more solid and adenofibromatous. The cystic tumors are more frequently papillary, whereas the tubulocystic pattern (Fig. 24.37) tends to dominate in the adenofibromatous tumors. The cystic variant is more frequently associated with endometriosis, suggesting that the 2 variants arise along different pathways (280).

The solid pattern of clear cell carcinoma is characterized by sheets of polyhedral cells with abundant, clear cytoplasm separated by delicate fibrovascular septae or dense fibrotic stroma (Fig. 24.38). The papillary pattern is characterized by papillae that are either fibrotic but more often are hyalinized. In fact, the hyalinized papillary cores are a very characteristic feature of this tumor. The tubulocystic pattern is characterized by varying size tubules and cysts (Fig. 24.37). The majority of tumors display combinations of all of these patterns. Despite its name, many of the cells comprising clear cell carcinoma contain slightly granular eosinophilic cytoplasm. The cells with clear cytoplasm

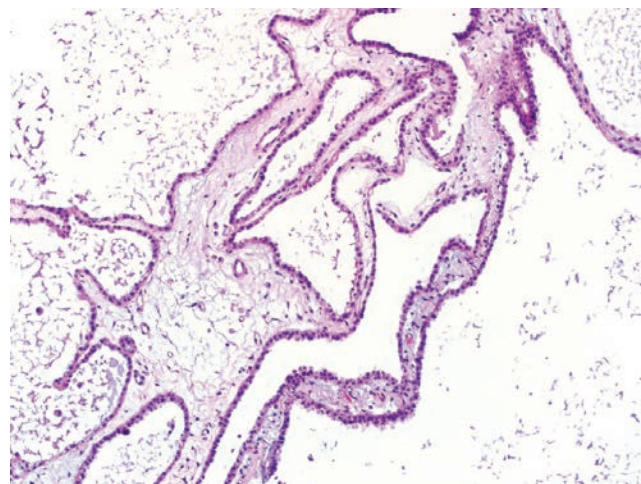


FIGURE 24.37. Clear cell carcinoma, tubulocystic pattern. This pattern is deceptively benign-appearing, characterized by cystic and glandular spaces lined by flattened to low cuboidal epithelium, often with only minimal cytologic atypia.

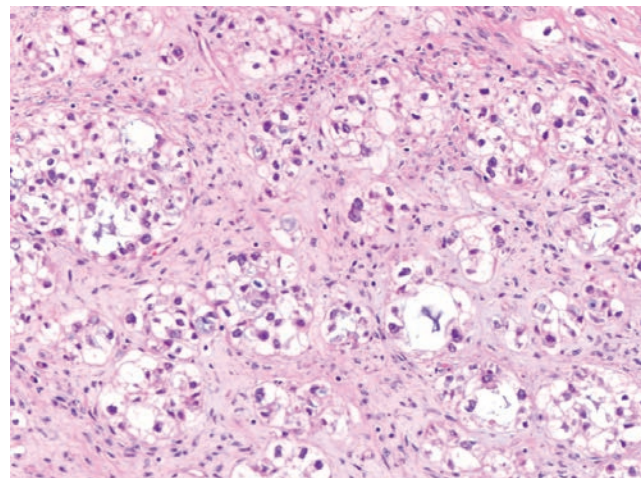


FIGURE 24.38. Clear cell carcinoma, glandular and solid pattern with an infiltrative pattern of small glands with severe cytologic atypia.

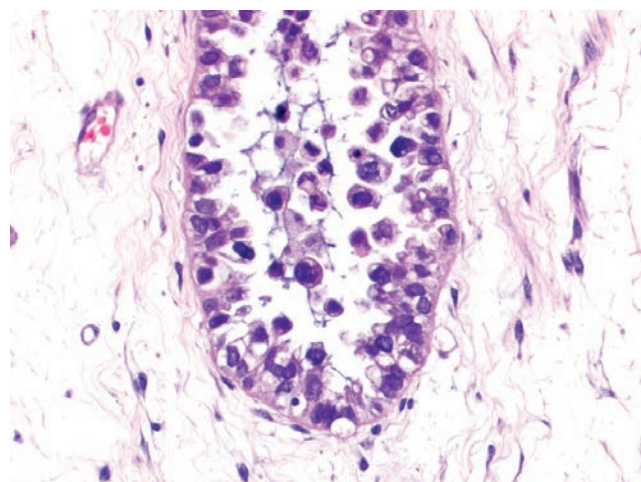


FIGURE 24.39. Clear cell carcinoma, hobnail pattern, displaying epithelial stratification of markedly atypical cells with clear cytoplasm and snouts protruding into the gland lumen.

contain glycogen. The nuclei vary from small and rounded and angular to large and pleomorphic with prominent nucleoli (Fig. 24.39). Often, the nuclear grade within a tumor varies from mild to markedly atypical. However, at least focally the nuclear grade is nearly always high. Clear cell carcinoma, though officially not graded, is considered high-grade in all cases. Mitotic activity tends to be low, exceeding 10 per 10 HPF in only one-fourth of cases. In the tubulocystic and papillary patterns, the cells often have a hobnail appearance with the nucleus protruding from the papillae, tubule or cyst, into the lumen (Fig. 24.39). Occasionally, the epithelium lining the tubules and cysts is flattened and the nuclear grade is low in these areas, but careful scrutiny will reveal cells with high-grade nuclei elsewhere.

Clear cell carcinomas arising in endometriosis are usually cystic and may display atypia of the lining of an endometriotic cyst with either a gradual or abrupt transition to cytologic features of malignancy and invasive clear cell carcinoma. This can be seen in one-third of clear cell carcinomas. If cytologic atypia is marked and invasion is absent, a diagnosis of APCCT with intraepithelial carcinoma is warranted. Cystic clear cell carcinomas are significantly more likely to be associated with endometriosis and atypical endometriosis as compared to the adenofibromatous type (280).

About one-third of reported ovarian clear cell carcinomas are associated with endometriosis either in the involved ovary or elsewhere in the pelvis or abdomen. These figures vary widely and many recent studies have observed 50% or greater associated with endometriosis (205). One recent large study found endometriosis to be present in about 90% of cystic clear cell carcinomas, while the association of endometriosis with adenofibromatous clear cell carcinomas was only 44% (280). When carefully sought, nearly all ovarian clear cell carcinomas are associated with endometriosis and at least one-third of cases can be demonstrated to have arisen within endometriosis, usually an endometriotic cyst.

Clinical Behavior

There are conflicting data on the behavior of clear cell carcinoma. In some studies, the prognosis appears similar to that for other ovarian carcinomas, but in others, the prognosis is said to be worse. Comprehensively staged ovarian carcinoma (of all histologic types) in FIGO stage I has a 90% or better 5-year survival, and several recent studies have shown comparable survival rates for clear cell carcinoma. Evidence that clear cell histology is an adverse prognostic factor in advanced stage is somewhat more convincing. However, recent refinements in the criteria for cell type assignment suggest that clear cell carcinoma has been overdiagnosed, as a small but significant minority of high-grade serous carcinomas contain clear cells. This misclassification removes some high-grade serous carcinomas from the serous group and thereby improves the survival of serous carcinomas by increasing the proportion of low-grade serous carcinoma (258). The improved survival of serous carcinoma may then appear better than that for clear cell carcinoma, which is always a high-grade tumor.

Brenner (Transitional Cell) Tumors

Transitional cell tumors comprise 10% of ovarian epithelial tumors. Nearly all of these are benign Brenner tumors; atypical proliferative and malignant forms are very uncommon. The transitional epithelial cell type, characterized by a relatively uniform population of stratified cells with ovoid nuclei displaying nuclear grooves, is named because of its resemblance to urothelium. Evidence suggests that Brenner tumors have some true urothelial differentiation, while transitional cell carcinoma

(unassociated with a benign Brenner component) is a variant of high-grade serous carcinoma.

Brenner (Benign Transitional Cell) Tumors

The mean patient age at diagnosis is 56 years. These are common incidental findings and are often microscopic in size. Most tumors are 2 cm or smaller. Multiple microscopic tumors are seen in 17% of patients. Occasionally they are large and may exceed 10 cm. Most tumors are well-circumscribed, firm and rubbery, with a smooth or slightly bosselated serosal surface. The cut surfaces are typically solid and fibrous, usually gray, white or yellow, and may be whorled or lobulated; occasionally a cystic component is present.

Microscopically, the characteristic feature is sharply demarcated epithelial nests in a dense fibrous stroma (Fig. 24.40). The epithelial cells are uniform in size with prominent cell borders and pale to eosinophilic cytoplasm. The nuclei are oval and longitudinal grooves are usually present. Atypia and mitotic activity are generally not present. A metaplastic mucinous component may occasionally form the dominant part of the tumor and accounts for the association of Brenner tumors with mucinous cystadenomas. It has been suggested that the majority of nonteratomatous mucinous tumors arise in Brenner tumors as an overgrowth of the mucinous component (285) (see below, Mixed Brenner-mucinous tumors). The stroma varies from closely resembling ovarian cortical stroma to densely fibrous. Hyalinized areas are common, and dystrophic, spiculated calcification is present in about half of the cases. The clinical behavior is benign.

Mixed Brenner-Mucinous Tumors

Tumors containing both Brenner and mucinous components are more common than previously appreciated (Fig. 24.32). These are believed to be variants of Brenner tumor and can be classified as metaplastic Brenner tumor or mixed Brenner-mucinous tumor. One-fourth of benign ovarian epithelial tumors that have a mucinous component also contain a Brenner component. Conversely, 16% of tumors with a Brenner component contain a mucinous component. These patients are significantly older than those with pure mucinous or pure Brenner tumor, with a mean age of 68 years. They are unilateral and most often have discrete Brenner and mucinous components, but in 30% the components are admixed. The

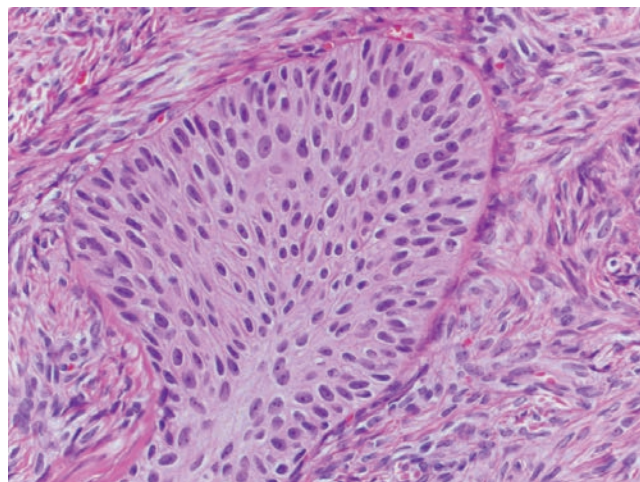


FIGURE 24.40. Brenner tumor. The transitional cell type is characterized by ovoid to spindle nuclei with prominent nuclear grooves, which resembles urothelium.

other clinical and pathologic features are similar to their pure counterparts (285).

Atypical Proliferative Brenner (Transitional Cell) Tumors

These rare neoplasms, also termed “atypical proliferative” or “borderline” transitional cell or Brenner tumor, or transitional cell or Brenner tumor “of low malignant potential,” present in patients whose mean age is 59 years. They are always unilateral and confined to the ovary. They are much larger than their benign counterparts, are usually cystic, and measure 10 cm to 28 cm with a mean diameter of 18 cm. Papillary or polypoid masses project into the cyst lumens, and there is usually a benign Brenner component present with a solid and fibrous cut surface. Microscopically, the intracystic papillary component is composed of transitional-type epithelium resembling low-grade noninvasive papillary transitional cell neoplasms of the urinary tract. Mucinous metaplasia may be present in the epithelium lining the papillae. Underneath the papillae and within the wall there may be solid areas of transitional epithelium with little intervening stroma (Fig. 24.41). Nearly all cases display areas of benign transitional cell neoplasm. The cytologic features are similar to those in benign transitional cell tumors, but occasionally significant atypia and mitotic activity are present. Among over 50 reported cases of atypical proliferative transitional cell tumors, there has been one local recurrence and no convincing evidence of malignant behavior. Accordingly, the term, “atypical proliferative transitional cell (Brenner) tumor” is preferred.

Malignant Transitional Cell Tumors (Malignant Brenner Tumors and Transitional Cell Carcinomas)

High-grade serous carcinomas may have focal areas that display features resembling transitional cell carcinoma. Nearly all tumors that have historically been classified as ovarian transitional cell carcinomas (TCC) are now regarded as high-grade serous carcinomas with transitional-like features by most but not all experts.

Some investigators have found that approximately 10% to 15% of advanced-stage ovarian carcinomas contain a transitional-like component; others have found that a transitional-like pattern predominates in 22% of advanced-stage ovarian carcinomas. In contrast, we have found only 3%

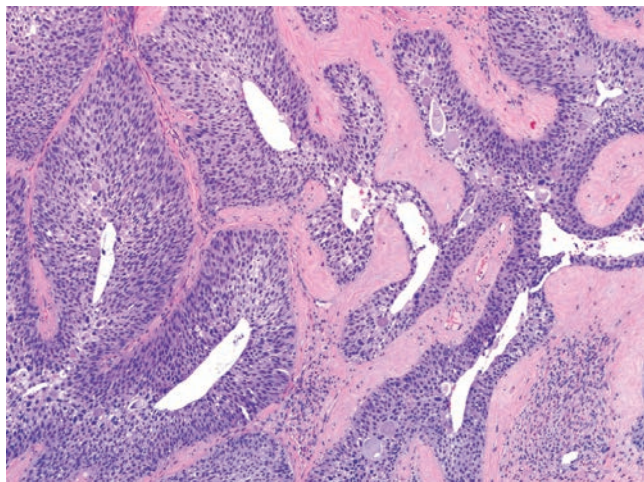


FIGURE 24.41. Atypical proliferative transitional cell (Brenner) tumor with expansile proliferation of transitional-type epithelium displaying mild to moderate cytologic atypia.

of advanced-stage serous carcinoma were classifiable as TCC. Some investigators have defined 2 clinicopathologic types of malignant transitional cell tumor: malignant Brenner tumor, in which a benign or atypical proliferative Brenner component is identified, and TCC, in which no benign or atypical proliferative Brenner component is identified.

Clinical and Operative Findings

Malignant Brenner tumors comprise 1% of ovarian carcinomas and occur at a mean age of 63 years, while TCCs present at a mean age of 56 years. The size of malignant Brenner tumors ranges up to 25 cm with a mean diameter of 14 cm. Among stage I tumors, 16% are bilateral. The stage distribution is as follows: stage I, 64%; stage II, 12%; stage III 18%; stage IV, 6%. In contrast, the majority of TCC present in advanced stage. The mean size of TCC is 10 cm.

Gross Findings

The gross appearance of TCC is similar to high-grade serous carcinoma that is typically solid and cystic. The cysts may exhibit polypoid, friable mural nodules, and the cyst fluid is watery or mucinous. Hemorrhage and necrosis may be prominent, and half have foci of gritty calcification. In the malignant Brenner tumor, the benign Brenner component may be identifiable as a solid fibrous nodule within a cyst wall. Sometimes malignant Brenner tumor is completely solid. Serous carcinomas that have a transitional cell component have the gross features of serous carcinoma.

Microscopic Findings

The histologic patterns of TCC are often mixed with other types of carcinoma, most often serous. Approximately 10% of ovarian carcinomas containing the TCC pattern are said to be pure. More than 50% of the tumor should display the patterns of TCC for a diagnosis of TCC. A diagnosis of malignant Brenner tumor is warranted when a benign or atypical proliferative Brenner component is identified within or is contiguous with the tumor.

The characteristic microscopic feature is thick, blunt, and often elongated papillary folds with fibrovascular cores, lined by transitional-type epithelium resembling urothelium. The papillae often appear to arise from a cyst wall with a similar lining of stratified and atypical transitional cells. A solid pattern is present in about half the cases. Stromal invasion is present and characterized by haphazard infiltrative growth of epithelium at the base of the papillae into the cyst wall, or extensive areas of solid epithelial proliferation with scant or no fibrovascular support. Another architectural pattern of malignant Brenner tumor is characterized by a solid tumor resembling benign Brenner tumor but the epithelial nests are more angulated and have a disorderly growth pattern which appears invasive (Fig. 24.42). In our experience, this latter pattern is the most common pattern of malignant Brenner tumor. In TCCs, cytologic atypia is usually prominent. High-grade pleomorphic nuclear features and bizarre giant cells occur in about one-third, further supporting the opinion that these tumors are transitional-like variants of serous carcinoma. In addition, malignant Brenner tumors, like their benign counterparts, often have prominent stromal calcification which is usually spiculated, in contrast to TCCs in which calcification is less common and more often psammomatous as in serous carcinomas.

Clinical Behavior

Limited data suggesting that TCC is more chemosensitive than serous carcinoma have not shown a prognostic difference independent of stage and volume of residual disease. TCC is clinically different from malignant Brenner tumor. TCC presents in

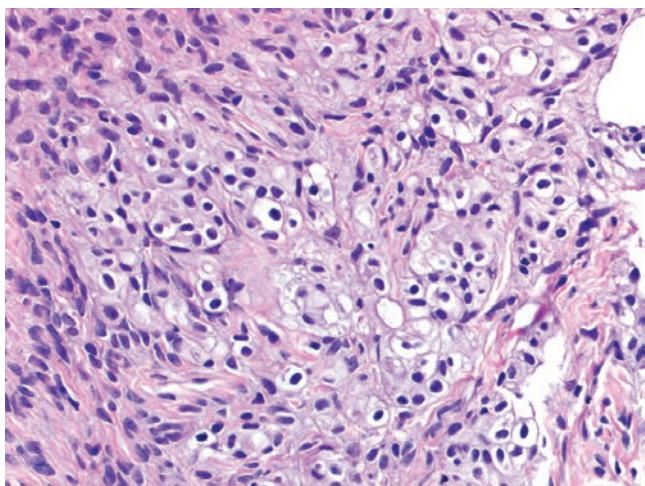


FIGURE 24.42. Malignant Brenner tumor characterized by small variably sized nests of transitional-type cells with an infiltrative pattern.

advanced stage, while most malignant Brenner tumors present in stage I. TCC is a variant of high-grade serous carcinoma and thus is a Type II tumor. This is supported by similar clinical and pathologic features between these 2 types of ovarian carcinoma, and an immunophenotype that more closely resembles serous carcinoma rather than TCC of the urinary tract. In contrast, malignant Brenner tumor has features of a Type I tumor (see Pathogenesis, earlier in this chapter).

Squamous Tumors

Epidermoid cysts comprise 1.4% of ovarian epithelial tumors. They are lined by squamous epithelium and lack teratomatous elements (286). Pure invasive squamous cell carcinoma is very rare, comprising 0.4% of ovarian carcinomas. In a series of 18 cases, endometriosis was found in 7 cases, and no underlying lesion was found in 11 cases. Invasive squamous cell carcinoma in the ovary is most commonly due to malignant transformation of a mature cystic teratoma; in such cases, the tumor is classified as a germ cell tumor with malignant transformation. Rarely, metastatic disease from the uterine cervix is the source of squamous cell carcinoma in the ovary.

The majority of patients with primary ovarian squamous cell carcinoma present with advanced-stage disease and die within 1 year. Although data are limited, this entity appears to confer a significantly worse prognosis than either high-grade serous carcinoma or squamous cell carcinoma arising in a mature cystic teratoma.

Mixed Epithelial Tumors

According to the WHO, the presence of 2 epithelial cell types in an ovarian epithelial neoplasm, each comprising at least 10% of the tumor, warrants a designation of a mixed epithelial tumor. Nonetheless, as mixed epithelial tumors are by necessity a heterogeneous group, it is more convenient and of no significant clinical import to ignore the minor components and classify tumors based solely on the predominant component, unless the minor component is malignant in an otherwise benign tumor, or is of a higher grade than the remainder of the tumor. As the prognosis for all cell types is essentially the same when stratified by stage, it is preferable to designate tumors based on the predominant component. Serous and endometrioid differentiation may occur together. In particular, poorly differentiated serous and endometrioid carcinomas often display overlapping

features, and at times, assignment to one or the other group is arbitrary and varies among observers. As discussed earlier, it has been suggested that there is no clinical or molecular basis for separating high-grade serous and endometrioid carcinomas. Many experts believe that these tumors are preferably classified as serous, reserving endometrioid for those tumors that display easily recognizable and characteristic features of eutopic endometrioid adenocarcinomas. Similarly, endometrioid and clear cell differentiation are not infrequently mixed. A mucinous component is often observed in benign transitional cell neoplasms (see above, mixed transitional cell-mucinous tumors).

Undifferentiated Carcinoma

Undifferentiated carcinomas show no readily identifiable features of any of the cell types of ovarian surface epithelial neoplasms. Therefore, any element of glands, papillae, or psammoma bodies removes a tumor from this category. Solid carcinomas with rare foci of glands or papillae are preferably classified as serous, although a few experts include such tumors in the undifferentiated category.

There are 4 types of primary ovarian undifferentiated carcinoma, referred to as follows: undifferentiated carcinoma not otherwise specified (NOS), non-small-cell neuroendocrine carcinoma, the hypercalcemic type of small cell carcinoma, and the pulmonary type of small cell carcinoma. When strict pathologic criteria are employed for these diagnoses, all types are very rare, together comprising less than 1% of invasive carcinomas. In the Washington Hospital Center series of 530 carcinomas (Table 24.11), there was a solitary case (0.2%) of undifferentiated small cell carcinoma (hypercalcemic type). In all cases when a diagnosis of undifferentiated carcinoma is considered, it is very important to exclude metastatic tumor, particularly from the lungs.

Although data are limited, undifferentiated carcinoma NOS appears to be more common than the other 3 types. The small cell type of undifferentiated carcinoma associated with hypercalcemia is the most common type of undifferentiated carcinoma in women under age 40 years. The usual type of undifferentiated carcinoma shares most clinical and pathologic features with high-grade serous carcinoma and therefore is probably a variant of this type. The mean age at presentation is 60 years and nearly all present in stages III and IV. Tumors are composed of solid sheets of large pleomorphic cells with high-grade nuclear features, and usually with abundant cytoplasm that is often eosinophilic. Overall, 22% survive 5 years, but only 14% of patients with stage III and IV disease survive 5 years. Although overall survival appears somewhat worse than that for serous carcinoma, data on this rare tumor are quite limited and when stratified by stage, patients with undifferentiated carcinoma do not have a significantly worse prognosis than those with high-grade serous carcinoma.

Non-small-cell neuroendocrine carcinoma is usually associated with another cell type of surface epithelial carcinoma, most often mucinous carcinoma, and therefore is best classified according to the better-differentiated component. Undifferentiated small cell carcinoma associated with hypercalcemia is a distinctive neoplasm occurring in young women with a mean age of 23. There is a characteristic microscopic pattern with sheets of small cells with interspersed follicle-like spaces. It is associated with a poor prognosis.

Malignant Mixed Mesodermal Tumor (Carcinosarcoma)

Although they were previously thought to be rare, carcinosarcomas comprise about 6.4% of ovarian carcinomas in the United States (Table 24.11) and 2.5% in Thailand (287). The mean age

at diagnosis, 64 to 66 years, is higher than that for serous carcinoma. These tumors are typically large, ranging from 15 cm to 20 cm in diameter. The stage distribution is identical to that of serous carcinoma. The morphology is similar to its uterine counterpart. The characteristic microscopic feature is an intimate admixture of malignant epithelial and stromal elements. The malignant epithelial element is most commonly a high-grade serous or endometrioid carcinoma, but can be of any of the surface epithelial cell types of ovarian tumors. The stromal component usually contains sheets of hyperchromatic rounded to spindled cells with marked nuclear atypia and a high mitotic index. Heterologous elements, most commonly cartilage, osteoid, and rhabdomyoblasts, are commonly found and, as in the uterine counterpart, their frequency depends on the diligence with which they are sought. Occasionally, a tumor that is otherwise a typical carcinoma has a small focus of malignant stroma. Although there are few published data on such tumors, they are classified as malignant mixed mesodermal tumors (MMMTs). Immunohistochemical stains for epithelial markers are often positive in the sarcomatous component, and their behavior and patterns of spread are similar to high-grade serous carcinomas. Like endometrial carcinosarcomas, the majority have been demonstrated to be monoclonal. These observations indicate that these tumors should be classified as metaplastic carcinomas like their uterine counterparts, and accordingly represent a Type II tumor (see Pathogenesis, earlier in this chapter). In the older literature, MMMTs were considered aggressive, rapidly fatal tumors with a median survival of approximately 1 year, but more recent data suggest that with cisplatin and either a taxane or ifosfamide therapy, survival rates approaching those for serous carcinoma can be achieved (288). When stratified by stage, some but not all studies have shown that the prognosis does appear to be worse than that for serous carcinoma. Most but not all studies have shown that, like their uterine counterpart, the presence of heterologous elements does not influence prognosis.

Sarcomas

Although primary, pure, or mixed sarcomas of the ovary are very uncommon, they constitute a heterogeneous group with 4 different types of neoplasms: endometrioid stromal sarcoma, adenosarcoma, sarcoma arising in a mature teratoma, and miscellaneous soft tissue sarcomas. Most carcinosarcomas are no longer considered sarcomas (see Malignant mixed mesodermal tumors, above). All of these tumors are extremely rare. Sarcomas arising in teratomas are classified as germ cell tumors with secondary malignant transformation.

Endometrial Stromal Sarcoma

Endometrioid stromal sarcoma (ESS; comprising the group of tumors formerly known as low-grade endometrial sarcoma) is an extremely rare primary ovarian neoplasm that is morphologically identical to its uterine counterpart. Among approximately 27 reported cases, 63% have been closely associated with endometriosis from which the tumor probably arises. The mean patient age is 52 years. The mean tumor size is 10 cm. Over 70% present in advanced-stage (FIGO II–III). Since primary uterine ESS is often slow growing and prone to late recurrence, it is important to consider the possibility of metastatic tumor from a uterine primary, even if the patient has had a hysterectomy in the remote past. Ovarian sex cord-stromal tumors with a predominant spindle cell component, including cellular fibroma, thecoma, and poorly differentiated Sertoli-Leydig cell tumor, are also important differential diagnostic considerations, and rarely an ovarian stromal tumor will have spindle cell patterns that are virtually identical to ESS. The behavior appears to parallel that of advanced-stage uterine ESS, although data are limited.

Mullerian Adenosarcoma and “Aggressive Endometriosis”

Mullerian adenosarcoma of the ovary is very rare. It is morphologically similar to its uterine counterpart. Nearly 60 cases have been reported (289). The mean age is 54 years and the mean tumor size is 14 cm. Sixty-five percent present in FIGO stage I. Nearly all cases are unilateral. Grossly, the majority are predominantly solid with some cystic areas, and 10% are predominantly cystic. The characteristic microscopic feature is periglandular stromal condensation with atypia and mitotic activity in these hypercellular areas of stroma. Leaflike processes of stroma covered by a single layer of benign epithelium is another characteristic pattern. About 15% have sex cord-like elements and 30% have sarcomatous overgrowth. In the largest series (289), among 40 cases, 9 tumors were considered high-grade (moderate or severe atypia and/or 10 or more mitoses per 10 hpf in the most active areas) and 31 were low-grade. Sixty-three percent of stage I tumors recurred. The 5-year recurrence free survival was 45% for women with low-grade stage I disease and 25% for women with high-grade stage I disease. The overall 5-year survival is about 65%. Interestingly, among 40 patients, 2 had small synchronous adenosarcomas that appeared to be independent: one in the endometrium and one arising in appendiceal endometriosis.

Rarely, histologically benign endometriosis appears infiltrative to the surgeon and/or displays perineural and vascular invasion. The stroma can be cellular but there is no atypia and mitotic activity is very low. It can prove difficult to resect and consequently may display low-grade malignant behavior. This may be a form of low-grade adenosarcoma and has been referred to as “aggressive endometriosis.” It has also been suggested that these are low-grade endometrial stromal sarcomas with endometrioid glandular differentiation. There are no large series of this entity and it is therefore poorly understood.

Tumors of the Fallopian Tubes

Benign Tumors

The most common benign tumor of the fallopian tube is adenomatoid tumor, also referred to as benign mesothelioma because of its histogenesis, which is now known to be mesothelial. These are nearly always incidental findings, typically 1 cm to 2 cm and often microscopic, and within the myosalpinx. They are firm and yellowish on cut section. Microscopically they display interanastomosing tubules and glands with no atypia or mitotic activity. The cytoplasm is eosinophilic and vacuolated. Of note, a small biopsy of a diffuse malignant mesothelioma can have an identical histological appearance. This is of little practical concern, as peritoneal mesotheliomas in women are exceedingly rare; we diagnosed 2 malignant peritoneal mesotheliomas during the same period as our consecutive series of 530 ovarian carcinomas over a 20-year period.

The tubal mucosa rarely gives rise to benign papillomas, SBTs and so-called metaplastic papillary tumor of pregnancy. This latter lesion is an epithelial metaplasia rather than a neoplasm. SBT more often arises within the leaves of the broad ligament. The myosalpinx, as it is composed of smooth muscle, occasionally gives rise to small leiomyomas. Occasional examples of tubal adenomyomas probably represent endometriosis with prominent smooth muscle proliferation. The peritoneal-lined serosal surface, in addition to adenomatoid tumor (see above), also may produce mesothelial/peritoneal cysts. When a mesothelial cyst is multiloculated, the pathologist may consider the possibility of so-called multicystic mesothelioma. However, this latter entity is exceedingly rare and probably not truly neoplastic. A diagnosis of cystic adhesions or multiloculated mesothelial/peritoneal cyst is most appropriate.

Female adnexal tumor of probable wolffian origin (FATWO) is a rare epithelial neoplasm that is usually found within the broad ligament and probably arises paratubally from mesonephric remnants. It is generally benign; however, it may recur. Several late recurrences and rare fatalities have been reported.

Malignant Tumors

High-grade Serous Carcinoma

The most common tubal malignancy is high-grade serous carcinoma, that is clinically and pathologically identical to high-grade serous carcinoma of the ovary and peritoneum. Until recently, carcinoma of the fallopian tube was thought to be rare, comprising less than 1% of gynecological malignancies. Over the past decade, evidence has been accumulating that a significant proportion of apparent ovarian and peritoneal high-grade serous carcinomas are associated with serous tubal intraepithelial carcinoma (STIC). STIC is usually fimbrial and is now felt by many but not all experts, to be the source of a majority of these tumors. This is discussed in greater detail earlier in this chapter (see Pathogenesis; and High-grade serous carcinoma).

There are very rare reports of clear cell and endometrioid carcinomas of the fallopian tube. Since these tumors, when ovarian, arise in endometriosis, tubal examples presumably arise in endometriosis as well. Several studies have shown that STIC is specifically associated with serous carcinomas (260,290), so that a tubal epithelial origin of clear cell or endometrioid carcinoma is unlikely.

Tubal carcinosarcomas (malignant mixed müllerian tumors) rarely occur and are classified as variants of high-grade serous carcinoma like their ovarian counterparts. Other types of sarcoma are exceedingly rare.

PROGNOSTIC FACTORS

Universally accepted prognostic factors for patients with ovarian cancer are FIGO stage, which reflects a combination of tumor size and disease distribution, and, in patients with stage IIIC and IV disease, volume of residual disease after surgical staging.

The issue of the prognostic importance of cell type and grade is complex because these features are interdependent, making it difficult to analyze them separately. Moreover, grade is poorly reproducible among pathologists. The vast majority of serous and clear cell carcinomas are high-grade regardless of the grading system used, while endometrioid and mucinous carcinomas are more often low-grade (263,291,301). As noted above (see Endometrioid Adenocarcinomas) overlap of both morphological and molecular features between high-grade endometrioid and high-grade serous carcinomas has led most authorities to assign the vast majority of gland-forming or near-solid cytologically high-grade ovarian carcinomas to the serous category, to the degree that “true” high-grade endometrioid carcinomas are uncommonly diagnosed.

Tumor Stage

Most patients with advanced-stage disease will have serous tumors. There is variability in survival for patients with the same FIGO stage, reflecting both the variability in completeness of staging (particularly for early-stage disease) and the variable biology of different histologic subtypes of ovarian cancer. SEER data suggest that 5-year relative survivals are 89% for patients with stage I disease, 45% for those with stage IIIa disease, 35% for those with stage IIIC disease, and 18% for those with stage IV disease. Ten-year figures decrease to 84%, 31%, 23%, and 10%, respectively (292). (Figure 24.43).

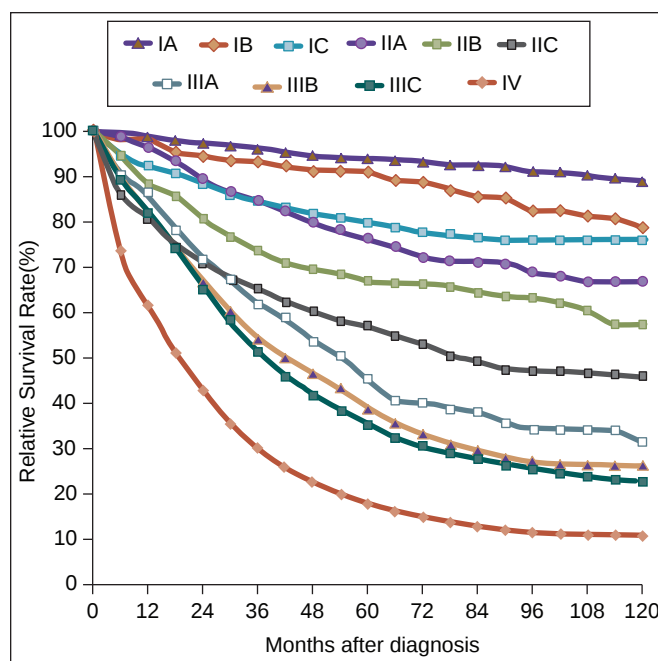


FIGURE 24.43. Adenocarcinoma of the ovary (all histologies but excluding borderline tumors): Relative Survival Rates (%) by AJCC Stage (SEER modified 3rd edition); Ages 20+, 12 SEER Areas, 1988–2001.

Source: Reprinted with permission from Kosary CL, SEER data.

Prognostic Variables in Early-Stage Disease

About one-third of patients present with stage I or II epithelial ovarian cancer (Table 24.1). Prognostic factors are particularly important in stage I disease because chemotherapy can be withheld for the subsets with best prognosis (see Fig. 24.44). Vergote et al. performed a large retrospective study using an international database of over 1,500 women with stage I invasive epithelial ovarian cancer to identify the most important prognostic variables. Routine peritoneal washings and lymphadenectomy were not performed, but palpable nodes were sampled. Twenty-eight percent of the tumors were serous, 27% were mucinous, 23% were endometrioid, 12% were clear cell, 3% were undifferentiated, and 6% were mixed. Chemotherapy administration was variable. The overall actuarial 5-year survival was 83% (disease-free survival 80%) (293,294). Multivariate analysis identified grade as the most powerful prognostic indicator of disease-free survival: patients with poorly versus well-differentiated disease on a 3-grade system had an 8.89 fold increased risk of recurrence. Other significant factors included rupture before surgery (Hazard Ratio (HR) 2.65); rupture during surgery (HR 1.65); and age (HR increased by 1.02 per year). Histologic subtype did not have independent prognostic significance. Size was not prognostic; low-grade early-stage tumors may be very large. A multivariable analysis of prognostic factors for recurrence in 2 GOG trials of women with surgically staged stage I and II disease, GOG #95 and GOG #157, identified 4 independent predictors: age > 60 years (HR 1.57), stage II (HR 2.7 versus stage IA or IB), grade 2 (HR 1.84 versus grade 1) or grade 3 (HR 2.47 versus grade 1), and positive cytology (HR 1.72). The 31% of the patients with stage II disease accounted for the majority of the recurrences (295).

Histologic Subtype

As noted above, the distribution of cell types in early-stage disease is very different from the distribution in advanced-stage disease. Most advanced-stage cancers are serous, whereas less than a third of early-stage cancers are serous (296). Endometrioid and clear cell cancers tend to present in an early-stage as

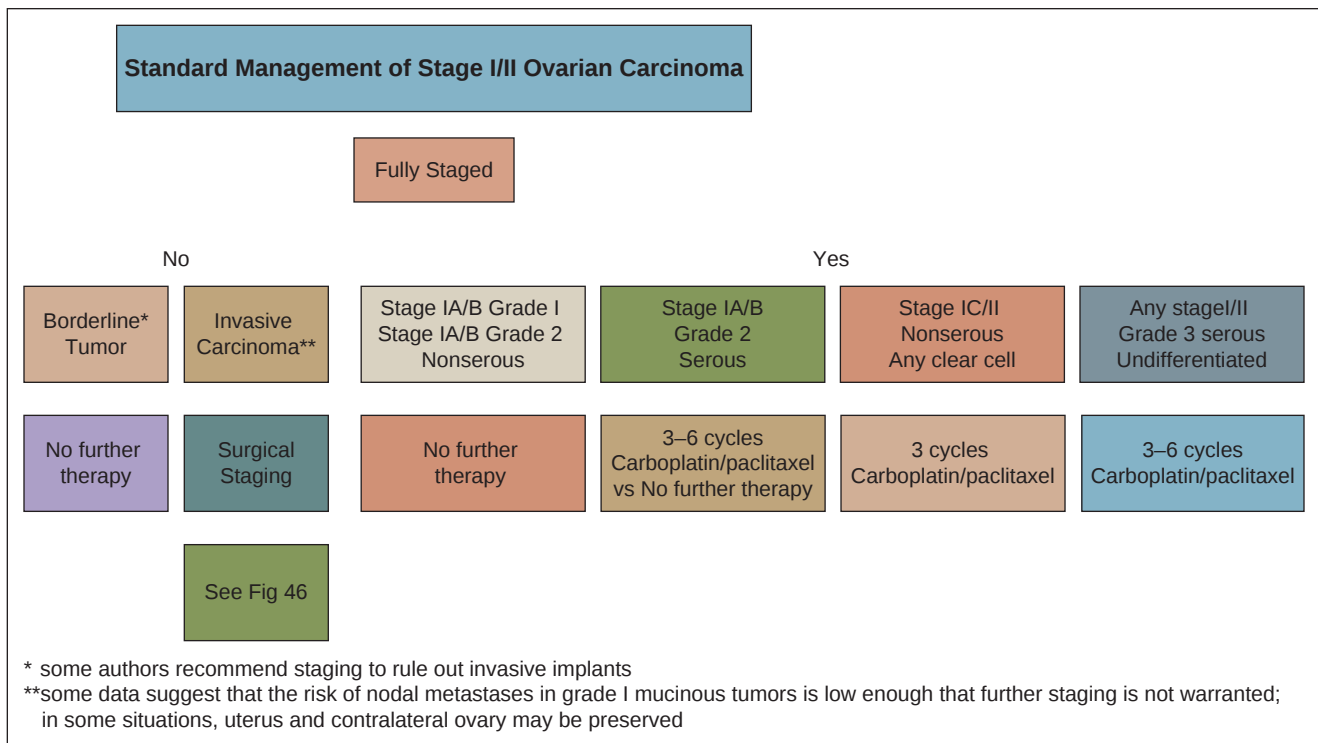


FIGURE 24.44. Standard Management of Stage I/II Ovarian Carcinoma.

a single mass. Serous histology has been reported to be a poor prognostic factor in stage I disease, especially in patients who have not been comprehensively staged (297). From 4% to 25% of patients with apparent stage I ovarian cancer will have nodal involvement when lymph nodes are pathologically examined; the risk for lymph node involvement correlates with histology (higher risk with serous and clear cell tumors) and grade (higher risk with higher grade).

Stage I clear cell carcinoma historically has been believed to be associated with a significantly worse outcome than the other cell types. However, several recent large recent series have not confirmed this (295,297–299). While advanced-stage mucinous tumors have a very poor prognosis, stage I mucinous tumors are generally low-grade, and have a good prognosis.

Grade

Despite the caveats mentioned above about interplay between histologic subtype and grade and about lack of reproducibility of grade, grade is associated not only with the likelihood of lymph node involvement in apparent stage I disease, but with the likelihood of recurrence in fully staged patients. From FIGO data for surgically staged patients (296) the overall 5-year survivals are 92%, 85%, and 79% for stage I grade 1, 2, and 3 tumors, respectively. Stage IA and IB grade 1 carcinomas have disease-specific survival rates as high as 97% in the absence of any adjuvant therapy (291).

Issues are less clear in more advanced-stage disease. Two recent large studies with uniform expert pathology, a Canadian population-based study of 575 patients with stage I–III optimally debulked patients (291), and a review of 1,895 stage III patients from a compilation of Gynecologic Oncology Group studies (300), review found that grade was not an independent prognostic factor in multivariate analysis.

A recently proposed binary grading system for serous carcinoma separates the majority of high-grade serous tumors from a small distinctive group of low-grade serous carcinomas (301).

Low-grade serous carcinoma, as currently defined by this system, is not simply a different grade of serous carcinoma (291,301); it is a distinctively different disease with specific molecular alterations, histopathology and clinical behavior (198). The low-grade group includes invasive MPSC as discussed earlier in this chapter (see section “Pathology”).

Surgical Prognostic Factors

Capsular rupture and malignant ascites are associated with worse outcomes, and are incorporated into stage. Tumor size is not prognostic. Uncertainty remains regarding adhesions. No problem regarding staging exists when the surgeon encounters discrete implants separate from the primary tumor or when solid tumor is found invading adjacent structures. However, more often, apparently benign adherence of a cyst to adjacent structures, in the absence of metastatic implants or obvious direct tumor extension, is found. There is an older body of evidence suggesting that such “benign” adhesions, when dense, are associated with a relapse risk equivalent to stage II, and that these patients should be considered to have stage II disease (302). Adherence is judged to be dense when so described by the surgeon, when sharp dissection was required to mobilize the tumor, when a raw area was left in the place of adherence, or when cyst rupture resulted from dissecting the adhesions free. Some clinical trials have advanced the stage of nonmetastatic but densely adherent tumors to stage II. However the retrospective international study of Vergote et al. (303) as well as a review by Seidman et al. (304) failed to identify dense adhesions as an independent prognostic factor. Adhesions are not used by the GOG to “upgrade” apparent stage I patients without histologic confirmation of disease.

CA125 Levels

A report analyzing data from 600 surgically staged (including lymphadenectomy) FIGO stage I epithelial ovarian cancer patients found preoperative serum CA-125 ≥ 30 U/mL to be an

independent predictor of decreased survival (HR 2.7). Clear cell and mucinous tumors had somewhat lower preoperative CA-125 levels. The only independent predictive factor other than CA-125 was age greater than 70 years (HR 2.6) (305).

Prognostic Variables in Stage III/IV Disease

Volume of Residual Disease After Surgery

As discussed more extensively in Section “Surgery,” the volume of residual disease following cytoreductive surgery is directly correlated with survival for both stage III and stage IV disease (see Figs. 24.15 and 24.16). Most series have focused on the size of the largest residual mass, and not the total number of lesions, but the number of residual masses may be an important prognostic factor as well. There is, of course, a correlation between volume of disease before surgery and residual disease remaining after surgery. While patients with stage IIIC disease who are without residual disease after surgery do better than patients with stage III C disease who have macroscopic residual disease, they still have a significantly worse prognosis than patients with stage IIIA disease (who are more likely to have low-grade tumors) (306). Women with a diagnosis of stage IIIC disease based solely on lymph node involvement have a better prognosis than those with a diagnosis of stage IIIC disease based on bulky upper abdominal metastasis (307).

Histologic Subtype and Grade in Advanced Disease

In advanced-stage disease, mucinous and clear cell histologies are associated with a significantly worse prognosis, possibly because of chemotherapy resistance. Advanced-stage endometrioid tumors are associated with a better prognosis than advanced-stage serous tumors. One retrospective series, which included patients with stages IIC–IV disease treated with paclitaxel/platinum following cytoreductive surgery showed median overall survivals of 121 months for low-grade serous tumors, 15 months for mucinous tumors, 64 months for endometrioid tumors, 29 months for clear cell tumors, and 45 months for a category including high-grade serous, unspecified and undifferentiated carcinomas (308). Not all series show such dramatic differences in prognosis for women with low-grade versus high-grade serous carcinomas. Seidman et al. compared 2 binary grading systems for serous carcinomas, and found that 5-year survival for women with high-grade versus low-grade stage III disease was 35% versus 39% using one system and 34% versus 56% using another (309). An analysis of tumors of women treated on GOG 158 (optimally debulked stage III disease) found that using the two-tier system developed at the MD Anderson Cancer Center, 8.7% of women had low-grade disease with a median progression-free survival of 45 months versus 19.8 months for the 91.3% of women with high-grade disease. Three-year overall survival was 90.5% for those with low-grade disease versus 67.6% for those with high-grade disease. Using FIGO grading the median progression-free survival for grade 1, 2, and 3 tumors was 37.5, 19.8, and 20.1 months, respectively (310).

Grade and stage are confounded: low-grade serous carcinoma (invasive MPSC) is more likely to be stage IIIA or IIIB as compared to high-grade serous carcinoma (Type II), which is nearly always presents as stage IIIC disease. In addition, low-grade serous tumors occur in younger women who tend to have fewer comorbidities (311). Regardless of the grading system used, low-grade serous tumors (Type I) make up only a small fraction of stage III serous tumors (less than 10% using the MD Anderson grading system). It seems likely, given the different molecular alterations seen in Type I versus Type II serous tumors, that in the future different systemic therapies will be used for each type. However, at this time, although some reports

suggest that cytotoxic chemotherapy is less effective against advanced-stage low-grade tumors (312), there are no good data to suggest appropriate alternative therapy.

CA-125 Levels in Advanced Disease

Although not all patients with advanced ovarian cancer have an elevated serum CA-125 level, serum levels of CA-125 generally reflect volume of disease. Prechemotherapy CA-125 levels have been shown on univariate analysis to be of prognostic significance, but on multivariate analysis, they are usually not an independent prognostic factor owing to their association with volume of disease (313). Postoperative CA-125 levels appear to have greater prognostic significance, and have been reported to be of independent prognostic significance in patients with or without residual disease. Decline of CA-125 with chemotherapy is also prognostic. In one study, normalization of CA-125 (level less than 35 U/mL) after the third cycle of treatment was associated with a median overall survival of 42 months compared to a median survival of 22 months for those whose CA-125 did not normalize. This association held true even within the subgroup of optimal microscopically debulked patients (314).

Other Prognostic Factors

Age is a strongly adverse prognostic factor in most studies. This may partially reflect comorbidities and the inability of older patients to tolerate intensive therapy, but nonetheless older patients are more likely to present with advanced-stage and high-grade disease. Poor performance status and an increased number of patient-reported symptoms, particularly lower extremity edema, are associated with worse outcomes (315). Perioperative infection has been reported to be an independent risk factor for poor outcomes, with an associated decrease in median survival by nearly 2 years (316). High maximum standardized uptake (SUVmax) of primary tumor on positron emission tomography (PET) scanning is correlated with stage (increased in higher stage tumors) and histology (increased in serous tumors), and is associated with shorter survival (317). Thrombocytosis has been reported to be associated with advanced disease and shortened survival (318). In the United States, African American race is associated with worse outcomes, and this disparity has been increasing over time; differences in access to care may account for a large portion of this finding, as studies at single institutions with consistent treatment of patients or on clinical trials do not show significant differences in outcomes by race (319–321). *BRCA1* and *BRCA2* mutations have been reported in most, but not all, series to be associated with both an improved survival and a higher response rate to platinum-based therapies (322–325). Microarray-based gene expression profiles with prognostic significance are being developed, but none have yet come into clinical use (326,327).

EARLY-STAGE (I AND II) OVARIAN CANCER

Approximately 25% of women with ovarian carcinoma present with stage I or II disease. Survival by stage is presented in Figure 24.43. An algorithm for standard management of early-stage disease is shown in Figure 24.44. Unlike advanced-stage ovarian cancers, which are usually high-grade serous tumors, around a third of early-stage tumors are low-grade, and mucinous and endometrioid tumors are about as common as serous tumors (Table 24.12). Clear cell tumors make up over 10% of early-stage disease (294,296).

Table 24.12 Relationship between Histology and Stage in Ovarian Cancer

	IA (n = 749) (%)	IIIC (n = 2,424) (%)
Serous	21	68
Mucinous	33	7
Endometrioid	24	11
Clear cell	14	4
Undifferentiated	2	6
Mixed	6	4

Source: Adapted from Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. *Int J Gynaecol Obstet* 2006;95(Suppl. 1): S161–192, with permission.

Surgical Therapy for Early-Stage Ovarian Carcinoma

Surgery will be curative for most patients with early-stage ovarian cancer. The optimal surgical procedure for most epithelial ovarian carcinomas is removal of the uterus along with both fallopian tubes and ovaries and complete surgical staging. This is discussed in more detail in section “Surgery.” There are a few situations in which full staging is not always needed, such as incompletely staged borderline ovarian carcinomas and grade 1 mucinous tumors (328,329). The general advantage of surgical staging in early ovarian cancer is that chemotherapy can sometimes be omitted in a fully staged patient.

Fertility Preservation

In the younger patient who wishes to retain her childbearing potential and who appears to have a curable cancer (i.e., a localized tumor with mucinous, endometrioid, or low-grade serous histology), it is appropriate to preserve the uterus and the contralateral ovary. Any abnormalities in the remaining ovary should be biopsied during surgery and sent for frozen section. If the frozen section is ambiguous as to whether the tumor is benign, borderline, or malignant, or if there is doubt about the extent of the disease, final pathology should be awaited and a two-step surgical approach employed. If both ovaries contain invasive tumor on frozen section ovarian preservation is usually not indicated.

Recommendations (330): FIGO IA, GI + II, serous, mucinous, endometrioid → Fertility sparing surgery

FIGO IA, clear cell cancer → Consider fertility sparing surgery

FIGO IC, GI + II, serous, mucinous, endometrioid → Consider fertility sparing surgery

FIGO IC, clear cell cancer → No fertility sparing surgery

FIGO IA + IC, GIII → No fertility sparing surgery

Postoperative Follow-up for Stage I Ovarian Carcinoma

As described above, patients with stage IA and IB grade 1 carcinomas have been reported to have disease-specific survival rates as high as 97% in the absence of any postoperative therapy.¹ Early GOG trials similarly showed that overall, patients with stage IA or IB and grade 1 or 2 disease had a 5-year disease-free survival rate (DFS) of 91% and a 5-year overall survival rate of 94% with surgery alone (331). Other patients with early-stage disease are considered to have a risk of recurrence high enough to warrant adjuvant therapy. However, the benefit of

such treatment has been difficult to prove because the number of patients with higher grade early-stage disease is small (so trials are difficult to complete) and the overall risk of recurrence is not that great (so large trials are needed). Published trials have included multiple histologic types with very different biology and variable staging, and generally have lacked the power to show interactions between treatment and grade or histologic subtype. In addition, treatment at recurrence may be curative for a small number of patients who did not receive initial adjuvant treatment.

Radiotherapy for Early-Stage Ovarian Cancer

External Beam Therapy

Early small randomized trials suggested that pelvic radiotherapy compared to observation for early-stage ovarian cancer reduced the rate of relapse in the pelvis, but had no impact on overall recurrence rate or survival because relapses occurred throughout the peritoneal cavity (332). Interest turned to abdominopelvic radiotherapy in the early 1980s after investigators from the Princess Margaret Hospital in Canada published results of a small study showing that for women with incompletely staged IB, II, or III optimally debulked ovarian cancer randomized to pelvic radiotherapy plus whole abdominal radiotherapy (WAR) had a survival advantage over those randomized to pelvic radiotherapy followed by chlorambucil (333). However, subsequent trials did not confirm this finding (334,335). Investigators at the M. D. Anderson Cancer Center randomized 156 patients with FIGO stage I, II, or III disease to melphalan alone versus abdominopelvic radiotherapy, and found similar relapse-free survival for both treatments in women with stage I or stage II disease (336). A later small trial published in 1994 showed a trend towards superiority of cisplatin/cyclophosphamide chemotherapy over WAR in women with high-risk early-stage disease (337).

Currently, radiation is rarely used as primary therapy for ovarian cancer, but interest in this approach remains. Given that pelvic radiotherapy can decrease local relapse, it is possible that the addition of radiotherapy to chemotherapy could improve disease control in some patients, such as those with bulky stage II disease, positive pelvic margins (pelvic sidewall or colon) or chemotherapy-resistant subtypes of disease, such as clear cell tumors. Swenerton et al. recently reviewed data on 703 women from Canada with no macroscopic residual disease after surgery who underwent platinum-based chemotherapy with or without sequential abdominopelvic radiotherapy. Among women with stage I or stage II clear cell, endometrioid, or mucinous histology, the addition of radiotherapy was associated with a 43% decrease in overall mortality (338). No benefit was seen for those with stage III disease or tumors of serous histology. The most common late side effect was chronic GI toxicity, with 41/351 women having chronic grade 2 or higher GI toxicity. A subsequent analysis from the same group looked only at clear cell carcinomas, and suggested a benefit specifically for stage IC and stage II disease (339). It seems possible that similar benefit and less toxicity could be seen with pelvic radiotherapy alone rather than abdominopelvic radiotherapy, and hopefully future trials will address this issue.

Radiocolloid Therapy

Since transcoelomic spread is the main route of dissemination of ovarian cancer, the intraperitoneal instillation of radiocolloids, which deliver high doses of radiation to the peritoneal surfaces, was historically used for early-stage disease. Intraperitoneal ³²P, which penetrates only 2 mm to 3 mm, was the isotope most commonly administered. Therapy was abandoned when

randomized data suggested better results with chemotherapy. In addition, a randomized comparison of ^{32}P versus observation did not show any decrease in the risk of relapse or improve survival in patients with more advanced-stage disease who had a surgically confirmed complete remission (340).

Chemotherapy for Early-Stage Ovarian Cancer

As shown in Figure 24.44, postoperative chemotherapy is usually recommended for patients with high-grade stage IA or IB tumors and most tumors of stage IC or higher. But it must be appreciated that we do not have strong evidence that such treatment improves overall survival. Randomized trials including platinum-based chemotherapy in early-stage ovarian cancer are summarized in Table 24.13. While individual trial results vary somewhat, as a group they have shown fairly consistent improvement in disease-free survival for postoperative chemotherapy versus observation or radiotherapy. However, the only clear demonstration of an overall survival benefit in the treatment of early-stage ovarian cancer comes from a joint analysis of 2 large European trials (the ACTION and ICON-1 trials), which together randomized 923 patients with early-stage disease to receive either platinum-based chemotherapy or no initial adjuvant treatment. Results of a pre-planned combined analysis indicated a statistically significant improvement in both disease-free survival (HR 0.64) and overall survival (HR 0.67) with adjuvant platinum-based therapy (Fig. 24.45) (341). Yet, even these results are not considered definitive proof of a benefit from chemotherapy in early-stage disease

because comprehensive surgical staging was not required for entry into these trials. In a retrospective subset analysis of the ACTION trial, the patients with optimal staging had no benefit from chemotherapy, raising concern that the overall positive results reflected the benefit of chemotherapy in women with low-volume stage III disease (341,342). However, only 151 patients were optimally staged, which is too few to provide statistical power for firm conclusions about the benefit of chemotherapy in this subgroup. Neither tumor grade nor histologic cell type predicted for relative benefit from treatment.

It has been suggested that the discrepancy between the benefit in disease-free survival and lack of benefit in overall survival seen in several of the randomized early-stage chemotherapy trials results from increased salvage rates for chemotherapy in patients who recur after observation or intraperitoneal ^{32}P . In an early Italian (Gruppo Interregionale Collaborativo in Ginecologia Oncologica; GICO) trial randomizing women to chemotherapy versus no adjuvant therapy, 1 of 7 women (14%) who relapsed after adjuvant chemotherapy was alive at the time of reporting, whereas 6 of 14 (43%) who relapsed after observation were still alive (343). However, most patients whose cancer recurs will die of their disease. Investigators at the Royal Marsden Hospital examined the salvage rate after relapse in their series of prospective observation for patients with stage I disease (344). Sixty-one (31%) of 194 patients relapsed at a median of 17 months (range, 6 months to 15.7 years), and 55 of them received platinum-based chemotherapy at the time of relapse. Progression-free survival at 5 years after relapse was 24%. In line with current thinking, although clear cell histology was not predictive for relapse, it was a poor prognostic factor for survival after relapse (345).

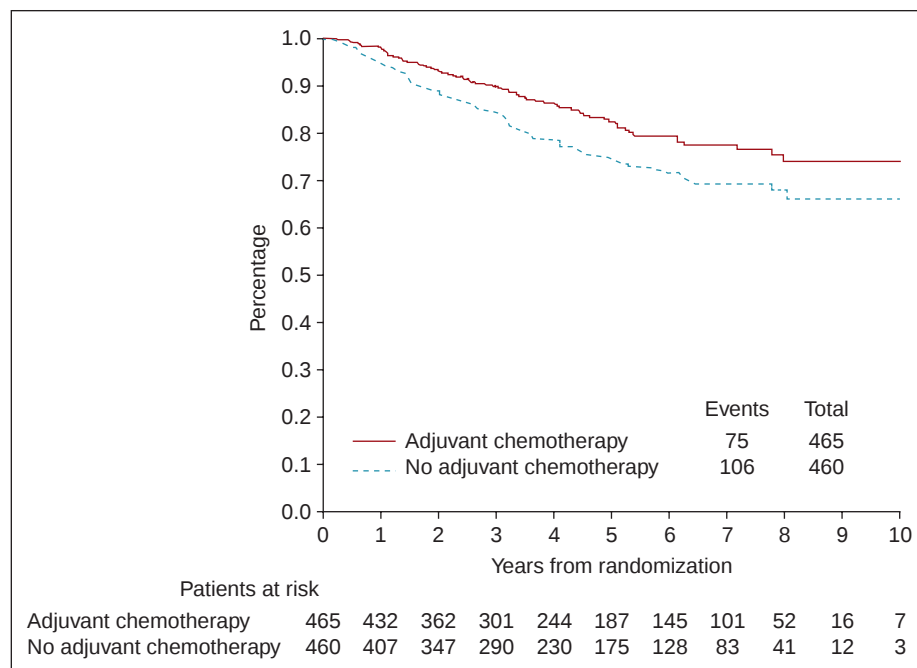
Table 24.13 Randomized Trials of Platinum-Based Chemotherapy in Early-Stage Ovarian Carcinoma

Author (yr)	N	Eligibility	Arms	Outcome
Vergote (1992) ⁵⁵⁰	347	Stage I, II, III without residual disease	^{32}P vs. Cisplatin	No difference in OS or DFS
Chiara (1994) ³³⁷	70	Stage IA/B Gr 3, Any IC, II	WAR vs. cisplatin/cyclophosphamide	5-yr OS 53% vs. 71% RFS 50% vs. 74% $p = \text{NS}$ Only 67% of patients completed WAR
Bolis (1995) ⁵⁵¹	83	Stage IA/B Gr 2/3	Observation vs. cisplatin	5-yr DFS 65% vs. 83% 5-yr OS 82% vs. 88%
Bolis (1995) ⁵⁵¹	152	Stage IC	^{32}P vs. cisplatin	5-yr DFS 65% vs. 85% 5-yr OS 79% vs. 81%
Trope (2000) ⁵⁵²	162	Stage I Gr 2/3 or Gr 1 aneuploid/clear cell	Observation vs. carboplatin	5-yr DFS 80% vs. 85% 5-yr OS 70% vs. 71% $p = \text{NS}$
Young (2003) ⁵⁵³	251	Stage IA/B Gr 3 or clear cell IC, II	^{32}P vs. cisplatin/cyclophosphamide	10-yr RFS 65% vs. 72% 10-yr OS: HR chemo 0.83 $p = \text{NS}$
ICON1 (2003) ³⁴²	477	Physician uncertain about need for chemotherapy	Observation vs. platinum-based chemotherapy	5-yr RFS 62% vs. 73% $p = 0.01$ 5-yr OS 70% vs. 79% $p = 0.03$
ACTION (2003) ¹⁵⁹	448	Stage IA/B Gr 2-3 All IC, IIA, and clear cell	Observation vs. platinum-based chemotherapy	5-yr RFS 68% vs. 76% $p = 0.02$ 5-yr OS 78% vs. 85% $p = \text{NS}$
Bell (2006) ³⁴⁶	427	Stage IA/B Gr 3 or clear cell All IC, II	Carboplatin/paclitaxel 3 cycles vs. 6 cycles	HR RFS 0.761 $p = \text{NS}$ 5-yr OS no difference
Mannel (2011) ³⁴⁹		Stage IA/B Gr 3 or clear cell, IC, II	Carboplatin/paclitaxel 3 cycles followed by observation vs. followed by weekly paclitaxel $\times 26$	5-yr RFS 77% vs. 80% $P = \text{NS}$

Note: DFS, disease free survival; Gr, grade; HR, Hazard Ratio; NS, not significant; OS, overall survival; RFS, relapse-free survival; WAR, whole abdominal radiotherapy.

FIGURE 24.45. Kaplan-Meier curves for overall survival in early-stage ovarian cancer patients treated with adjuvant chemotherapy (solid line) and no adjuvant chemotherapy (dotted line).

Source: Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant Chemotherapy in Ovarian Neoplasm Trial: 2 parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst.* 2003;95:105–112, with permission.



Duration of Chemotherapy for Early-Stage Disease

The GOG #157 trial randomized 427 eligible patients with early-stage disease and unfavorable prognostic markers (stage IA or IB grade 3, clear cell, stage IC, and completely resected stage II) to receive either 3 or 6 cycles of carboplatin (area under the curve [AUC] 7.5)/paclitaxel (175 mg/m²) chemotherapy. Surgical staging was required, but 29 percent of patients had surgical procedures that were considered inadequate or inadequately documented. Overall 5-year survival did not differ by treatment arm (HR 1.02). Adjusting for initial FIGO stage and tumor grade, the recurrence rate was 24% lower for patients getting 6 cycles, but this difference was not statistically significant (relative hazard 0.761, 95% CI, 0.512 to 1.13; $p = 0.18$) (346). There was a slightly lower estimated benefit of 6 cycles of chemotherapy in the completely staged group (HR 0.66 for incompletely staged versus 0.796 for completely staged patients, but there was no significant evidence of heterogeneity in the treatment effect. Toxicity was increased with 6 cycles; in particular the rate of grade III and IV neurotoxicity was 11% versus only 2% with 3 cycles. A subsequent exploratory analysis showed that for the 97 women with serous tumors the risk of recurrence was significantly lower after 6 versus 3 cycles of chemotherapy; 83% versus 60% (HR 0.33; CI, 0.14–0.77, $p = 0.04$), whereas for those with nonserous tumors, including clear cell carcinomas, no benefit was seen. However, a test of homogeneity did not show a difference in treatment effect across cell types. The 5-year overall survival for women with serous carcinomas was 86% for those receiving 6 cycles of therapy and 73% for those receiving 3 cycles of therapy; this difference did not reach statistical significance. Grade was not associated with benefit from chemotherapy, but women with low-grade stage IA and IB tumors were not eligible (347). One interesting retrospective nonrandomized analysis suggested that 6 (vs. 4) cycles of chemotherapy for early-stage disease delayed, rather than eliminated, recurrences (348). The GOG conducted a subsequent trial (GOG #175) in the same patient-population randomizing 542 eligible women to either 3 cycles of carboplatin (AUC 6)/paclitaxel (175 mg/m²) or 3 cycles of the same regimen followed by maintenance therapy with weekly paclitaxel 40 mg/m² for 24 weeks. No significant

difference in recurrence free interval (HR 0.807) or overall survival was seen. Only 29% of subjects had serous histology, and their results did not differ from that of the overall population (HR 0.822) (349).

At this time it is recommended that patients with comprehensively staged stage IA or IB grade 1 epithelial ovarian cancer receive no postoperative chemotherapy (see Fig. 24.44). Patients with grade III or stage IC disease have a relapse risk of at least 20%, and this may be reduced with platinum-based chemotherapy, particularly for those with serous tumors. Treatment of stage IA or IB grade 2 cancers remains an area of uncertainty, particularly given the lack of reproducibility of pathologist-assigned grade. If a dichotomous (high vs. low) grading system for serous carcinomas comes into use, this issue may be resolved. Paclitaxel/carboplatin for 3 to 6 cycles is the usual treatment for early-stage high-risk disease. It is hoped that future data will better address which women with early-stage ovarian cancers actually derive benefit from therapy.

Early-Stage Clear cell Carcinoma

In general, clear cell carcinomas of the ovary are not graded; they are all considered “high grade” for treatment purposes, and have traditionally all been treated with adjuvant chemotherapy. As discussed below (Section “Clear cell and Mucinous Tumors”), more recent series do not suggest an inferior prognosis for women with early-stage clear cell cancers, but do suggest decreased chemotherapy sensitivity for advanced-stage clear cell carcinomas. It is possible that observation is appropriate for some stage IA clear cell carcinomas. A recent series described 20 patients with stage IA clear cell carcinoma; 4 underwent chemotherapy, whereas the remaining 16 patients received no additional therapy. No recurrence was observed in either group (350). Seven to 11% of patients with apparent early-stage ovarian clear cell tumors will have retroperitoneal lymph node involvement (351), compared to 28% for early-stage serous carcinomas (352).

As described above, retrospective reviews have shown that prognosis in early-stage clear cell carcinoma might be improved by the addition of radiotherapy, and hopefully future trials will address this issue.

Early-Stage Fallopian Tube Carcinomas

A small number of patients present with obvious early-stage disease in the fallopian tubes. They are frequently incidentally detected after surgery for nononcologic indication such as incontinence or after prophylactic salpingo-oophorectomy performed for cancer prevention in women with a *BRCA* mutation. These patients should be fully surgically staged. Most fallopian tube carcinomas are of high-grade serous histology. Prognosis of early-stage disease has been reported to be dependent on depth of invasion of the tumor into the fallopian tube. When controlled for stage and grade, they appear to have a prognosis similar to that of early-stage ovarian cancer (353). FIGO data suggest that patients with stage I disease have a 5-year overall survival of 81% (354). Since advanced-stage fallopian tube carcinomas appear to respond to platinum-based therapies in a manner similar to that of ovarian carcinomas, and since many cancers formerly thought to be ovarian cancers or primary peritoneal cancers are now believed to have originated in the fallopian tube, adjuvant chemotherapy is currently used for early-stage disease in most situations.

MANAGEMENT OF BORDERLINE TUMORS

Borderline (low malignant potential; LMP) tumors comprise 10% to 20% of ovarian malignancies, and most are serous or mucinous. They were first described by Taylor in 1929 and recognized by FIGO in 1971 as a distinct histologic subtype. Their histology is reviewed in detail in section “Pathology.” In general, patients with borderline tumors present at a younger age (on average 10 years younger), and have earlier-stage disease than women with invasive ovarian carcinomas. They also have a longer survival and a risk for late recurrences.

As discussed in the pathology section, current concepts suggest that borderline tumors are precursors to Type I invasive tumors; SBT are precursors to low-grade (not high-grade) serous tumors and MBTs are precursors to invasive mucinous tumors. SBT are more common than MBTs in the United States; in Asia, the rate of MBTs has been reported to be similar or higher than that of SBT (355). Approximately 75% to 80% of borderline tumors are diagnosed at an early stage. For practical purposes, all MBTs are early-stage. Even when SBT present with more advanced-stage disease, survival is prolonged. A review of borderline tumors entered into the NCI SEER database between 1988 and 1997 (when SEER stopped collecting data on ovarian borderline tumors) showed 10-year relative survivals of 99% for stage I, 98% for stage II, 96% for stage III, and 77% for stage IV disease (356). The very long natural history makes accurate collection of outcomes and performing clinical trials challenging. Because these tumors are particularly likely to affect young women, decisions regarding fertility-sparing and premature hormonal deprivation are often pertinent.

Early-Stage Borderline Tumors

Surgery

Surgery is the cornerstone of treatment for early-stage borderline ovarian tumors. It is often not known preoperatively whether an ovarian mass will prove to be a borderline tumor, and the accuracy of frozen section in the diagnosis of ovarian tumors has been reported to be low; 20% to 30% of ovarian tumors diagnosed as borderline at the time of frozen section examination proved to be invasive carcinomas on further sampling (357). Issues of surgical management of an ovarian mass

are covered in Section “Surgery.” In general, a systematic, full staging of borderline tumors has been recommended along with salpingo-oophorectomy and omentectomy. This includes biopsies taken from pelvic and abdominal peritoneum, omentum, and retroperitoneal lymph nodes. Appendectomy is recommended as part of staging for MBTs to exclude an appendiceal primary tumor (358). For serous tumors, the prognosis and, in some instances therapy, may depend upon the stage and the presence of invasive implants. However, lymph node involvement in borderline serous tumors has not been shown to affect prognosis, and the role of lymphadenectomy is therefore not clear. In patients undergoing fertility-sparing surgery, a biopsy of a normal contralateral ovary is no longer recommended. In the presence of bilateral adnexal masses, intra-operative decision-making is more difficult if the patient desires fertility-sparing surgery. Removing the more suspicious (excrecences, solid, enlarged) ovary for frozen section analysis and then performing a cystectomy on the contralateral ovary followed by staging biopsies is a reasonable compromise allowing preservation of fertility while providing prognostic information.

Despite the generally accepted recommendation to stage all patients with borderline tumors if detected intra-operatively, the more recent literature shows no substantial clinical benefit to surgical staging of borderline tumors (359). Also there is currently no evidence that prophylactically removing the uterus after completion of childbearing will improve prognosis. Therefore, the role of restaging borderline tumors not fully staged at the time of initial surgery is controversial, and most experts would follow these patients without additional surgery after obtaining a baseline abdominopelvic CT scan and CA-125 (serous) or CEA (mucinous) tumor marker. Some, though not all, series report a higher recurrence rate after incomplete staging, but restaging will have little effect on management in most cases. The relevance of stromal microinvasion, which is found in about 10% of SBT, as an indication for staging is controversial; it is a poor prognostic factor for serous tumors, and is associated with micropapillary histology and peritoneal implants (355). The most relevant situation for restaging appears to be in women with apparent stage I SBT with micropapillary histology, which have the highest risk of invasive implants.

Since many women with borderline tumors are in their childbearing years, the efficacy and safety of conservative surgery are important. There is no evidence that fertility-sparing surgery has an adverse effect on survival in patients with stage I borderline tumors. Even though patients treated with a unilateral oophorectomy have a higher recurrence rate than patients treated with a total hysterectomy and bilateral oophorectomy, effective surgery achieving complete removal of all visible lesions for recurrent disease leads to equivalent survival. At the time of recurrence, most surgeons will perform a hysterectomy and remove the contralateral ovary, especially if a woman has completed childbearing. Whether even more conservative surgery (e.g., cystectomy) has an adverse impact on survival remains a subject of debate. Although cystectomy for a borderline tumor may increase the recurrence rate (up to a 58% recurrence rate has been reported), it may not have an adverse effect on survival, at least for serous tumors. A study reviewing the experience within the Kaiser Permanente medical system found that women treated by cystectomy had a 23% recurrence rate versus 7% in women treated by salpingo-oophorectomy (360). However, in order to avoid recurrences and still maintain fertility, there appears to be little, if any, disadvantage to performing a unilateral oophorectomy. Most patients are able to conceive and deliver after unilateral removal of one ovary. Because of the high risk of death for women with recurrent mucinous tumors, cystectomy for mucinous borderline lesions is not advisable and, in general, every effort should be made to remove mucinous tumors specifically and any other ovarian tumors in general surgically intact. In

patients who present with stage II borderline tumors, a total abdominal hysterectomy and bilateral salpingo-oophorectomy with appropriate staging of the peritoneal cavity is usually recommended.

Prognosis

Early-Stage Serous Borderline Tumors

Approximately 5% to 10% of early-stage SBT have been reported to ultimately recur, although it has been argued (see section “Pathology”) that recurrences of well-staged and sampled stage I tumors are, in fact, very unusual. Recurrences can present very late, 10 to 15 years after the initial diagnosis. In one representative report of 160 stage I SBT, 11 patients developed recurrent tumor at a median of 16 years after initial surgery (range, 7 to 39 years), and 8 died of the disease (361). While the risk of recurrence has been reported to be higher for borderline tumors with micropapillary histology, this may be related to an increased rate of invasive implants; in most series, stage I SBT with micropapillary histology appear to have the same rate of recurrence as stage I SBT without micropapillary patterns. Microinvasion of SBT is discussed in detail in the section “Pathology.” In general, while microinvasion is associated with an increased risk of recurrence, it is also associated with peritoneal implants, and there is no consensus on whether microinvasion is an independent risk factor or whether it, in isolation, warrants restaging surgery (355).

Early-Stage Mucinous Borderline Tumors

MBTs tend to be large, and areas of microinvasion can easily be missed if they are not sampled thoroughly. However, the clinical relevance of this is unclear, as microinvasion does not have clear prognostic significance. A review of 8 series including 116 patients with mucinous ovarian tumors and stromal microinvasion reported that none developed an invasive recurrence. However, median follow-up in a number of these series was under 5 years. In general, while the overall prognosis of early-stage MBTs is excellent, they can occasionally recur, and may recur late. Khoskas and colleagues reported that the rate of recurrence as invasive mucinous tumors after 10 years was 13%. Patients with these recurrences, like those with other advanced-stage mucinous tumors, do poorly.

Systemic Therapy

Chemotherapy is not indicated for stage I or II borderline tumors, regardless of histology or microinvasion.

Advanced-Stage Serous Borderline Tumors

Surgery

Since the role of chemotherapy in the treatment of borderline tumors is unclear, surgery is the primary treatment. Retrospective studies suggest that the proportion of patients achieving optimal cytoreductive surgery is stage-for-stage higher for patients with serous low malignant potential tumors and low-grade serous cancers than for those with serous epithelial ovarian cancer (362). As with higher-grade ovarian tumors, residual disease is an important prognostic factor for both recurrence-free and overall survival. In a series of 168 FIGO stage II and III SBT, 5-year disease-free survival was 75% in patients with no residual disease, 76% in those with residual disease less than or equal to 2 cm, and 56% in those with residual disease greater than 2 cm. No patient with residual disease in this series received adjuvant chemotherapy (363,364).

Prognosis

Residual disease after surgery, the presence of advanced disease prior to surgery, and invasive implants showing clear stromal invasion are poor prognostic factors. Seidman and Kurman reported on a review of 97 publications including 4,129 patients, and noted that after 7.4 years of follow-up, the survival of patients with non-invasive peritoneal implants was 95.3% as compared with 66% for those with invasive implants. Lymph node involvement, as noted above, did not confer a poor prognosis, and was associated with a 98% survival rate at 6.5 years (309). Another report suggested that women diagnosed with invasive implants have 5- and 10-year survival rates of approximately 70% and 40% (365).

It has been suggested that patients with invasive implants recur earlier and those with noninvasive implants recur later. The University of Texas MD Anderson group retrospectively identified 39 patients with ovarian SBT with invasive implants. At a median follow-up of 111 months, 12 (31%) had progressed or recurred with median time from diagnosis to recurrence of only 24 months (366). They also reviewed 80 cases of stage II to IV ovarian SBT with noninvasive implants. Fifty received postoperative chemotherapy. Thirty-five (44%) developed recurrences, 10% within 5 years, 19% between 5 and 10 years, 10% between 10 and 15 years, and 5% more than 15 years after primary resection. Recurrences in patients with noninvasive implants may be either invasive (low-grade serous tumors) or noninvasive. In the series above, 2 of the 35 recurrences were not histologically examined, 6 were recurrent borderline tumors, and 27 were low-grade serous tumors. The patients with recurrent borderline tumors were all alive without evidence of disease 3 to 14 years after the recurrence. Twenty of the 27 patients with low-grade serous carcinomas at the time of recurrence died of disease between 1 and 18 years (median 3 years) after recurrence; the other 7 were alive with progressive disease a median of 4 years after recurrence. Older age was a poor prognostic factor for survival. Shvartzman et al. identified 112 patients with *de novo* low-grade serous carcinomas and 41 with invasive recurrences of borderline tumors. There were no statistically significant differences between the 2 groups in median age (42.7 vs. 45.4 years [at relapse]), progression-free survival (19.5 vs. 25 months), or overall survival (81.8 vs. 82.8 months) (367).

Adjuvant Systemic Therapy

There is no known evidence of benefit of adjuvant systemic therapy for any subset of advanced-stage borderline tumors, although current practice is often to treat patients with invasive implants with chemotherapy similar to that used for ovarian carcinomas (355). Gershenson et al. reported on a representative series of patients with serous borderline ovarian tumors who had macroscopic residual disease after initial surgery, received chemotherapy, and subsequently underwent second-look laparotomy. Three of 20 (15%) patients with noninvasive implants and 4 of 7 (57%) patients with invasive peritoneal implants had a response to chemotherapy (366). Recent data on treatment for low-grade serous carcinomas with chemotherapy are even more discouraging (see treatment for recurrence, below), and the effect of treatment on survival is very uncertain. Shih et al. reported on a retrospective series of 65 patients with stage III/IV disease, of whom 17 received adjuvant chemotherapy. Three-year PFS was 89.9% for patients who did not receive adjuvant chemotherapy, and 70.6% for those who received it. These data were not broken down by type of implant (368). It should be recalled that, as discussed above, not all patients with invasive implants recur, and expert pathological review by a dedicated gynecologic pathologist is recommended if true invasion is suspected. Patients will have a long time to live with any toxicities from chemotherapy and may develop leukemia or other late

side effects. A Cochrane meta-analysis did not find that evidence supported use of any specific type of adjuvant treatment (369).

Therapy for Recurrence

Low-grade serous carcinomas have been reported to be relatively chemotherapy resistant, and surgery remains the mainstay of treatment for recurrent disease. Bristow et al. reported on a series of 26 patients with recurrent low-grade serous carcinoma (370). Twenty-one had received platinum-based chemotherapy after primary surgery. Twenty-one underwent secondary debulking surgery, and 15 were optimally debulked. The median overall survival post recurrence was 56 months, and optimal debulking was the strongest predictor of survival after recurrence. Of 12 patients who received chemotherapy and had measurable disease, 2 had a CR and one had a PR (response rate of 25%). Gershenson et al. reported on a retrospective review of 108 chemotherapy regimens administered to 58 patients with low-grade serous ovarian tumors. There was an overall response rate of 3.7%, with one complete and 3 partial responses. The median time to progression was 29 weeks (312).

Over 90% of serous borderline ovarian tumors are estrogen-receptor positive (371), and there are case reports of major responses to tamoxifen, leuprolide, and anastrozole. The MD Anderson group retrospectively reviewed outcomes of 219 hormonal therapy regimens in 133 women with recurrent low-grade serous carcinomas of the ovary or peritoneum. The overall response rate was 9%, with 6 complete and 2 partial responses (to anastrozole, letrozole, and tamoxifen). Median time to progression was 7.4 months. Time to progression was longer for tumors that were positive for both estrogen and progesterone receptors than for those tumors positive only for estrogen receptors (372).

Bevacizumab has been reported to produce complete responses in 2 women with heavily pretreated recurrent low-grade ovarian tumors (373), and other antiangiogenic agents are of interest in this disease. The Gynecologic Oncology Group has established a separate series of trials for women with low-grade tumors. Since initial reports suggested a high frequency of *KRAS* and *BRAF* mutations in low-grade serous carcinomas, a trial was undertaken with AZD6244 (sulemetenib), which inhibits MEK-1/2 (downstream signaling effectors of *KRAS*/*BRAF* activating mitogenic signaling) in women with low-grade serous carcinomas. The majority had at least 3 prior cytotoxic regimens. Preliminary results suggested a 15% response rate with a median PFS of 11 months. Of patients for whom sufficient tumor material was available, 5% had *BRAF* mutations, 15% had *NRAS* mutations, and 51% had *KRAS* mutations. No correlation between response and mutation status was observed (374,560). Other data also suggest that *BRAF* mutations, while common in early-stage borderline tumors, are rare in advanced-stage low-grade serous carcinomas (375), and therefore agents targeting *BRAF* may not be useful in the treatment of recurrent disease.

MANAGEMENT OF ADVANCED-STAGE DISEASE

A simplified algorithm for the management of presumed advanced-stage ovarian cancer is shown in Figure 24.46. Clinical diagnosis is discussed on page 774.

Surgery

Surgery for advanced-stage disease is covered in the Section “Surgery.” Upfront surgery for definitive diagnosis and removal of as much tumor as possible has long been the standard in ovarian cancer therapy. It is clear that women who are successfully

surgically debulked to minimal or no residual disease have an improved survival, although how much of this is a direct result of the surgical effort and how much reflects unknown biologic/genetic, social, or health factors in patients who have debulking disease, remains unclear. One randomized trial has shown a benefit for “interim debulking” surgery (376). Whether surgery must be performed upfront for optimal benefit, or whether similar outcomes would be achieved with surgery after neoadjuvant chemotherapy, is open to debate.

Postoperative Chemotherapy

Surgery is rarely curative for women with advanced-stage ovarian carcinoma, even when there is no residual disease. As discussed above (see prognostic factors), outcomes are dependent on stage, grade, and histologic subtype. Overall 5-year relative survivals from SEER data are 45% for those with stage IIIa disease and 35% for those with stage IIIc disease (see Fig. 24.43) (292). The most common front-line adjuvant therapy currently used in the United States is 6 cycles of postoperative intravenous paclitaxel/carboplatin administered every 3 weeks. Some physicians administer 8 or 9 cycles of therapy, particularly when interval debulking is performed. However, 3 small, randomized trials that investigated the benefit of prolonging duration of treatment beyond 6 cycles showed an increase in toxicity but no improvement in outcomes (377–379).

Approximately 50% to 70% of patients with measurable disease after surgery will have a complete or partial response to platinum-based first-line postoperative therapy (380,381). In trials including optimally and suboptimally debulked patients, at least half will generally have a complete clinical response to platinum-based regimens, with disappearance of all disease on scan and normalization of CA-125 (382). Unfortunately, even among those with complete clinical remission, the majority eventually develop recurrent disease. In general, primary serous peritoneal cancers, ovarian cancers, and fallopian tube cancers are treated in a similar manner, and are eligible for the same protocols. Areas of controversy or uncertainty include the use of neoadjuvant therapy (discussed above), the use of intraperitoneal chemotherapy, the use of bevacizumab, and the use of dose-dense paclitaxel. Neither addition of other cytotoxic agents nor maintenance therapy after attaining remission has been shown to improve survival.

Platinum Use

Platinum agents are the most active group of chemotherapy drugs in the treatment of ovarian cancer. This may partially be accounted for by the fact that tumors of *BRCA* mutation carriers appear to have particular sensitivity to platinum. The GOG performed a comparative trial of a platinum-containing regimen versus a non-platinum-containing regimen in the pre-taxane era (382). Two hundred twenty-seven patients with advanced ovarian cancer were randomized to receive doxorubicin/cyclophosphamide treatment with or without the addition of cisplatin. Complete response rate (51% vs. 26%) and median overall survival (15.7 vs. 9.7 months) were both superior for the cisplatin-containing regimen. A meta-analysis confirmed that platinum-based therapy produces a survival benefit compared to nonplatinum-based therapy. Subsequently, multiple randomized trials and a meta-analysis have confirmed that carboplatin is as active as cisplatin when both are given intravenously (383), and since carboplatin produces substantially less neurotoxicity, nausea, and ototoxicity, it has become the standard for intravenous use. An early meta-analysis of over 60 published trials showed a correlation between dose intensity of cisplatin and observed response rate, but the correlation held only over a range of doses lower than those used in clinical practice today (384). A large number of trials of varying design have tested higher versus lower

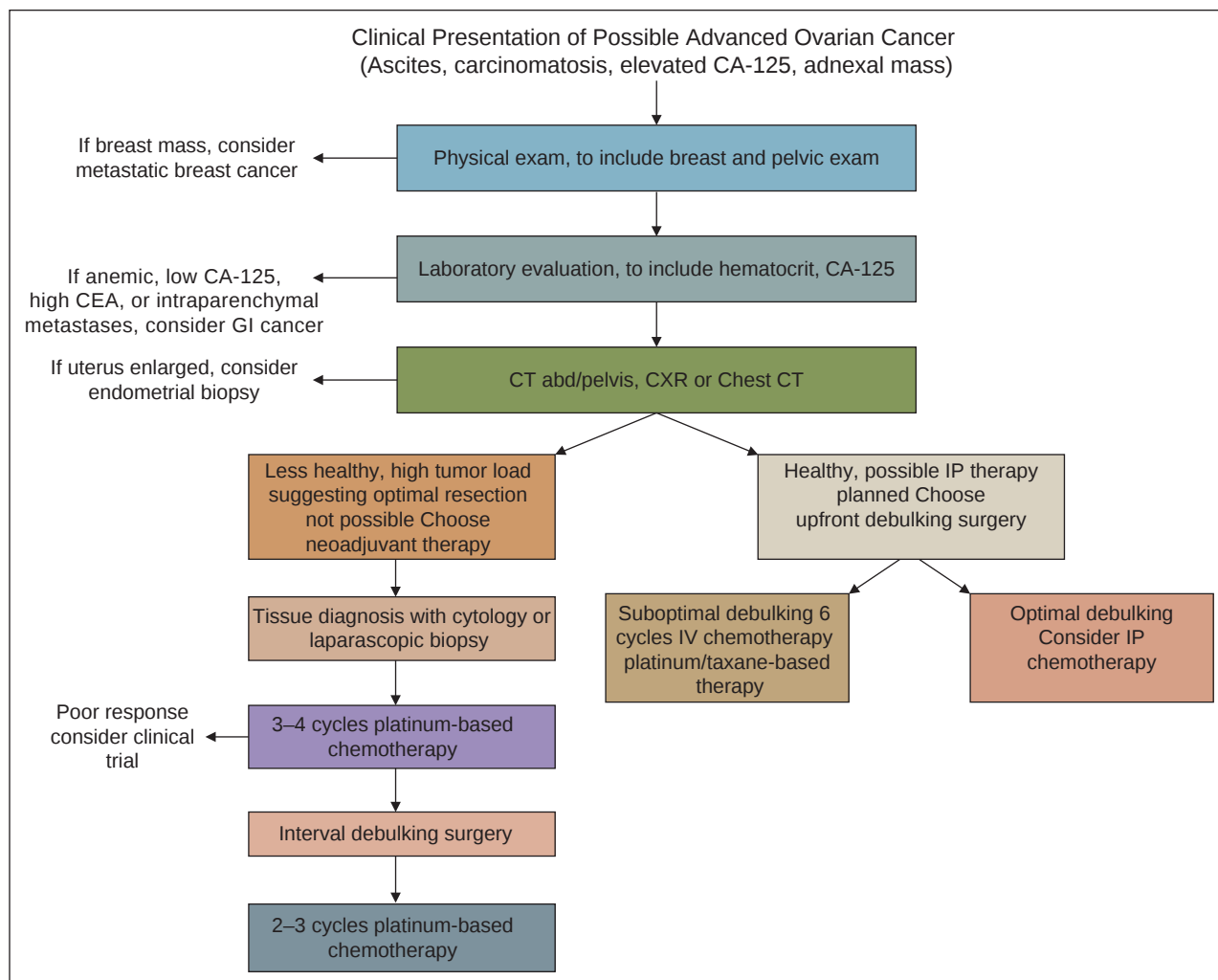


FIGURE 24.46. Simplified Management of Patients Presenting with Probable Advanced Ovarian Cancer

doses of platinum agents, including trials using doses of carboplatin requiring stem cell support, but no good evidence supports the use of doses of cisplatin above 50 mg to 100 mg/m² every 3 weeks or doses of carboplatin over AUC 5 to 7.5 every 3 weeks. AUC 6 is the most common dose used for first-line therapy.

Oxaliplatin, a third-generation platinum agent that produces an unusual cold-triggered neurotoxicity, has a theoretical benefit in activity against tumors that exhibit mismatch repair deficiency, but there is no clinical evidence that it is non-cross-resistant with other platinum agents in general. A GOG trial of oxaliplatin in women with platinum-resistant tumors revealed negligible activity (385). A small ($n = 177$) randomized trial comparing oxaliplatin/cyclophosphamide to cisplatin/cyclophosphamide as first-line therapy in women with ovarian cancer showed no difference in progression-free or overall survival between the 2 treatment groups (386). Oxaliplatin is FDA-approved in the United States for use in colon cancer and, as described below, is being tested as front-line therapy for mucinous ovarian ovarian cancers.

Addition of Paclitaxel to Platinum Chemotherapy

In the 1980s a great deal of excitement was generated by the demonstration that single-agent paclitaxel had substantial activity against platinum-resistant ovarian cancer. A number of

randomized trials were rapidly launched comparing platinum-based regimens with and without taxane in the first-line treatment of ovarian cancer.

The results of the first 2 of these trials (GOG #111 and OV-10) clearly demonstrated that combination chemotherapy with paclitaxel and cisplatin prolonged both progression-free and overall survival as compared with cyclophosphamide/cisplatin (380,387,388). In GOG #111, which included 386 women with suboptimally debulked or stage IV disease, the median overall survival was 37 months for those treated with paclitaxel and cisplatin as compared to 25 months for those receiving cyclophosphamide and cisplatin. Similar results were found in the more inclusive (stages IIB-IV) European OV-10 trial, which reported a median overall survival of 36 months for the paclitaxel containing arm versus 26 months for the cyclophosphamide-containing arm.

The other 2 trials did not as clearly support the addition of paclitaxel to front-line therapy. The 3 arms of GOG #132 were single-agent paclitaxel (200 mg/m² over 24 hours), single-agent cisplatin (100 mg/m²), and the combination of cisplatin 75 mg/m² plus paclitaxel 135 mg/m² over 24 hours (380). Six hundred fourteen women with suboptimally debulked or stage IV disease were treated. The response rate to single-agent paclitaxel in patients with measurable disease was significantly lower than to either of the platinum-containing regimens (42% vs. 67%, $p < 0.01$). However, the difference in median overall survival

(30.2, 25.9, and 26.3 months for patients randomized to cisplatin, paclitaxel, or the combination, respectively) was not statistically significant. The investigators speculated that the lack of benefit for the combination arm related to the fact that almost 50% of patients on the single agent arms began subsequent treatment (frequently with the therapy of the alternate arm, that is, cisplatin for women who were randomized to paclitaxel and paclitaxel for women who were randomized to cisplatin) prior to overt clinical progression, presumably on the basis of a rising CA-125. By way of contrast, paclitaxel was seldom used as salvage therapy in GOG #111 because of its limited availability at the time, and while 48% of patients in the cisplatin/cyclophosphamide arm of OV-10 crossed over to paclitaxel as first salvage treatment, it appears that they did so after overt clinical progression. ICON3, a large ($n = 2,075$) multinational trial which randomized women with stage I–IV disease to carboplatin AUC 6/paclitaxel chemotherapy versus single-agent carboplatin AUC 6 or CAP (cisplatin/doxorubicin/cyclophosphamide) chemotherapy found no superiority for the taxane-containing combination in either progression-free or overall survival (hazard ratio for overall survival 0.98; 95% CI, 0.87 to 1.10) (561). About a third of patients on carboplatin in the control group went on to receive a taxane at some stage, mostly after the disease had progressed. The results of this trial also appear to contradict those of OV-10 and GOG #111, and the explanation remains unclear. However, given that carboplatin plus paclitaxel combination therapy is certainly at least as active as single agent carboplatin, that the combination has been reported to improve survival in a trial for women with recurrent disease (389), and that the doublet is both relatively well tolerated in general and platelet-sparing relative to single agent carboplatin, the combination has become standard.

Alternate Paclitaxel Dosing

The standard dose of paclitaxel in front-line therapy was 135 mg/m² when it was used as a 24 hour infusion and is currently 175 mg/m² as a 3-hour infusion. Neither increasing the dose nor using prolonged infusions is associated with improved outcomes. Paclitaxel was initially administered as a 24-hour infusion to minimize hypersensitivity reactions and to diminish neurotoxicity when it was administered in combination with cisplatin. Since an early randomized phase II trial had suggested slightly better disease-related outcomes with a 24-hour versus a 3-hour paclitaxel infusion, the GOG completed a trial (GOG #162) randomizing women with ovarian cancer to cisplatin 75 mg/m² plus paclitaxel 135 mg/m² with the paclitaxel administered as either a 24- or a 96-hour infusion. There was no difference in overall or progression-free survival (390). Attempts at escalating the paclitaxel dose have also been made. A prospective, randomized trial in previously untreated advanced ovarian cancer patients compared 2 different doses of paclitaxel (175 vs. 225 mg/m²), with all patients receiving carboplatin at an AUC of 5. No improvement in survival was reported for the higher-dose regimen (391).

More recently, based on data in women with metastatic breast cancer that weekly paclitaxel was superior to every 3 week paclitaxel in terms of response and survival, the Japanese Gynecologic Oncology Group randomly assigned 637 women with stages II to IV ovarian cancer, primary peritoneal cancer, or fallopian tube cancer to treatment with standard therapy with carboplatin AUC 6 plus paclitaxel 180 mg/m² over 3 hours every 21 days weeks or dose-dense therapy with carboplatin AUC 6 every 21 days plus paclitaxel 80 mg/m² on days 1, 8, and 15 of a 21 day cycle. The dose dense regimen was superior in terms of both progression-free (28 vs. 17 months; HR 0.71; 95% CI, 0.58–0.88) and 3-year overall survival (72% vs. 65%; HR 0.75 (95% CI, 0.57–0.98)). All subgroups (age, stage, residual disease) appeared to benefit except for women with clear cell or mucinous tumors (392). The advantage of dose dense therapy was maintained at

6.5 years median follow-up; 5-year OS was 59% versus 51%; HR 0.79 (95% CI, 0.63–0.99) (393). Widespread adoption of the regimen has been hindered by concerns about toxicity and desire to see efficacy results confirmed. The dose dense regimen was more myelotoxic than standard therapy, and required an increased number of dose delays and reductions. There has also been concern that patients in Japan might have a different genetic predisposition to myelotoxicity from the weekly regimen than Western populations. Two large confirmatory trials of dose-dense paclitaxel are therefore underway: GOG #262 and ICON 8. GOG #262 randomized women to 6 cycles of either carboplatin AUC 6 plus paclitaxel 175 mg/m² every 3 weeks or carboplatin AUC 6 every 3 weeks plus weekly paclitaxel 80 mg/m². Bevacizumab, given with chemotherapy and then until progression, was optional, but was selected by most patients. This trial has completed accrual, and results should be available soon. ICON 8 is an ongoing 3-arm trial testing standard therapy with carboplatin every 3 weeks plus paclitaxel every 3 weeks, a regimen of carboplatin every 3 weeks plus weekly paclitaxel, and a regimen in which both carboplatin and paclitaxel are given weekly.

Alternate Taxanes

The Scottish Gynaecological Cancer Trials Group tested the incorporation of docetaxel into front-line therapy (394). One thousand seventy-seven women with stage IC to IV ovarian or primary peritoneal carcinoma were randomized to 6 cycles of carboplatin AUC 5 and either docetaxel 75 mg/m² or paclitaxel 175 mg/m². At a median follow-up of 23 months, there was no difference in progression-free (15 months for docetaxel, 14.8 months for paclitaxel) or overall survival (2-year overall survival 64% for docetaxel and 69% for paclitaxel). This was confirmed in a subsequent report with longer follow-up. Docetaxel was associated with less neurotoxicity (11% vs. 30% grade ≥ 2 neurosensory toxicity) and more myelotoxicity (11 patients vs. 3 patients with neutropenic fever). Docetaxel represents an attractive option for patients with or at risk for neurotoxicity.

Albumin-bound paclitaxel has been shown to have activity in ovarian cancer, but has not been compared to paclitaxel. Xyotax, a microparticle-bound paclitaxel, is being tested by the GOG in a randomized trial as consolidation therapy.

Addition of a Third Cytotoxic Agent to Front-Line Chemotherapy

There are no data that addition of any third cytotoxic agent to front-line chemotherapy of ovarian cancer improves outcomes, despite an immense amount of investigation of this strategy. Multiple randomized phase III trials testing the addition of doxorubicin, epirubicin, gemcitabine, and topotecan to a platinum/taxane backbone either sequentially or all at the same time have all been negative. In addition, an international multiarm randomized study was led by the GOG (GOG #182-ICON5) to definitively answer whether triplet cytotoxic chemotherapy improves survival (395). A total of 4,312 advanced-staged ovarian cancer patients were randomized to carboplatin/paclitaxel or carboplatin/paclitaxel combined with either gemcitabine, liposomal doxorubicin, or topotecan. Progression-free survival ranged from 15.4 to 17.5 months across the 4 treatment arms, with an HR of 0.94 to 1.07, which was not statistically different among any of the combination regimens studied.

Substitution of an Alternate Cytotoxic Agent for Paclitaxel

A randomized phase III trial substituting gemcitabine for paclitaxel as front-line therapy showed inferior overall survival for women on the gemcitabine-containing arm (396). Results with

liposomal doxorubicin have been more interesting. The phase III Multicentre Italian Trials in Ovarian Cancer-2 (MITO-2) trial, randomly assigned 820 chemotherapy-naïve patients with stage IC to IV ovarian cancer to carboplatin AUC 5 plus paclitaxel 175 mg/m² or to carboplatin AUC 5 plus PLD 30 mg/m², every 3 weeks for 6 cycles. The primary end point was progression-free survival (PFS). Median PFS was 19.0 and 16.8 months with carboplatin/PLD and carboplatin/paclitaxel, respectively (HR, 0.95; 95% CI, 0.81 to 1.13; $p = 0.58$). Median overall survival times were 61.6 and 53.2 months with carboplatin/PLD and carboplatin/paclitaxel, respectively (HR, 0.89; 95% CI, 0.72 to 1.12; $p = 0.32$). Carboplatin/PLD produced less neurotoxicity and alopecia but more hematologic adverse effects. There was no relevant difference in global quality of life after 3 and 6 cycles (397). This regimen has not been widely adopted for front-line therapy, in part because the usual dose of carboplatin in the United States is AUC 6, and there are concerns about hematologic toxicity if this dose were added to PLD, partly because of new data about possible superiority of weekly paclitaxel (393), and partly because paclitaxel has been relatively easy to combine with other nonneurotoxic agents, and PLD can be more problematic in this regard. There was, moreover, a shortage of PLD in 2012. Nonetheless, the regimen appears at least as effective as standard dose paclitaxel/carboplatin, and may be an option for patients with severe neuropathy or taxane allergies.

Addition of Bevacizumab to Primary Chemotherapy

Bevacizumab is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). Elevated vascular endothelial growth factor (VEGF or VEGF-A) expression occurs in all stages of ovarian cancer and is associated with poor prognosis, including shorter survival. Bevacizumab as a single agent has produced response rates in the range of 15% to 20% in the setting of recurrent ovarian cancer (398,399,400), which are higher than the response rates seen for other solid tumors. There was therefore great enthusiasm for the addition of bevacizumab to up-front chemotherapy, and 2 large randomized trials have been performed in this setting, both showing an improvement in progression-free survival, but no improvement in overall survival (Table 24.14).

GOG #218 was a placebo-controlled 3-arm study in women with stage III (incompletely resectable) and stage IV disease (401). This trial compared a control group receiving carboplatin AUC 6/paclitaxel 175 mg/m² to carboplatin/paclitaxel with concomitant bevacizumab (15 mg/kg every 3 weeks) and to carboplatin/paclitaxel with concomitant bevacizumab followed by maintenance

bevacizumab for an additional 16 doses (once every 3 weeks). In groups receiving bevacizumab, it was not started until cycle 2, to avoid postoperative wound healing problems. Median PFS for the 3 arms was 10.3 months, 11.2 months, and 14.1 months, respectively, but there were no significant differences in overall survival between the groups. The experimental regimen was tolerable; bowel perforation or fistula requiring medical intervention occurred in 1.2% of patients in the control arm, 2.8% of patients in the concomitant-only bevacizumab arm, and 2.6% of patients in the concomitant plus maintenance bevacizumab arm. As the primary endpoint of the study was progression-free survival, the blind was not maintained after progression, and the authors noted that the endpoint of overall survival could be contaminated by effect of postprogression therapy.

A second trial, ICON7, was led by European investigators (381). This study had only 2 arms: carboplatin/paclitaxel and carboplatin/paclitaxel with concomitant and 12 additional cycles of consolidation bevacizumab). There was no placebo, the bevacizumab dose used was 7.5 mg/kg every 3 weeks rather than the 15 mg/kg used in the GOG #218 trial, and women with both high-risk early-stage and with more advanced disease were eligible to participate. The median PFS for the control group was 17.3 months versus 19 months for the group receiving bevacizumab. Overall survival was not mature at the time of publication. The hazard ratio for death in the bevacizumab group was 0.85 (0.69–1.04). The most important increase in toxicity was a risk of grade 2 or higher hypertension (18% with bevacizumab and 2% with standard therapy) and the risk for grade 3 or higher thromboembolic events (7% with bevacizumab vs. 3% with standard therapy). A separate analysis was conducted in the 30% of participants considered “at high risk for progression,” that is, stage IV or stage III with more than 1.0 cm residual disease after debulking surgery, and this showed a median PFS/overall survival of 10.5 months/28.8 months for the control arm versus 15.9 months/36.6 months for the bevacizumab-containing arm (Fig. 24.47).

Based on the results of GOG 218 and ICON7, the European Medicines Agency approved the use of bevacizumab in combination with paclitaxel plus carboplatin for the front-line treatment of advanced ovarian cancer in the European Union. Bevacizumab is not FDA-approved in the United States for any use in ovarian cancer at the time of this writing. Issues discussed have included uncertainty about the appropriate duration of bevacizumab therapy, the lack of overall survival benefit seen with bevacizumab in either study as a whole, lack of any molecular predictors for benefit in a specific patient, and the cost of the drug. Since the progression-free survival curves for both GOG #218 and ICON 7, which administered bevacizumab only for a fixed period of time after completion of chemotherapy,

Table 24.14 Randomized Trials ± Bevacizumab

Trial Name	Population	Arms	Results Median PFS/OS*
GOG #218 (Burger, 2011 ⁴⁰¹)	Stage III–IV first-line	Bev + Carbo + Paclitaxel → Bev Bev + Carbo + Paclitaxel → Placebo Placebo + Carbo + Paclitaxel → Placebo	14.1/39.7 mo 11.2/38.7 mo 10.3/39.3 mo
ICON 7 (Pennell, 2011 ³⁸¹)	Stage IIB–IV first-line Stage I–IIA if gr3 or clear cell	Bev + Carbo + Paclitaxel → Bev Carbo + Paclitaxel	19 mo/HR death 0.85 17.3 mo/(0.69–1.04)
OCEANS (Aghajanian, 2011 ⁵⁰³)	Platinum-sensitive first recurrence	Gem + Carbo + Bev → BevGem + Gem + Carbo + placebo → Placebo	12.4/33.2 mo 8.4/33.3 mo RR = 78% RR = 57%
AURELIA (Pujade-Lauraine, 2012 ⁵⁰⁴)	Platinum-resistant recurrence, 1–2 prior regimens	Chemotherapy + Bev → BevChemotherapy (x over at progression) Chemotherapy = PLD, topotecan, or weekly paclitaxel	6.7 mo/NA3.4 mo/NA 31%13%

*for all studies, OS date are immature. Bev=bevacizumab, Carbo=carboplatin, Gem=gemcitabine, mo=month

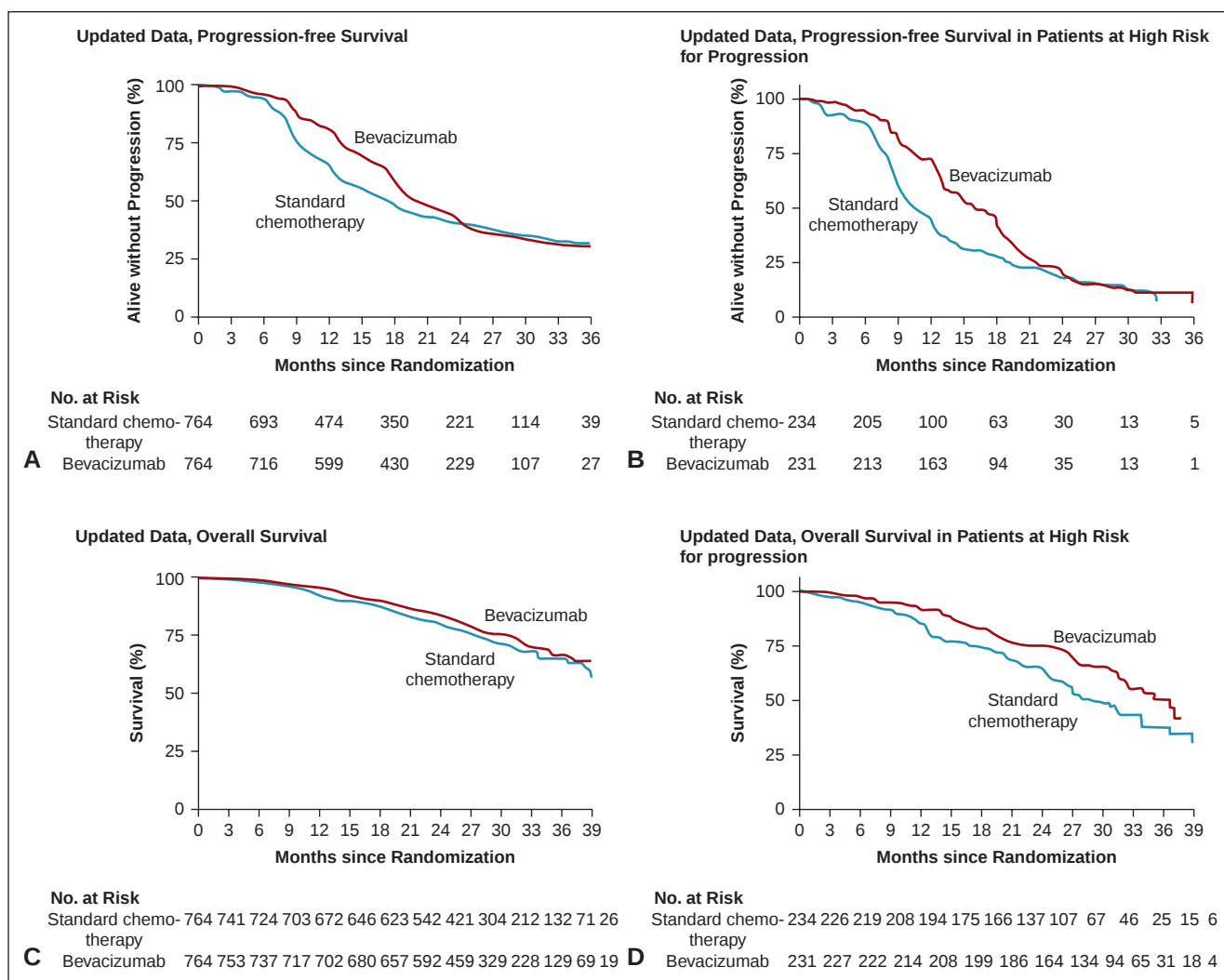


FIGURE 24.47. ICON 7 updated data on progression-free survival are shown according to treatment group in the total study population (Panel A) and in patients at high risk for progression (Panel B). Updated data on overall survival are shown according to treatment group in the total study population (Panel C) and in patients at high risk for progression (Panel D).

Source: Perren et al. *NEJM* 2011;365:2484.

appeared to converge at some point after discontinuation of bevacizumab (nonproportional hazards), it has been hypothesized that the bevacizumab benefit is dependent on continued administration. In addition, there is concern about the lack of overall survival benefit seen in the 2 studies as a whole, and while this might be the result of crossover to receive bevacizumab after progression in the U.S. GOG #218 trial, this is less likely to have been the case for the largely European ICON 7 trial. If the overall benefit of bevacizumab can be realized by administration in the second-line setting (see treatment of recurrent disease, below), fewer women might need to be exposed to the agent for similar benefit.

Intraperitoneal Chemotherapy

Intraperitoneal (IP) chemotherapy is a form of dose-escalation; it provides a means by which high concentrations of drugs and long durations of tissue exposure can be attained at the peritoneal surface. Since intraperitoneal progression of disease remains the major source of morbidity and mortality in ovarian cancer, it is a theoretically attractive approach in the treatment of this disease. Many chemotherapeutic agents, including those used for the treatment of ovarian cancer such as cisplatin,

carboplatin, topotecan, and paclitaxel have been tested for feasibility with intraperitoneal administration. Larger or less water-soluble molecules will stay longer in the peritoneal cavity, and have a higher peritoneal cavity-to-plasma concentration ratio (sometimes referred to as “pharmacologic advantage”), but may not get into the bloodstream. The direct penetration of chemotherapy agents into tumor masses is limited to 1 to 2 mm from the tumor surface. Early work by Los et al., using a rat intraperitoneal tumor model, found that the concentration of cisplatin at the periphery of tumor nodules was higher after IP administration of cisplatin, but the concentration at the center of the nodules was identical after IP and intravenous administration (402). Hence (a) the theoretical benefit is only for very small tumor volumes, and (b) agents that do not reach therapeutic systemic levels when given by the intraperitoneal route need to be administered intravenously as well. Cisplatin has a 10- to 20-fold pharmacologic advantage when given intraperitoneally. For a given dose of cisplatin, peak concentrations are higher with intravenous cisplatin, and this has resulted in somewhat decreased toxicity in a randomized comparison of the same doses of cisplatin given intraperitoneally versus intravenously, including less hearing loss and neuromuscular toxicity (403). However, the amount of cisplatin recovered in the urine, reflecting total systemic exposure, is similar regardless of whether the

administration is intravenous or intraperitoneal. Similarly, carboplatin given IP at an AUC of 6 has been shown to produce an AUC in the peritoneal cavity about 17 times higher than that of carboplatin given intravenously while producing a very similar serum AUC (404). Paclitaxel, on the other hand, has a pharmacologic advantage of about 1,000, and significant levels persist in the peritoneal cavity 1 week after drug administration. However, the dose that can be given is limited by abdominal pain, and serum paclitaxel concentrations detected in patients treated with intraperitoneal paclitaxel at feasible doses are low (405).

Clinical Use of Intraperitoneal Therapy for Ovarian Cancer

In January 2006, the NCI issued a clinical alert supporting the use of intraperitoneal cisplatin chemotherapy in women with optimally surgically debulked ovarian cancer (406). A meta-analysis of 8 trials comparing intraperitoneal to intravenous platinum-based chemotherapy (all but one used cisplatin) showed an average 21.6% decrease in the risk of death (hazard ratio 0.79; 95% CI, 0.70 to 0.89). Since the expected median duration of survival for women with optimally debulked ovarian cancer receiving standard treatment is approximately 4 years, this size reduction in the death rate was estimated to translate into about a 12-month increase in overall median survival. The power of this analysis was based primarily on the survival benefits for intraperitoneal chemotherapy observed in each of the 3 relatively large randomized trials summarized in Table 24.15 (403,407,408).

Despite these results, intraperitoneal therapy has not yet been consistently adopted for the treatment of women with optimally debulked ovarian cancer in the United States, and has not been widely adopted internationally. There are several reasons for this.

First, intraperitoneal therapy, as used in the reported trials, is technically demanding. Administration of paclitaxel over 24 hours, which is necessary to reduce the neurotoxicity when

paclitaxel is combined with cisplatin, is inconvenient and, if it requires hospitalization, expensive. Use of IP catheters is not routine in many oncology practices, and is associated with a number of complications. A recent review of published reports (409) noted that complications involving fully implantable peritoneal catheters used for peritoneal access occurred at overall rates of 6.8% to 40.5% and were responsible for the failure to complete planned IP chemotherapy in 1.9% to 26.2% (mean 12.6%) of patients. Obstruction (37.6%) and infection (31.4%) were the most common complications. Other issues included leakage, retraction of the catheter, rotation of the portal, difficulties with access, and perforation of the bowel. There are no proven methods to minimize these complications. Although infection may theoretically be reduced by the avoidance of placement during grossly contaminated surgeries, there are no hard data on the influence of associated bowel surgery at the time of intraperitoneal catheter placement. There is no proven way to prevent the adhesions that cause catheter obstruction. The review did not find any difference in the rates of complications between fenestrated or unfenestrated ports.

Second, all of the large randomized studies used cisplatin in both the intraperitoneal and intravenous arms, whereas carboplatin, which is less toxic and easier to administer, has become the standard intravenous platinum agent in the treatment of ovarian cancer. Although intraperitoneal carboplatin can be safely used and appears to have favorable pharmacokinetics (pharmacologic advantage combined with good systemic drug exposure), there is not yet evidence that it will provide the same survival benefits as intraperitoneal cisplatin.

Finally, the heterogeneity and toxicity of the intraperitoneal regimens used have left some confusion as to the most important elements of intraperitoneal therapy. For example, the trial reported by Markman et al. used 2 cycles of carboplatin AUC 9 (as “chemical debulking” prior to starting intraperitoneal therapy), which resulted in significant hematologic toxicity and difficulty delivering the IP regimen (408). The Armstrong trial (GOG #172) incorporated both intraperitoneal cisplatin and intraperitoneal paclitaxel. Intravenous paclitaxel was given day

Table 24.15 Selected Randomized Trials of Intraperitoneal Versus Intravenous Chemotherapy in Optimally Debulked Ovarian Cancer

Author (yr)	N	Regimens	Median PFS	Median OS	Comments
Alberts (1996) ⁴⁰³	546	IV cyclophosphamide 600 mg/m ² plus IP cisplatin 100 mg/m ² × 6 vs. IV cyclophosphamide 600 mg/m ² plus IV cisplatin 100 mg/m ² × 6	N/A	49 mo vs. 41 mo <i>p</i> = 0.02	<2 cm residual disease permitted; 58% of patients in both groups completed 6 cycles of cisplatin
Markman (2001) ⁴⁰⁸	462	IV carboplatin AUC 9 × 2 followed by IV paclitaxel 135 mg/m ² /24 h plus IP cisplatin 100 mg/m ² × 6 vs. IV paclitaxel 135 mg/m ² /24 h plus IV cisplatin 75 mg/m ² × 6	28 mo vs. 22 mo <i>p</i> = 0.01	63 mo vs. 52 mo <i>p</i> = 0.05	18% of patients on IP arm got ≤2 cycles of IP therapy
Armstrong (2006) ¹⁸³	416	D1 IV paclitaxel 135 mg/m ² /24 h D2 IP cisplatin 100 mg/m ² D8 IP paclitaxel 60 mg/m ² vs. D1 IV paclitaxel 135 mg/m ² /24 h	24 mo vs. 19 mo	67 mo vs. 50 mo	49% of patients received ≤3 cycles of IP therapy

Note: IV, intravenous; IP, intraperitoneal; OS, overall survival; PFS, progression-free survival; mo, months.

1 and intraperitoneal paclitaxel day 8, leading to speculation that the benefit of the regimen was related to the day 1,8 schedule of paclitaxel administration (“dose-dense”) rather than the intraperitoneal route of chemotherapy administration.

Despite these uncertainties, a potential 1-year survival advantage is certainly meaningful. In GOG #172, the survival benefit was seen even though only 42% of patients on the IP arm received the 6 planned cycles of intraperitoneal therapy due either to cisplatin-related toxicities or catheter problems. The option of intraperitoneal therapy should be discussed with all healthy patients who have optimally debulked ovarian cancer.

Ongoing Trials with Intraperitoneal Therapy

Ongoing trials, including GOG #252, JGOG-3019, and OV-21, are addressing some of the issues regarding optimization of IP chemotherapy regimens. GOG #252 has 3 arms: the carboplatin plus dose-dense paclitaxel (all intravenous) regimen published by the JGOG, the same regimen with the carboplatin administered intraperitoneally instead of intravenously, and a third arm which is a modification of the regimen used in GOG #172 and prescribes paclitaxel 135 mg/m² intravenously over 3 hours day 1, cisplatin 75 mg/m² IP on day 2 and paclitaxel 60 mg/m² IP on day 8. All 3 arms are combined with bevacizumab, which is administered every 3 weeks and continued for 22 cycles. GOG #252 has completed accrual, and results are pending. In the iPocc trial (GOTIC-001/JGOG-3019), dose-dense weekly paclitaxel at 80 mg/m² intravenously is administered in combination with either IV or IP carboplatin AUC 6 every 3 weeks. Patients with stages II to IV disease are eligible; hence this study will explore the potential of IP chemotherapy in suboptimally debulked disease. It is certainly possible that intraperitoneal therapy might benefit women other than those with initially optimally debulked cancer. For example, some patients might be “chemically debulked” by their first few cycles of chemotherapy. The Alberts trial (Table 24.15), perhaps the cleanest test of intraperitoneal therapy in that all variables were the same in both arms except the route of cisplatin administration, permitted accrual of women with up to 2 cm of residual disease. Benefit of therapy was not influenced by extent of residual disease ($p = 0.93$ for interaction of treatment and residual disease, microscopic vs. ≤ 0.5 cm vs. >0.5 to 2 cm). The third ongoing randomized trial of IP therapy is the OV-21/GCIG study lead by the Canadian National Cancer Institute, and incorporates intraperitoneal therapy after neoadjuvant treatment. Patients with stage III disease receive neoadjuvant chemotherapy. Those who respond will receive interval debulking surgery, and if the residual disease after interval debulking surgery is less than 1 cm, they are randomized to one of the 3 arms. The control arm is the combination of intravenous paclitaxel at 135 mg/m² followed by intravenous carboplatin AUC 5 on day 1, and then intravenous paclitaxel at 60 mg/m² on day 8. The second arm is same as the control arm except that carboplatin and day 8 paclitaxel are given by the IP route. The third arm is the same as the second arm, except that intraperitoneal cisplatin 75 mg/m² is substituted for intraperitoneal carboplatin. One of these 2 IP arms (arm 2 or arm 3) will be chosen as a randomized phase II winner, and will then be compared to the control arm in a phase III manner.

Consolidation/Maintenance

Many women with ovarian cancer have an excellent response to first-line chemotherapy, but most will nonetheless relapse and die of their disease. Approximately two-thirds of patients with advanced ovarian cancer will achieve a clinical complete remission following chemotherapy, that is, have no evidence of disease on physical examination or in radiographic studies together with a serum CA-125 in the normal range. In the days

when second-look laparotomy was used, about one-third of all patients with advanced ovarian cancer were free of disease at a second-look laparotomy following primary cisplatin-based therapy. Such operations, whose purpose was prognostic, are no longer generally performed, because no therapy instituted as a result of disease found at second-look surgery was found to alter prognosis, and over half of those patients who initially presented with stage III or IV disease will recur after a negative second-look operation.

Further therapy after a clinical complete remission would clearly be warranted for many women if an effective treatment could be found. However, despite extensive investigation, no trials of consolidation or maintenance therapy have produced any survival benefit to date. The most promising strategies tested have been maintenance paclitaxel and maintenance bevacizumab, both of which appear to delay progression without improving overall survival.

Consolidation with Intraperitoneal Chemotherapy

The EORTC randomized women with a pathologic complete remission to front-line platinum-based therapy to no further therapy versus 4 cycles of intraperitoneal cisplatin at 100 mg/m². The trial closed early with less than half of its planned accrual. After a median follow-up of 8 years, the hazard rates for progression-free survival (PFS) and overall survival (OS) were 0.89 (95% CI, 0.59 to 1.33) and 0.82 (95% CI, 0.52 to 1.29). These results were felt to be suggestive of a treatment benefit but insufficient to change practice (410).

Consolidative Radiotherapy

A randomized trial conducted by the GOG of intraperitoneal ³²P versus observation after pathologic complete response to primary therapy was negative (340). Whole abdominal radiotherapy after chemotherapy is problematic because of complications including myelosuppression, radiation enteritis and bowel obstruction. Using conventional techniques, WAR is not able to deliver adequate radiation doses to the upper abdomen, due to limiting toxicities to organs such as liver and kidneys. Several very small randomized trials have been conducted with contradictory results. Nonetheless, some of the results have been intriguing. For example, the Swedish-Norwegian Ovarian Cancer Study Group randomly assigned 98 patients with stage III ovarian cancer who had a pathologic complete response (CR) at second-look surgery after 4 courses of cisplatin/anthracycline chemotherapy to no further therapy, continued chemotherapy with cisplatin/anthracycline to ten courses total, or whole abdominal radiotherapy. Progression-free survival was significantly better (5-year PFS, WAR = 56%, chemotherapy = 36%, control = 35%, $p = 0.032$) and overall survival trended toward better in the group receiving WAR (411). As discussed above in Section “Early-Stage Disease,” there may be a role for radiation in early-stage clear cell carcinomas, and in this situation pelvic radiotherapy might be able to produce the same benefit as whole abdominal radiotherapy.

Consolidative/Maintenance Chemotherapy

As is the case for use of a third cytotoxic agent in front-line combination therapy, use of a third cytotoxic agent for consolidation/maintenance therapy has not proven effective to date. Two large trials of 4 cycles of consolidative topotecan after primary chemotherapy have both been negative, although they did not require a complete response after primary chemotherapy for eligibility (412,413). Consolidation therapy with epirubicin also failed to improve survival in patients who achieved a clinical complete

remission following platinum-based induction therapy (414). Two small prospective trials of high-dose consolidation therapy with hematopoietic stem cell support have both been negative (415,416).

Paclitaxel Maintenance Therapy

The most promising trial of maintenance therapy to date has been a Southwest Oncology Group (SWOG)/GOG trial randomizing women in clinical complete remission to either 3 or 12 cycles of intravenous paclitaxel 175 mg/m² every 4 weeks (417). The trial was halted by its data and safety monitoring board after a planned interim efficacy analysis at a point when there was a statistically significant improvement in time to progression but no difference in overall survival between the treatment arms (PFS 28 vs. 21 months, one sided $p = 0.0035$). Because insufficient patients to detect a survival difference had been randomized at the time the study was stopped ($n = 262$), and because patients receiving 3 cycles of therapy were allowed the option of crossing over to 12 cycles, a survival comparison was not possible. The neurotoxicity observed was substantial, even though patients with higher than grade 1 neurotoxicity were excluded from the trial, and the dose of paclitaxel was decreased during the study conduct to 135 mg/m² every 4 weeks. However, not very many patients had accrued to the lower dose at the time of study closure, and they were not included in the analysis, so the effect of this dose reduction on therapy efficacy is uncertain. An unplanned retrospective subgroup analysis suggested a trend toward survival benefit in the group of patients who started maintenance therapy with a CA-125 level of less than ten (418).

A subsequent Italian study group randomized 200 patients with stages IIb to IV disease who were in clinical or pathologic complete response after 6 courses of paclitaxel/platinum-based chemotherapy to either observation or 6 consolidation courses of paclitaxel 175 mg/m² every 3 weeks. Grade 2 or greater sensory neurotoxicity was reported in 28.0% of the paclitaxel-arm patients. Two-year progression-free survival rates were 54% and 59% ($p =$ not significant) in the control and maintenance arms, respectively. Corresponding 2-year overall survival rates were 90% and 87% ($p =$ not significant) (419). The GOG is currently conducting a larger trial, GOG #212, randomizing women after clinical complete remission after primary therapy for stage III or IV disease to one of 3 arms: no further therapy, paclitaxel 135 mg/m² every 4 weeks for 12 cycles, or Xyotax (CT-2103, a microparticle-bound paclitaxel) 135 mg/m² every 4 weeks for 12 cycles. This trial has overall survival as the endpoint.

Maintenance with Noncytotoxic Agents

Noncytotoxic agents such as interferon (420), a monoclonal antibody targeting CA-125 (oregovomab) (421), radioimmunoconjugates including intraperitoneal administration of a 90Y-conjugated antimucin antibody (422), and matrix metalloproteinase inhibitors have all been tested in phase III trials with no improvement in survival. The EORTC recently reported that the use of the epithelial growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for 2 years after nonprogression on front-line therapy provided no benefit (423). The use of bevacizumab is discussed above. Since the GOG #218 trial showed no benefit in terms of progression-free survival when bevacizumab was given concomitantly with chemotherapy but not as maintenance thereafter, it seems probable that the benefit is derived from the maintenance administration of the agent. However, as discussed, no overall survival benefit was seen even with concomitant and maintenance administration of bevacizumab. Numerous trials of other antiangiogenic agents in the consolidation/maintenance setting are ongoing.

SPECIFICS OF EPITHELIAL OVARIAN CANCER WITH CLEAR CELL AND MUCINOUS HISTOLOGY, INCLUDING ADVANCED DISEASE

Until recently, clinical trials for epithelial ovarian cancer included all histologic subtypes together. However, it is becoming increasingly obvious that this is not appropriate, and that the different histotypes are both biologically and clinically distinct, a fact supported by both clinical observation and molecular profiling (424). Because high-grade serous tumors make up about two-thirds of advanced-stage disease (see Table 24.12) there has generally been little power to draw conclusions about the relative benefit of the treatment under study to less common subtypes. However it has become obvious that advanced-stage clear cell and mucinous tumors have a worse prognosis than advanced-stage serous tumors, which may be related to lower sensitivity to standard cytotoxic chemotherapy. A review of all patients entered into advanced-stage GOG ovarian cancer trials from 1976 to 1982, when response was commonly surgically assessed, revealed no negative second-look laparotomies among women with clear cell or mucinous histology (425).

Clear cell Carcinomas

Clear cell carcinoma accounts for 1% to 12% of epithelial ovarian carcinomas in the United States, but 15% to 25% of epithelial ovarian cancers in Japan. Asian women in the United States who get ovarian cancer are twice as likely to have a clear cell cancer as White women. In Japan, as in Western countries, clear cell carcinoma tends to present at an early-stage; in one review, 39% of clear cell cancers were stage I, 13% stage II, 30% stage III, and 6% stage IV (426). Histologic diagnosis may be challenging (see Section “Pathology”), since some high-grade serous carcinomas have a clear cell component, and may be misclassified as clear cell carcinomas. A high-frequency of capsular rupture during surgery for clear cell carcinoma has been reported. In the EORTC-ACTION trial, capsule rupture was reported in 44% of clear cell carcinomas versus 19% of serous tumors. The vast majority were due to intraoperative rupture. A recent review of early-stage clear cell ovarian cancer in British Columbia found that 5-year disease survival for all patients with FIGO stage IC clear cell disease was 67% versus 84% for those stage IA/B clear cell tumors. Patients with capsular rupture alone, with no positive cytology or surface involvement, had a prognosis similar to those with stage IA disease (339).

Molecular studies suggest a distinct profile for clear cell carcinomas. Unlike high-grade serous tumors, they are generally p53 wild-type, and they have a lower frequency of *BRCA 1* and 2 germline mutations than high-grade serous tumors. They have low levels of chromosomal instability and a high frequency (up to 40%) of phosphoinositide 3-kinase catalytic alpha (PIK3CA) mutations. *ARID1A*, a tumor suppressor gene, appears to be mutated in almost half of clear cell carcinomas (36). Gene expression profiling suggests similarities between clear cell carcinomas of the ovary, endometrium, and kidney. For example, the VHL target, HIF1A, appears to be expressed at a higher level in ovarian clear cell carcinoma compared to other histologic types (427). However the somatic and germline mutations of the VHL gene observed in renal clear cell carcinoma have not been observed in ovarian clear cell tumors (351).

As discussed above (Section “Early-Stage Disease”), the implications of clear cell histology in early-disease are not clear; in some reports it seems to portend a high-risk of recurrence, and in others it appears to have little prognostic significance. The benefits of adjuvant chemotherapy are uncertain, and some reviews have suggested little benefit (428). A subgroup analysis

of the EORTC-ACTION trial also suggested that clear cell carcinomas did not appear to benefit from chemotherapy, but the numbers were small. Five-year disease-free survival in the 37 patients on the observational arm was 71%, while it was 60% in patients treated with chemotherapy. It has been suggested that radiation therapy might improve survival in women with stage IC/II disease (339).

Regardless, it has become increasingly clear that advanced-stage clear cell carcinomas do not respond as well to platinum-based chemotherapy as do high-grade serous tumors, possibly because of their lower proliferation rate. As early as 1996, Goff et al. reported that 52% of stage III clear cell tumors of the ovary versus 29% of serous tumors progressed clinically during the course of primary platinum chemotherapy (429). Reported response rates for women with clear cell carcinomas in front-line trials range from 22–56% versus over 70% for women with serous carcinomas (351), variability that may be due, in part, to misclassification of high-grade serous tumors with clear cells as clear cell carcinomas (see section “Pathology”). Survival is also poorer. In 2010 a meta-analysis which included data from over 8,000 patients on 7 international front-line trials using platinum-based regimens identified 221 women with stage III/IV clear cell carcinoma. These women had a median overall survival of 21.3 months versus 40.8 months for women with serous carcinomas (430).

Even worse results have been reported in the setting of recurrent disease, and it does not seem to matter whether the disease is platinum-sensitive or platinum-resistant by traditional definitions. Investigators from M. D. Anderson published a retrospective review of 51 patients treated at their institution for recurrent clear cell carcinoma. Among those with platinum-sensitive disease, only 2 (9%) of 22 patients had a partial response to retreatment with carboplatin and paclitaxel; none of 29 patients given second-line therapy for platinum-resistant disease responded (431). In another study of 75 Japanese women with at least 2 lines of prior systemic therapy, those whose tumors recurred greater than 6 months after completion of chemotherapy had a response rate of 8% versus a response rate of 6% for those whose tumors progressed within 6 months of completing primary chemotherapy (351). This may be because most recurrences occur in women who presented with completely resected stage I disease, and hence there was no way of knowing if the tumor actually shrank in response to chemotherapy, making “platinum sensitive” a misnomer.

There are few data suggesting what treatments might be effective for clear cell carcinomas. Based on some reports that irinotecan plus cisplatin had activity in some patients with clear cell carcinoma, a randomized phase II front-line study was performed by the Japanese Gynecologic Oncology Group (JGOG). Women were randomized to therapy with either carboplatin/paclitaxel or cisplatin/irinotecan (432). Among patients with measurable disease the response rate was 25% (2 of 8) in the irinotecan/cisplatin arm and 40% (2 of 5) in the carboplatin/paclitaxel group. Among women with no residual disease over 2 cm, PFS tended to be longer in the cisplatin/irinotecan group, though the difference was not statistically significant. A multinational phase 3 study for stage I to IV clear cell carcinoma of the ovary using the same 2 regimens has been completed, and results are awaited.

There has also been interest in the use of mTOR inhibitors, because they have activity in patients with advanced renal cell carcinoma, and because PIK3CA mutations have been reported to be common in clear cell carcinomas of the ovary. A report of use of weekly temsirolimus in 5 evaluable patients with heavily pretreated clear cell carcinoma of the ovary noted one partial response of 14 months duration (433). The GOG has launched a frontline single-arm phase II trial (GOG #268) testing the combination of carboplatin, paclitaxel, and temsirolimus followed by consolidation temsirolimus in the treatment of stage III/IV clear cell carcinoma of the ovary. Antiangiogenic agents, which likewise have activity in the treatment of renal cell carcinoma,

may also be useful. There is anecdotal evidence of the activity of sunitinib in clear cell carcinoma of the ovary, and the GOG is performing a trial, GOG #254, of sunitinib in the treatment of persistent or recurrent clear cell carcinoma. One report described one partial response and 2 patients with stable disease among 5 women with ovarian clear cell carcinoma who were treated with gemcitabine (434).

Interestingly, multiple reports suggest that women with clear cell carcinomas are more likely to have a thromboembolic event. Goff et al. noted that 42% of patients with stage III clear cell tumor had deep venous thrombosis (DVT) or pulmonary embolus (PE) versus 18% of patients with serous tumors (429); another more recent retrospective study reported that 42% of patients with clear cell carcinoma had a venous thromboembolic event versus only 22% of patients with other histologies. Half of the events occurred postoperatively (435). Hypercalcemia related to paraneoplastic expression of parathyroid hormone-related peptide has also been reported to be more common in clear cell carcinoma of the ovary than in other subtypes (436).

Mucinous Tumors

When gene expression arrays are performed, mucinous tumors group separately from serous, endometrioid and clear cell ovarian carcinomas. They often more often have *K-RAS* mutations. Unlike colorectal adenocarcinomas, they are often immunoreactive for CK7; unlike other ovarian cancers they are frequently immunoreactive for CK20 and CDX2 (which are usually diffusely and strongly reactive in colorectal adenocarcinomas), though the staining is often weak and focal (437). Early-stage mucinous tumors tend to be low-grade and have a good prognosis. They are unlikely to have metastasized to lymph nodes, and as discussed above (see Section “Early-Stage Disease”), lymph node dissection may not be needed in stage IA mucinous tumors. Advanced-stage mucinous tumors, which are uncommon, respond poorly to chemotherapy and are associated with a short survival for both stage III and stage IV disease (300,438). The overview cited above by MacKay et al. found the median disease free survival for women with stage III/IV mucinous tumors to be only 14.6 months, even shorter than that for women with clear cell disease. It is now known that many tumors thought initially to be advanced-stage mucinous tumors in older studies actually represent metastatic disease from another site, so it is difficult to interpret published results. In a recent international front-line trial for stage III/IV disease that tested 5 different regimens of cytotoxic chemotherapy in 4000 women, 44 cases were classified as mucinous adenocarcinoma. Only about one-third of these judged to be primary mucinous carcinomas by the 3 central reviewers; the remainder were thought to represent metastatic disease from another site. The median survival did not differ significantly between the groups considered primary or metastatic, but survival for both groups was significantly shorter than the survival for women with serous carcinoma (14 versus 42 months, $p < 0.001$) (439).

Based on similarities of mucinous ovarian cancers to colorectal carcinomas, a currently active international trial, GOG #241, is comparing carboplatin/paclitaxel with or without bevacizumab to capecitabine/oxaliplatin with or without bevacizumab.

CARCINOSARCOMA

Ovarian carcinosarcomas tend to present with advanced disease, and early-stage tumors are unusual. Stage III ovarian carcinosarcoma is more common than either stage III mucinous ovarian cancer or stage III clear cell cancer (Table 24.11). Ovarian

carcinosarcoma occurs at a slightly older age and has a worse prognosis overall than epithelial ovarian cancer without sarcomatous differentiation (440), with a median overall survival in the range of 9 to 24 months (441). One small series reported a median overall survival of 62 months for 9 patients with stage I/II disease (442). In recent reports the presence of homologous versus heterologous elements has not been found to have any clear influence on outcomes. The presence of more than 25% sarcomatous histology has been linked to a worse prognosis. Although prospective data regarding the value of debulking surgery do not exist, optimal cytoreduction is associated with improved outcomes, and it is recommended that operative management of these tumors resemble that of epithelial ovarian cancer. Adjuvant chemotherapy is also generally recommended, although randomized trials showing benefit do not exist. Prospective GOG trials reported response rates of 10% for single agent doxorubicin, 18% for ifosfamide, and 20% for cisplatin. Retrospective series have suggested that platinum-containing regimens produce higher response rates than non-platinum-containing regimens, but the optimal regimen remains unknown, and it is unknown whether the percentage of sarcomatous histology in the tumor should influence choice of regimen. One series suggested improved outcomes with cisplatin/ifosfamide versus carboplatin/paclitaxel; another suggested superior outcomes with carboplatin/paclitaxel versus other regimens (440). Ifosfamide-containing regimens are generally more toxic. A case-control series of 50 cases of carcinosarcoma of the ovary treated with first-line platinum-taxane based therapy and 100 cases of papillary serous ovarian cancer matched by age, stage, and year of diagnosis showed response rates to chemotherapy of 62% for carcinosarcomas and 83% for epithelial ovarian cancers, with median PFS of 11 versus 16 months and median OS of 24 versus 41 months (441). Current GOG trials allow patients with carcinosarcoma of the ovary to participate in trials for carcinosarcoma of the uterus, and in the current front-line study, GOG #261, women with stage I-IV disease are randomized to either paclitaxel plus carboplatin or ifosfamide plus paclitaxel.

FOLLOW-UP OF PATIENTS WHO ARE CLINICALLY WITHOUT EVIDENCE OF DISEASE-SURVIVORSHIP ISSUES

There are relatively few studies of long-term effects of therapy for ovarian cancer. The majority of women who present with advanced-stage disease ultimately recur, and anxiety about recurrence is very common. Recent survey studies also identify sexual dysfunction, peripheral neuropathy, hearing loss or tinnitus, cognitive changes, gastrointestinal symptoms, fatigue, and insomnia as issues of great concern (443–445).

Matulonis et al. studied survivors of early-stage ovarian cancer and found that 90% had either no interest in sex or were not sexually active (446). In premenopausal women with ovarian cancer, the removal of the ovaries results in premature menopause. Consequently, they have symptoms including hot flashes and vaginal dryness, and those who achieve long-term survival are at increased risk for osteoporosis. There is some concern about prescribing HRT to ovarian cancer survivors because (1) epidemiologic evidence (described above) suggests that estrogen replacement therapy slightly increases the risk of developing ovarian cancer *de novo*, and (2) antiestrogens, such as tamoxifen, may produce tumor shrinkage in a small subset of women with advanced ovarian cancer. However, there is no evidence that hormone therapy increases the risk of recurrence. One small randomized, controlled trial reported that estrogen replacement therapy has no detrimental effect on disease-free or overall survival in women with ovarian

cancer (447). Short-term estrogen replacement therapy, particularly in symptomatic women who were premenopausal prior to their surgery for ovarian cancer, would appear reasonable. Screening for osteoporosis in women who have early-stage disease and do not opt for HRT is appropriate, since there are alternate treatments, such as raloxifene, bisphosphonates, or alendronate, available. Issues of sexual dysfunction may be related to side effects from surgery (scarring, shortening of the vagina) and feelings of anxiety as well as estrogen deprivation. HRT can relieve the estrogen deprivation-related symptoms and cancer support groups and/or qualified psycho-oncologic help can address the general anxiety. Refractory and bothersome sexual problems might require referral of women and their partners to practitioners with expertise in the area.

A group of Italian investigators reported on long-term neurologic evaluations in 120 ovarian cancer patients treated with a front-line carboplatin AUC5/paclitaxel 175 mg/m² regimen. There was a 15% chance of residual neuropathy 6 months after the completion of chemotherapy (448). This will be higher with more dose-intense (e.g., weekly) paclitaxel regimens such as the one recently published by the Japanese Gynecologic Oncology Group (JGOG, see “alternate paclitaxel dosing” above) and with cisplatin-containing regimens, which currently includes most intraperitoneal chemotherapy. While there are agents, such as duloxetine, that can provide some symptomatic alleviation (449) for neuropathy, it is best prevented. Patients should be questioned about numbness and tingling in their hands and feet at each visit during treatment, and agent substitution (e.g., docetaxel for paclitaxel, carboplatin for cisplatin) or dose modification should be considered before neuropathy becomes severe, particularly in patients whose life might be affected by neuropathy (e.g., piano player). Interestingly, neuropathy is the one symptom that has consistently been reported to be worse in elderly patients than in younger patients across studies.

Risks of second primaries, particularly for patients with a *BRCA* mutation or Lynch syndrome should be kept in mind. Patients may have been too overwhelmed at the time of diagnosis to consider genetic counseling, and other family members may develop cancers as time goes by, so the issue should be reconsidered during follow-up visits.

CA-125 Follow-Up of Patients in Remission

National Comprehensive Cancer Network (NCCN) Guidelines for follow-up of patients with ovarian cancer who enter a clinical complete remission (450) include a history and clinical exam every 2 to 4 months for 2 years, then 3 to 6 months for 3 years, then annually after 5 years, with CA-125 or other tumor markers at every visit if initially elevated, and imaging only as clinically indicated. Pelvic exam should be performed periodically. Unlike the situation in general screening (451), a rise in CA-125 in patients with high-grade serous cancers after primary treatment is fairly specific for recurrence, particularly if the pretreatment CA-125 was significantly elevated and a second confirmatory CA-125 shows that the titer is continuing to rise. The CA-125 may rise prior to any evidence of disease on imaging, and in about a third of all women over 6 months will elapse before they develop symptoms. Recurrent ovarian cancer is not curable, and it is not clear that earlier detection can improve either survival or quality of life. The Medical Research Council (OV-05) and the European Organization for the Research and Treatment of Cancer (EORTC 55955) conducted a phase 3 trial in which 1,442 women with a clinical complete remission after first-line platinum containing therapy were followed with serial CA-125 levels followed by randomization to either initiate treatment at the time of biochemical recurrence (defined as a CA-125 exceeding twice the upper limit of normal) versus waiting until the time of clinical evidence of recurrence. Five hundred twenty-nine women were randomized.

Twenty percent of women had a rise in CA-125 within 6 months of completing primary chemotherapy, 33% between 6 and 12 months, and 45% after 12 or more months. Treatment at the time of CA-125 rise resulted in starting chemotherapy 4.8 months earlier compared to patients treated at the time of clinical recurrence. However survival (defined as survival from the time of CA-125 rise) did not differ between the 2 groups, at 25.7 months for women assigned to early treatment, and 27.1 months for those assigned to delayed treatment. Most importantly, women receiving early treatment had a worse quality of life as measured by a shorter time to deterioration of the global health score on the EORTC QLQ-C30 questionnaire (452). Issues concerning the use of CA-125 as part of follow-up should be discussed with patients. Detection of disease while it is not symptomatic may allow patients more opportunity to participate in trials of new agents, but it cannot be claimed to improve survival, and some women may opt for less aggressive monitoring.

USES OF CA-125 IN OVARIAN CANCER TREATMENT

Tumor markers in general are discussed in Chapter 6. As discussed above, the current usefulness of CA-125 for screening of asymptomatic women is limited, in part because many stage I ovarian cancers are not associated with an elevated serum level of CA-125, and a variety of nonmalignant conditions (endometriosis, tuberculosis, abdominal infections, hepatitis) can elevate CA-125, particularly in premenopausal women. Current large-scale screening trials use a ROCA (risk of ovarian cancer algorithm) which establishes a CA-125 baseline for each woman and screen for changes in slope (453). Results of these trials are awaited. Newer markers such as human epididymis protein 4 (HE4) and CA72.4 are not influenced by the hormonal fluctuations of the menstrual cycles, but have not been shown to improve overall outcomes for screening although they might increase specificity (454). HE4 is FDA-approved as part of the ROMA (risk of malignancy algorithm) used to determine the likelihood of malignancy of an indeterminate adnexal mass. CA-125 is also widely used to monitor for cancer recurrence in patients with complete remission after front-line therapy, but as described above, this has not been shown to improve survival. For women with a high CA-125 at baseline, the marker correlates with volume of disease, and is often checked with each cycle of chemotherapy. Multiple studies have shown that the rapidity of CA-125 normalization and depth of CA-125 nadir after completion of primary therapy have prognostic value. For example, one group found median progression-free and overall survival for women with stage III or IV ovarian cancer who achieved a value of less than 35 U/mL after third cycle to be 18 months and 42 months respectively, compared to 9 months and 22 months for patients whose tumor marker did not normalize ($p < 0.001$) (314). The authors suggested that in future trials women whose CA-125 does not normalize after the third cycle should be switched to an alternate regimen. However, at this time there are no clinical interventions known to improve outcomes for those women who do not show the desired decline in CA-125.

CA-125 may be useful for monitoring the effectiveness of second-line chemotherapy, decreasing the need for frequent imaging. A number of CA-125 response definitions, such as 50% or 75% decline, have been developed (455). Herzog et al. reported that in a large phase III ovarian cancer trial of salvage chemotherapy (OVA-301, pegylated liposomal doxorubicin plus trabectedin versus pegylated liposomal doxorubicin alone) the concordance between CA-125 using modified Rustin criteria (which define a CA-125 response as $\geq 50\%$ reduction in CA-125 levels from pretreatment values, maintained at least 28 days) (456,457) and RECIST (Response Evaluation Criteria in Solid Tumors

1.0) criteria was 79%. The negative predictive value of CA-125 was 89% to 90%, indicating that in most cases lack of CA-125 response predicts lack of radiologic response. However, the positive predictive value of CA-125 was only 59% to 68%, indicating that response by CA-125 does not always predict a RECIST response. Changes in CA-125 tended to occur first: radiologic response was preceded by a CA-125 decrease in a high proportion of patients, and CA-125 progression preceded RECIST progression in 35% of patients, with a median lead time of 8.4 weeks (458).

Caution should be used when relying on CA-125 to assess response to therapy, particularly in women with heavily pretreated disease. It can occasionally happen that major discordance develops, and the cancer progresses while the CA-125 value declines. In addition, caution should be used in discontinuing a therapy after the first cycle of chemotherapy based solely on rise in CA-125. Sabbatini et al. reported that only half of the patients who eventually had a CA-125 decline with liposomal doxorubicin therapy had a decline prior to the second cycle of therapy (459). Questions have also been raised as to whether CA-125 response criteria are valid in the setting of anti-VEGF targeted therapy, since it has been noted that patients on maintenance bevacizumab were noted to sometimes have clinically stable disease for a prolonged period after a rise in CA-125 that would have qualified as progression (460). It is unclear if the issue is unreliability of CA-125, or ability of the targeted agent to provide continued benefit even in the setting of slight tumor growth. Removal of ascites will affect CA-125 levels; renal dysfunction does not (461).

TREATMENT OF PERSISTENT/RECURRENT DISEASE

Ovarian cancer that is resistant to primary chemotherapy or recurs at some point after primary chemotherapy is generally not curable. Nonetheless, some women with recurrent disease will have prolonged survival. Of the women who are not cured by their primary therapy, about 10% will progress on primary platinum treatment, and are described as having disease that is “platinum-refractory,” about 15% will progress 0 to 6 months after completion of completion of primary therapy and are said to have “platinum-resistant” disease, and 75% have disease that recurs more than 6 months after primary therapy, which is termed “platinum-sensitive” (462–464).

Secondary Cytoreductive Surgery

Surgery in the treatment of recurrent ovarian cancer is covered in the Section “Surgery”. It is generally considered indicated when the cancer recurs a prolonged time after primary therapy and/or in a limited site. Two current randomized trials, GOG #213 and the DESKTOP III trial, are addressing whether surgery plus chemotherapy improves survival over chemotherapy alone in women with platinum-sensitive recurrent disease.

Second-Line Chemotherapy

In 1991 Markman et al. published an influential retrospective review of 72 patients who had responded to initial platinum-based therapy and were subsequently retreated with a platinum-based regimen (465). The response rate for women with a “platinum-free interval” of 5 to 12 months was 27%, for 13 to 24 months was 33%, and for over 24 months was 59%. Women who had a greater than 24-month interval with no therapy (as opposed to just no platinum-based therapy) had a 77% response rate with a 32% rate of surgically confirmed complete

remission. Subsequent clinical trials have generally be conducted separately for patients with tumors classified as “platinum-resistant”, usually meaning progressive disease less than 6 months after most recent platinum dose and those with tumors classified as “platinum-sensitive,” usually meaning progression more than 6 months after most recent platinum dose. The term “platinum-refractory” usually refers to disease with less than a CR to primary platinum therapy, although it can also be used for disease that progresses on any line of platinum therapy.

As a general rule, the platinum-free interval after first treatment is predictive for overall survival as well as response to chemotherapy, including nonplatinum chemotherapy. In a randomized trial of pegylated liposomal doxorubicin (PLD) versus PLD plus trabectedin as first salvage chemotherapy, the overall survival was 13.6 months for women with a platinum-free interval of less than 6 months, 20.3 months for those with a platinum-free interval of 6 to 12 months, and 32.5 months for those with a platinum-free interval of over 12 months (466). An exception to this general rule may be the small fraction of women with advanced-stage low-grade serous tumors whose disease is slower growing, but not generally very chemotherapy sensitive. Women with high-grade tumors whose disease has less than a partial response to primary platinum plus taxane therapy have a very poor prognosis, and response to any subsequent treatment is unlikely.

While categories of “platinum sensitivity” are useful shorthand predictors of the likelihood of response to further treatment, they have primarily been created for use in clinical trials and must be used with clinical judgment when selecting therapy in individual cases. For example, a woman with stage I clear cell carcinoma that recurs with diffuse disease 7 months after completion of adjuvant chemotherapy probably had no response to treatment at all, and her cancer will likely be refractory to further chemotherapy. On the other hand, a woman with suboptimally debulked stage IV serous carcinoma that has responded completely to primary chemotherapy and who has a rise in CA-125 5 months later, probably has chemotherapy-sensitive disease, and is very likely to have at least some tumor shrinkage with a second line of treatment.

Time since most recent platinum therapy is not the only means of predicting benefit from future treatment. Eisenhauer et al. analyzed results for 704 patients who had recurrence or persistent disease after primary platinum-based therapy and were treated on a variety of second-line chemotherapy trials (467). Independent predictors of a positive response to second-line therapy were a largest tumor diameter of less than 5 cm, fewer sites of disease, and serous histology. Time to recurrence since primary therapy, when analyzed as a continuous variable, was not independently prognostic, and was closely correlated with tumor size. Lee et al. published a nomogram for predicting progression-free survival in women with platinum-sensitive recurrent ovarian cancer. The most important factor contributing to shorter progression-free survival was size of the largest tumor; other descriptors remaining significant in multivariable analysis were platinum-free interval, CA-125 (higher values being worse), number of organ sites of metastasis, and white blood count (higher being worse) (468). The effects of prolonged consolidation therapy on future sensitivity of the tumor to treatment have not been well studied, and are likely to vary with the agent used.

Patients with a complete response to second-line platinum therapy will usually have a shorter time to recurrence after the second treatment regimen than after the first (469), and recurrent ovarian cancers eventually become resistant to platinum and all other chemotherapy agents. Hoskins et al. developed a statistic for estimating benefit from further therapy in patients who had received multiple regimens. Women with a time from first to third (or second to fourth, third to fifth, etc.) relapse or progression of 6 months or less had a median survival of under 3 months. In other words, women with minimal or no benefit (with prolonged disease stabilization considered a benefit)

from 2 different therapies in a row have a very poor prognosis (470). This is in line with the current American Society of Clinical Oncology (ASCO) recommendation that cancer-directed therapy should, in general, not be used for patients who have low performance status and have not had benefit from prior evidence-based interventions (471).

Platinum-Sensitive Disease

Single Agent Cytotoxic Therapy in

Platinum-Sensitive Disease

Response rates in multicenter trials testing single-agent cisplatin or carboplatin in women with platinum-sensitive disease are generally 30% to 50% (472,473), and, as discussed above, tend to be higher in women with a longer platinum-free interval. Response rates in multicenter trials to single-agent paclitaxel, topotecan, or liposomal doxorubicin in platinum-sensitive disease have generally been in the range of 20% to 35% (472,474). Platinum agents are the most active front-line drugs for the treatment of ovarian cancer and are generally considered to be the most active agents in women with platinum-sensitive relapsed disease, particularly for women who relapse more than 12 months after completing primary therapy. However, there are very few randomized data directly comparing single-agent platinum compounds to other single agents in women with platinum-sensitive disease. The EORTC randomized 86 women to either single-agent paclitaxel or single-agent oxaliplatin. Responses among the 63 platinum-resistant patients were 5 out of 31 (16%) for paclitaxel and 2 out of 32 (6%) for oxaliplatin. Responses among the platinum-sensitive patients were 2 out of 10 (20%) for paclitaxel and 5 out of 13 (38%) for oxaliplatin (475).

Platinum-Based Combination Cytotoxic Therapy in Platinum-Sensitive Disease

Results of several retrospective analyses of carboplatin/paclitaxel combination therapy in women with platinum-sensitive disease showed strikingly high response rates of 70% to 90% (476,477), and raised the question of whether combination therapy was superior to single-agent therapy in this setting. There have been several randomized trials comparing platinum-based combination cytotoxic therapy to single-agent platinum therapy (472,473,478) (Table 24.16). In general, these show superior response rates and superior progression-free survival with combination therapy. Results regarding overall survival are conflicting. Only the ICON4/AGO-OVAR-2.2, a combined analysis of 2 parallel trials comparing paclitaxel plus platinum to “conventional platinum-based chemotherapy” (71% received single-agent carboplatin, 17% cisplatin/doxorubicin/cyclophosphamide, and 12% other nontaxane platinum-based regimens), showed convincing survival benefit; the absolute improvement in overall survival was 5 months (from 24 months to 29 months) (389). Only about 40% of the patients in this analysis had received prior taxane therapy, and this has raised concern about the generalizability of the results although there was no significant statistical interaction between survival benefit and prior taxane therapy. It was noted that only 31% of patients in the nontaxane arm received taxane therapy at the time of progression. Other trials have not shown a survival benefit to combination chemotherapy in women with platinum-sensitive disease. The GCIIG trial randomizing women to carboplatin and to carboplatin plus gemcitabine was not powered to show an overall survival difference; however, despite a superior response rate (complete response was achieved in only 6% of women on single agent therapy versus 15% of women on the combination regimen) and a longer progression-free interval with combination treatment, there was no evidence of a trend to survival benefit (473). There were no differences in quality of life scores

Table 24.16 Combination Cytotoxic Therapy in Platinum-Sensitive Recurrent Ovarian Cancer

Author (yr)	n	Regimen	RR	Median PFS	Median OS
Bolis (2001) ⁵⁵⁴	190	Carboplatin	56%	3 yr	3 yr
		Carboplatin +	62%	12%	29%
		Epidoxorubicin	$p = \text{NS}$	3 yr 25%	3 yr 42% $p = \text{NS}$
Cantu (2002) ⁵⁵⁵	97	Paclitaxel	45%	9 mo	26 mo
		CAP	55%	16 mo	35 mo
			$p = \text{NS}$		
Parmar (ICON4/AGO-OVAR 2.2) (2003) ³⁸⁹	802	Platinum ^a	54%	10 mo	24 mo
		Platinum +	66%	13 mo	29 mo
		Paclitaxel	$p = 0.06$		
Pfisterer (2006) ⁴¹²	356	Carboplatin	31%	5.8 mo	17.3 mo
		Carboplatin +	47%	8.6 mo	18 mo
		Gemcitabine	$p = 0.0016$	$p = 0.0031$	
Alberts (2008) ⁵⁵⁶	61	Carboplatin	32%	8 mo	18 mo
		Carboplatin +	67%	12 mo	26 mo
		liposomal/doxorubicin	$p = 0.02$	$p = 0.06$	$p = 0.02$
Monk (2010, 2012) ^{485,466}	218 ^b	PLD	22.6%	7.5 mo	24.1 mo (PFI > 12 mo) 16.4 mo (PFI 6-12 mo)
		PLD +	35.3%	9.2 mo	
		trabectedin			27 mo (PFI > 12 mo) 22.4 mo (PFI 6-12 mo)
Pujade-Lauraine (2010) ⁵⁵⁷	466	Carboplatin + PLD	N/A	11.3 mo	Not mature
		Carboplatin+paclitaxel		9.2 mo	

Note: CAP, cisplatin/doxorubicin/cyclophosphamide; NS, not significant; OS, overall survival; PFS, progression-free survival; RR, response rate, PFI Platinum free interval, PLD pegylated liposomal doxorubicin.

^acontrol arm in CAP or single agent carboplatin.

^bsubset of a larger trial.

between the 2 arms; the primary difference in toxicities was increased hematologic toxicity of the combination regimen, with 27% versus 8% grade 3/4 anemia, 70% versus 12% grade 3/4 neutropenia, and 35% versus 11% grade 3/4 thrombocytopenia.

Several trials in women with platinum-sensitive disease have compared platinum-based combinations to each other. Most notably the CALYPSO trial compared carboplatin AUC 5 plus pegylated liposomal doxorubicin (PLD) 30 mg/m² every 4 weeks to carboplatin AUC 5 plus paclitaxel 175 mg/m² every 3 weeks, and showed superior PFS for the PLD regimen. Again, toxicities differed: the PLD regimen produced less alopecia and neuropathy, but more nausea, mucositis, and hand-foot syndrome (479). The HECTOR trial, which has been reported only in abstract form, compared carboplatin AUC 5 plus topotecan 0.75 mg/m² days 1,2,3 every 3 weeks with standard therapy consisting of physician/patient choice of either carboplatin plus paclitaxel, carboplatin plus gemcitabine, or carboplatin plus pegylated liposomal doxorubicin. 78% of patients in the standard therapy group chose gemcitabine plus carboplatin. There was no

significant difference in response rate, progression free survival, or overall survival between the 2 arms (480).

Platinum-Resistant Disease

In general, tumors resistant to platinum are more resistant to any cytotoxic agent. A number of phase 3 randomized trials including paclitaxel (474), topotecan (474,481), pegylated liposomal doxorubicin (474), and gemcitabine (482) as single agents have been informative in guiding our treatment of platinum-resistant disease. They show that response rates to conventional single-agent therapy in this group of women are about 10%, median progression-free survival is about 3 to 4 months, and median overall survival is 9 to 12 months. Significant differences in terms of response rate or survival between various agents in platinum-resistant disease are not usually seen.

Combinations of cytotoxic agents have not been shown to be superior to single agent therapy in women with platinum-resistant disease. A small trial randomized 234 women whose

disease had recurred within 12 months of initial platinum-based therapy (median, 3 months) to single-agent paclitaxel versus epirubicin plus paclitaxel (483). The response rate was 37% for the combination and 47% for single-agent paclitaxel; median survival was 12 months and 14 months, respectively. A small randomized phase II GINECO (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens) trial comparing single agent weekly paclitaxel to weekly paclitaxel plus carboplatin or weekly paclitaxel plus weekly topotecan in patients with platinum-resistant ovarian cancer showed no improvement in response rate or PFS with combination therapy (484). A randomized trial of trabectedin plus pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone showed that in women with platinum sensitive disease both disease response rates and progression-free survival were improved (35% versus 23%; 9.2 versus 7.5 months), whereas for women with platinum-resistant disease they were not (12% versus 13%; 3.7 versus 4.0 months) (485). On the basis of these results, trabectedin plus PLD was approved for the treatment of women with platinum sensitive relapsed ovarian cancer in the European Union, although not by the U.S. Food and Drug Administration (U.S. FDA).

In summary, platinum-based combinations improve response rates and progression-free survival and have become the usual treatment in the United States as the first salvage regimen for women who relapse more than 12 months after the completion of primary therapy, with single-agent therapy usual in women who have an initial treatment-free interval of less than 6 months, and individualized decisions in those with a 6- to 12-month treatment-free interval. Treatment is not curative, and there are situations in which a patient with late relapse may choose single agent or nonplatinum therapy; it is unlikely that survival is significantly compromised by such a choice.

Drugs Useful in Treatment of Recurrent Ovarian Cancer

Taxanes, liposomal doxorubicin, topotecan, and gemcitabine have been studied in randomized trials, as discussed above. They are discussed in slightly more detail below. A number of other agents are occasionally useful. Hexamethylmelamine (altretamine) is an older alkylating agent with the advantages (patient convenience) and disadvantages (inappropriate for patients with episodic or partial small bowel obstruction, limited availability for patients without good insurance coverage for outpatient medication) of an oral therapy. It is rarely used, as it produces significant amounts of neuropathy, nausea, and vomiting. A GOG phase 2 trial of single-agent hexamethylmelamine in women with platinum-resistant ovarian cancer demonstrated a 10% response rate and a 21% rate of grade 3 emesis (486). Oral etoposide, a topoisomerase II inhibitor, is better tolerated and may be slightly more active. It is leukemogenic, which has limited enthusiasm for attempts to incorporate it into front-line therapy, but it remains a useful salvage agent. Interestingly, intravenous etoposide appears to have minimal activity in women with pretreated ovarian cancer. Ifosfamide has produced response rates of 10% to 20%, but the toxicities, hematologic and neurologic, are excessive compared to those of other available agents, and it is rarely used (487). Irinotecan is associated with substantial diarrhea and nausea, which can be particularly troublesome in ovarian cancer patients with some preexisting level of bowel dysfunction; it will hopefully be better tolerated as part of the ongoing front-line international trial for clear cell carcinoma. Vinorelbine, capecitabine and pemetrexed (488) may sometimes be useful; none of them are FDA approved for use in ovarian cancer.

Taxanes

Although in most parts of the world taxane therapy is now part of front-line treatment for ovarian cancer, taxanes remain very useful in treating recurrent disease. Both weekly paclitaxel (489,490)

and docetaxel (491) have shown response rates of 20% to 30% in women who recurred within 6 months of primary platinum-taxane-based combination therapy. Weekly paclitaxel is particularly useful, as it tends to be less myelotoxic than many other regimens. Nab-paclitaxel is a newer taxane with the advantage that it does not require steroid premedication to avoid hypersensitivity reactions. Nab-paclitaxel on a schedule of 100 mg/m² days 1, 8, 15 on a 28-day schedule produced a response rate of 23% in women with platinum/paclitaxel resistant ovarian cancer (492).

Topotecan

Topotecan, a topoisomerase I inhibitor, is FDA-approved for the treatment of recurrent ovarian cancer, and as discussed above, is as effective as or more effective than paclitaxel or liposomal doxorubicin in women with platinum-resistant disease. In a phase III trial comparing IV topotecan on the FDA-approved schedule of 1.5 mg/m²/day × 5 days to oral topotecan at a dose of 2.3 mg/m²/day × five days every three weeks in women with ovarian cancer, the response rate to intravenous topotecan for women with platinum-refractory disease was 5% and the response rate for women with platinum-resistant disease was 11% (493). However, the daily × 5 regimen is not convenient and has proved more myelosuppressive than most treating physicians deem reasonable in the palliative setting. Lower starting doses of 1.0 to 1.25 mg/m² are better tolerated, although their efficacy is not as well documented. Individuals at increased risk for myelotoxicity include those with impaired renal function, older age, extensive prior therapy, or prior pelvic irradiation.

Weekly bolus topotecan has been shown to have some activity in a number of small trials, and has come into common use because the schedule is convenient and produces less myelosuppression (494). The maximum tolerated dose (MTD) in phase 1 studies was 4 mg/m² with dose-limiting toxicities of anemia, chronic fatigue, and gastrointestinal distress. A randomized phase 2 trial of topotecan 4 mg/m², given 3 weeks out of 4 versus topotecan 1.25 mg/m² daily × 5 in 194 women with platinum-resistant ovarian cancer showed a numerically lower response rate for the weekly schedule (2 of 28 vs. 5 of 21 for the daily × 5 regimen) as well as a nonsignificantly decreased PFS (3.0 vs. 4.4 months). Overall survival was similar (9.6 vs. 9.3 months) (495). It is possible that difference between the 2 schedules would be more evident in patients with platinum sensitive disease. The GOG attempted to randomize women with platinum sensitive disease to a weekly versus daily regimen, but enrollment was slow, and the trial was changed to a single arm phase II trial of weekly topotecan. The response rate for the 15 patients receiving the daily × 5 regimen was 27%, but the confidence intervals around this response rate were very wide given the small number of patients; response rate for the 65 women receiving the weekly regimen was 12% (496).

Liposomal Doxorubicin

Liposomal doxorubicin is also FDA approved for the treatment of recurrent ovarian cancer. The every-4-week schedule of administration is convenient, and the lack of alopecia is attractive to patients. However, there is a high incidence of palmar-plantar erythrodysesthesia using the approved dose of 50 mg/m². Markman et al. published a nonrandomized phase 2 trial suggesting that there was only a 12% incidence of grade 2 and no grade 3 palmar-plantar erythrodysesthesia when the starting dose was lowered from 50 mg/m² to 40 mg/m². The response rate was 9%; all patients were platinum/paclitaxel resistant with a median of 2 prior regimens (497). It is not known if doxorubicin or epirubicin would have similar activity; these drugs have well-documented activity in ovarian cancer, mostly in the front-line setting, but a very different side effect profile. One small phase II trial reported a response rate of 18%

to epirubicin at a dose of 150 mg/m² in women with platinum-resistant ovarian cancer (467).

Gemcitabine

As discussed above, gemcitabine has modest activity in the treatment of recurrent ovarian cancer. Based on experimental models, it was hypothesized that combining gemcitabine with cisplatin might reverse platinum resistance. Cisplatin-resistant cells upregulate nucleotide excision repair complexes, which are thought to be inhibited by gemcitabine. Preclinical models suggested synergy between cisplatin and gemcitabine in platinum-resistant cell lines. A multicenter GOG trial of the combination as second-line therapy in women with platinum-resistant ovarian cancer reported a response rate of 16% (498).

Bevacizumab

Elevated vascular endothelial growth factor (VEGF or VEGF-A) expression occurs in all stages of ovarian cancer and is associated with poor prognosis, including shorter survival. In addition, VEGF (which is also known as vascular permeability factor) overexpression is directly associated with the production of ascitic fluid.

Bevacizumab is a humanized anti-VEGF monoclonal antibody. Prospective trials have reported activity of single-agent bevacizumab against pretreated ovarian cancer to be in the range of 15% to 20%. It is generally well tolerated; however, notable toxicities include hypertension, proteinuria, excess venous thrombosis, and bowel perforation and fistulization. The GOG evaluated single-agent bevacizumab in 63 patients treated with one to 2 prior regimens of cytotoxic chemotherapy who had recurred within 12 months of treatment with a platinum agent. The overall response rate was 21% with a median response duration of 10 months (499). Twenty-five of 62 patients had a progression-free survival (PFS) of ≥ 6 months. Cannistra et al. evaluated 44 patients with platinum-resistant disease that had progressed after second-line topotecan or liposomal doxorubicin. The overall response rate was 16% (7 out of 44) (500). This study closed early due to the higher than expected number of gastrointestinal perforations (5 out of 44), 1 of which was fatal. Since that time, most trials with bevacizumab exclude patients with evidence of bowel obstruction or bowel invasion by tumor. Another trial evaluated the combination of bevacizumab and metronomic (daily low-dose) oral cyclophosphamide in 70 women who had been treated with up to 3 prior chemotherapy regimens. Fifty-six percent of patients were progression-free at 6 months and the overall response rate was 24% (501). The response rate for women with platinum sensitive disease was higher than the response rate for women with platinum-resistant disease (33% versus 12%) although the difference was not statistically significant. The cyclophosphamide in this regimen was postulated to have an antiangiogenic effect. Interestingly, a subsequent study in women with heavily pretreated ovarian cancer (a median of 4 prior regimens) and known *BRCA* mutations reported a response rate to single agent oral cyclophosphamide of 13% (502).

Recent interest has focused on combinations of bevacizumab and cytotoxic agents. Trials in both platinum-sensitive and platinum-resistant disease have shown improvements in response rate and progression-free survival when bevacizumab is combined with standard therapy. The OCEANS trial (Table 24.14) was a randomized, double-blind placebo controlled trial comparing the combination of gemcitabine plus carboplatin plus bevacizumab to the combination of gemcitabine plus carboplatin plus placebo in women with platinum sensitive recurrent ovarian cancer. Chemotherapy was continued for a planned 6 cycles, or up to ten cycles in patients with continued response. After completion of chemotherapy, bevacizumab or placebo were continued until progression. Overall response rate and median progression-free survival were both significantly improved with

the addition of bevacizumab (78%; 12.3 months versus 57%; 8.6 months). Overall survival data were immature at the time of publication, but, as is the case with front-line therapy, there was no apparent difference between the arms, at 33.3 months for the bevacizumab arm and 35.2 months for the placebo arm (503). The AURELIA trial (Table 24.14) was conducted in platinum-resistant patients; results have been presented in abstract form (504). 361 women with platinum-resistant ovarian cancer and one or two prior regimens were randomized to standard therapy, consisting of investigators choice of pegylated liposomal doxorubicin, topotecan, or weekly paclitaxel, with or without bevacizumab. Patients in the chemotherapy arm were permitted to cross over to bevacizumab monotherapy at the time of progression. Overall response rate was significantly improved from 12.6% to 30.9% and progression-free survival was improved from 3.4 months to 6.7 months by the addition of bevacizumab.

Platinum Hypersensitivity

Repeated courses of carboplatin therapy place patients at risk for hypersensitivity reactions. These reactions usually occur during drug infusion and are associated with flushing, nausea, and hypertension. They may be severe and/or fatal. Atypical hypersensitivity reactions, occurring after drug infusion, have also been described (505). A number of desensitization protocols have been published and appear to be generally effective (506); they often involve premedication with steroids and antihistamines, and starting infusions very slowly then gradually increasing the rate over 4 to 24 hours. These regimens are inconvenient and should be used primarily in patients who are likely to benefit from platinum treatment and who do not have good alternate treatment options. Not all patients allergic to carboplatin will be allergic to cisplatin. Interestingly, hypersensitivity reactions have been reported to be lower with some second-line combinations than others. The HECTOR trial reported the rate of hypersensitivity reactions to be 15% with topotecan plus carboplatin, 12.7% with paclitaxel plus carboplatin, and only 8.5% with gemcitabine plus carboplatin (480). The CALYPSO trial reported rates of hypersensitivity to be lower with the combination of liposomal doxorubicin plus platinum (15.5%, with 2.4% $>$ grade 2) than with the combination of paclitaxel plus carboplatin (33.1%, with 8.8% $>$ grade 2) (507). Interestingly, elderly patients in this study had a significantly decreased risk for hypersensitivity reactions (508). Weekly carboplatin may be associated with an increased risk for hypersensitivity reactions. One phase II trial of weekly docetaxel and carboplatin reported that 33% of patients discontinued therapy because of hypersensitivity reactions. Routine use of diphenhydramine premedication was reported to produce a nonsignificant decrease in the rate of these reactions (509).

Hormonal Therapy

Epithelial ovarian cancers frequently express estrogen and progesterone receptors, and higher levels of PR expression are associated with lower-grade and improved survival (169). Multiple attempts have been made to treat ovarian carcinoma with hormonal therapy, including progestins, antiestrogens, and gonadotropin-releasing hormone (GnRH) analogs. The response rates generally are quite low, in the range of 10% (510). Many of the trials were performed decades ago, before steroid receptor analysis was available, and the role of steroid receptors in predicating response of ovarian carcinomas to hormonal therapy remains unclear. Over 90% of serous borderline ovarian tumors are estrogen-receptor positive (371), and there are case reports of responses to tamoxifen, leuprolide, and anastrozole. The MD Anderson group retrospectively reviewed outcomes to various hormonal therapy regimens in 133 women with recurrent low-grade serous carcinomas and found a 9% response rate (372).

Progestins/Antiproggestins

A review of 13 trials of 10 patients or more (432 patients total) treated with progestins (medroxyprogesterone acetate or megestrol acetate) revealed a major response rate of 7.2%, with stable disease in 10.9%. Progestins have well-documented activity in the treatment of recurrent endometrial carcinoma, and it has therefore been hypothesized that they will have activity in the endometrioid subset of ovarian cancers, which tend to express high levels of progesterone receptors. A series of 43 patients with ovarian endometrioid carcinoma who used medroxyprogesterone acetate as first-line therapy postsurgery or postradiotherapy was reported in 1982. Eighty-four percent of the patients had well-differentiated disease. Forty-one of them underwent second-look laparotomy after 6 to 8 months of therapy. Twenty-three had evidence of tumor regression and 8 had no evidence of disease. Tumor regression was observed in 68% of the 31 cancers that were positive for both estrogen receptor (ER) and PR and in none of the cancers that did not express either receptor (511). In one phase 2 study of megestrol acetate in 36 platinum-refractory ovarian cancer patients, 3 complete responders were observed; all had tumors of endometrioid histology (512).

RU486 (mifepristone) is a synthetic antiprogesterin that competitively binds the progesterone receptor (as well as the glucocorticoid receptor) and inhibits ovarian cancer cell growth *in vitro*. Rash tends to be the limiting toxicity. One phase 2 trial using RU486 in the treatment of platinum-resistant ovarian cancer patients reported a 26.5% response rate, including one complete response of over 3 years' duration, but a more recent GOG trial found a response rate of only 4.5% (one of 22).

Estrogens and tamoxifen have the ability to upregulate progesterone receptor expression, and have therefore been used to try to improve the benefit observed with progestin therapy. Two trials treated women with sequential ethinyl estradiol 50 µg per day and medroxyprogesterone acetate 200 mg per day with response rates of 14% and 17% (513,514). Some patients required dose reduction of the ethinyl estradiol because of severe nausea. Two trials have also treated women with sequential tamoxifen and progestins; no responses were observed.

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) with estrogen agonist activity on some tissues (such as bone) and antagonist activity on breast cancers. One review of 18 trials testing tamoxifen in the treatment of advanced ovarian cancer, with a cumulative total of 648 patients, found an overall 13% response rate (515). There was marked heterogeneity in the response rates, suggesting that selection bias (for unknown factors) may be very important. A randomized controlled trial comparing tamoxifen to triptorelin showed no responses in either arm (516). In the 1980s the GOG conducted a trial of tamoxifen 20 mg po bid (twice the dose commonly used in the treatment of breast cancer) in 105 women with previously treated ovarian cancer. There was an overall 17% response rate, including 13% complete responses. Median duration of response was 4.4 months. Eight of the 9 patients achieving a complete response had elevated levels of estrogen receptor (517). However, the difference in response by estrogen receptor status was not statistically significant. It has been suggested that tamoxifen might be an appropriate therapy for women with small-volume asymptomatic recurrences. The GOG completed a randomized trial comparing tamoxifen to thalidomide for the therapy of women who have CA-125 marker elevation but no measurable recurrence of disease. Women treated with thalidomide had a median progression-free survival of 3.2 months versus 4.5 months for those treated with tamoxifen, which may suggest some benefit for tamoxifen (518).

GnRH Agonists

GnRH receptors are expressed on about 80% of ovarian cancers. A summary of 12 published trials using GnRH agonists in women with recurrent ovarian cancer noted an overall 5.7% response rate and a disease stabilization rate of 21% with only one complete responder (510). In the largest trial, which was conducted by the EORTC, there were no responders among 68 evaluable patients. Like other hormonal therapies, GnRH agonists have been suggested to have activity against stromal tumors. Of 12 patients treated in 4 reports of the use of GnRH agonists for ovarian granulosa cell tumors, there were 4 patients with a partial response and 4 with stable disease (510). A novel attempt at therapy is linking a chemotherapy to a GnRH agonist, and at least one agent with this design, AEZS-108 has entered clinical trials (519).

GnRH antagonists cause rapid suppression of gonadotropin secretion without the initial gonadotropin release caused by GnRH agonists. There has been one trial of the GnRH antagonist cetrorelix in 17 patients with ovarian or müllerian carcinoma refractory to platinum chemotherapy. Three patients (18%) experienced a partial remission (520).

Aromatase Inhibitors

The major source of estrogen (principally estrone) in postmenopausal women is aromatization of androstenedione in the skin and adipose tissues. Commercially available third-generation aromatase inhibitors include anastrozole, letrozole, and exemestane. Five phase 2 trials of aromatase inhibitors reported 7 major responses among 179 patients with measurable disease by RECIST criteria (4%) and 16 CA-125 responses among 124 patients with CA-125 evaluable disease (13%) (510).

Androgen/Antiandrogen Therapy

About half of ovarian cancers have been reported to express the androgen receptor. Two studies of androgen therapy did not report any objective responses. Two small studies of the nonsteroidal antiandrogen flutamide noted response rates of 4.3% and 8.7% and disease stabilization rates of 8.7% and 28% (510).

NEW THERAPEUTICS

Targeted therapy

It has been increasingly recognized that low-grade serous cancers, clear cell cancers, and mucinous cancers represent tumors that are biologically very different from high-grade serous cancers, and trials in ovarian cancer have begun to "target" by histologic subtype. The regimen of oxaliplatin/capecitabine with or without bevacizumab is being tested in an international first-line trial for mucinous carcinomas, and a front-line phase III international trial in clear cell carcinoma testing the combination of cisplatin and irinotecan has completed accrual. Given the genetic similarities of kidney cancer and clear cell ovarian cancer, temsirolimus and sunitinib, which are FDA-approved for use in kidney cancer, are being tested in trials specifically for clear cell ovarian cancer. While the response rate in the GOG phase II trial of temsirolimus in women with epithelial ovarian cancer unselected for histology was disappointing at 9.3%, one of the 3 patients with clear cell histology did have a partial response lasting 4 months.

With the exception of antiangiogenic agents (see below) studies in ovarian cancer with what are traditionally considered "targeted therapies" have not yet resulted in any approved agents. For example, detectable expression of EGFR has been reported

in 19% to 92% of ovarian cancers (521), with studies suggesting that EGFR dysregulation is associated with worse survival. However, separate phase 2 trials of the anti EGFR monoclonal antibodies, cetuximab and matuzumab were both negative (522,523), and 4 phase 2 trials using single-agent anti-EGFR small molecule tyrosine kinase inhibitors (3 with gefitinib and one with erlotinib) reported response rates of 0% to 6% (522,524–526). Interestingly, the trial with erlotinib did report that patients with any grade rash had a significantly longer survival than those without (9.9 vs. 3.6 months, $p = 0.009$), which is consistent with what has been observed in other disease sites (521), and one of the trials with gefitinib noted that the only patient with a partial response was also the only one found to have an EGFR mutation. Finally, as noted above, the EORTC/GCIG randomized phase 3 trial of erlotinib for 2 years versus observation in women with responding or stable disease after first-line platinum-based therapy did not show any benefit to the erlotinib.

A role for HER2 targeting therapy in ovarian cancer has also been explored. The GOG found that 11.2% of women with progressive or recurrent ovarian cancer had tumors that stained 2+ or 3+ for HER2 (527). However the response rate to the anti-HER2 monoclonal antibody trastuzumab in this group of women with 2+ or 3+ expression by immunohistochemical evaluation was only 7.3%. Gene amplification was not assessed in this study, and it is possible that therapy would be more effective in HER2-amplified disease, as it is in breast cancer, but this comprises a small subset of ovarian cancers. A recent report found HER2 amplification of 6/33 (18%) of mucinous ovarian carcinomas, and described one dramatic response to the combination of trastuzumab plus carboplatin in this usually chemotherapy-resistant tumor. Pertuzumab is a monoclonal antibody that binds to an epitope on HER2 distinct from the trastuzumab-binding site, and prevents dimerization of HER2 with other receptors. It has recently been approved by the U.S. FDA for treatment of HER2 positive metastatic breast cancer in combination with trastuzumab. A randomized phase 2 trial tested 2 different doses of pertuzumab in heavily pretreated ovarian cancer patients (median of 5 prior chemotherapy regimens). Five of 123 had a partial response (528). A subsequent trial that randomized women with platinum-resistant ovarian cancer to gemcitabine or gemcitabine plus pertuzumab showed a 5% response rate for gemcitabine versus 14% for the combination (529).

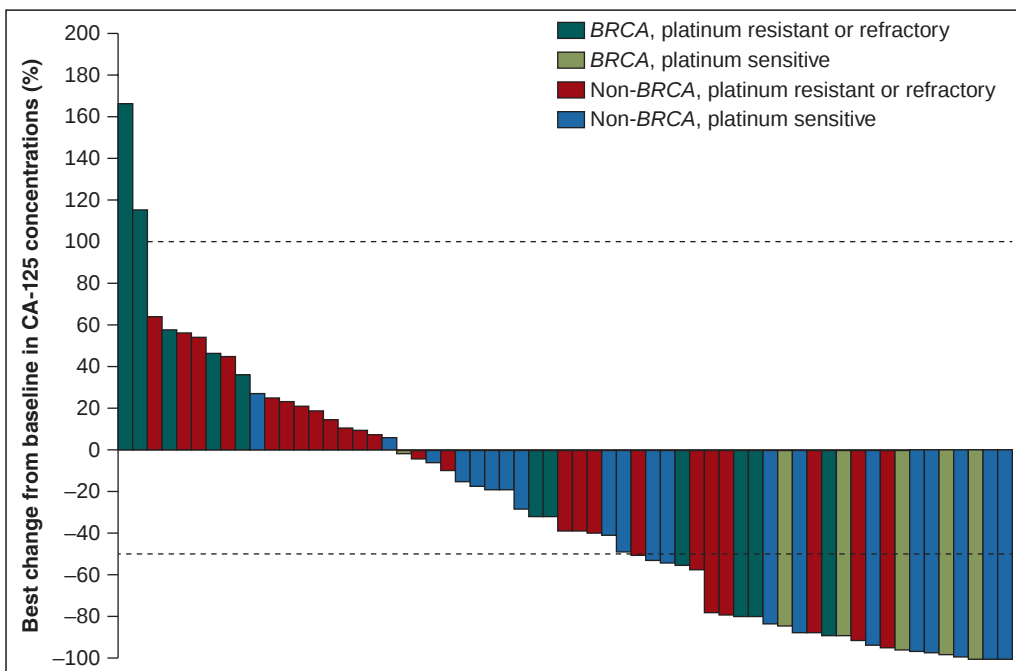
High frequency “druggable” mutations that would be analogous to the BCR-ABL gene in CML do not appear to exist in ovarian cancer. The Cancer Genome Atlas project analyzed messenger RNA expression, microRNA expression, promoter methylation and DNA copy number in 489 high-grade serous ovarian adenocarcinomas and the DNA sequences of exons from coding genes in 316 of these tumors. High-grade serous ovarian cancer is characterized by multiple mutations, with an average of 61.9 per tumor (530). Almost all tumors (96%) have TP53 mutations, but there were no other high-prevalence mutations found. A few low prevalence but statistically recurrent somatic mutations in genes including NF1, BRCA1/2, RB1 and CDK12 were described. Pathway analyses suggested that homologous recombination is defective in about half of the tumors analyzed, and this may help direct development of some agents, such as PARP inhibitors (see section on risk factors for a discussion of “synthetic lethality”). Investigators are working to develop algorithms to define so-called “BRCA-ness” of ovarian cancers in women who do not carry a mutation, but none have come into clinical use (326).

PARP Inhibition

A number of PARP [poly (ADPribose) polymerase] inhibitors have been under clinical development. The rationale for their use is discussed earlier, under Clinical features of BRCA-associated ovarian cancer. As single agents they appear to have significantly more *in vitro* activity against cell lines with BRCA1 or 2 deficiency than against wild-type cell lines. Olaparib (AZD2281) has been the most widely tested in ovarian cancer to date. Several studies have evaluated olaparib monotherapy in women with recurrent advanced epithelial ovarian cancer. Gelmon et al. treated 64 women with measurable ovarian cancer with single agent olaparib at a dose of 400 mg orally twice a day. One hundred ninety-six participants had a median of 3 prior chemotherapy regimens. Confirmed objective responses were observed in 41% of patients with BRCA1 or BRCA2 mutations, and 24% of women without mutations. Among women with platinum sensitive disease, responses were seen in 60% (3 of 5) BRCA1 or BRCA2 mutation carriers and in 50% (ten of 20) who did not carry a germline mutation; among women with platinum resistant disease responses were seen in 33% (4 of 12) BRCA1 or BRCA2

FIGURE 24.48. Single agent olaparib therapy. Best percentage change from baseline CA-125 concentrations, by platinum sensitivity and resistance.

Source: From Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852–861, with permission.



mutation carriers but in only 4% (one of 26) women who did not carry a germline mutation (Fig. 24.48). The most common side effects were fatigue, nausea, and vomiting. All observed responses were partial responses, and the median overall progression-free survival was 219 days. Resistance to single agent therapy PARP inhibitor therapy usually develops in less than a year. Cancers in women with a germline *BRCA1* or *BRCA2* mutation can develop secondary genetic changes that restore the reading frame of the *BRCA* protein. Such secondary mutations are associated with the development of platinum-resistance and some similar mutation likely allows development of resistance to PARP inhibitors.

A randomized phase II trial of the oral PARP inhibitor olaparib (high or low dose) versus pegylated liposomal doxorubicin (PLD) in ovarian cancer patients with a germline *BRCA1* or *BRCA2* mutation who had recurred within 12 months of their most recent platinum-based regimen showed a median PFS of 8.8 months for the high-dose olaparib arm (400 mg twice a day), 6.5 months for the lower-dose olaparib arm (200 mg twice daily) and 7.1 months for the PLD group, which were not significantly different. The RECIST response rate was 31% in the high-dose olaparib arm and 18% in the PLD arm. One heavily pretreated patient receiving low-dose olaparib died of myelodysplastic syndrome. The PFS of 7.1 months seen with PLD exceeded that seen in a previous large randomized trial of patients with unknown *BRCA* status and similar proportions of patients with platinum-resistant and platinum-sensitive disease (4 months); it has been reported that patients with germline *BRCA1/2* mutations, derive more benefit from PLD treatment than women with nonhereditary ovarian cancers (531).

A randomized placebo-controlled phase II trial tested olaparib 400 mg bid versus placebo in 265 women with platinum-sensitive relapsed high-grade serous ovarian carcinomas who were in partial or complete response following their last platinum-containing regimen. *BRCA1/2* mutation status was not required. Median progression-free survival was significantly longer with olaparib than with placebo (8.4 vs. 4.8 months). Overall survival data were not mature, but a preliminary analysis showed no difference between the groups (29.7 months for olaparib versus 29.9 months for placebo). The most common toxicities were low-grade nausea, vomiting, fatigue, and anemia (532).

Yet another phase II trial randomized 162 women with platinum sensitive recurrent disease, again unselected for *BRCA1/2* mutation status, to carboplatin AUC6/paclitaxel 175 mg/m² chemotherapy for 6 cycles followed by no further therapy versus the combination of open label olaparib plus carboplatin AUC4/paclitaxel 175 mg/m² chemotherapy followed by olaparib maintenance. A lower carboplatin dose had to be used in the combination regimen because olaparib adds to hematologic toxicity. Results have been reported in abstract form. Response rates were similar for the 2 arms at 64% for olaparib and 58% for chemotherapy alone; progression-free survival was improved at 12.2 versus 9.6 months (533).

In summary, while olaparib clearly has single agent activity with what appears to be an acceptable toxicity profile, and has a compelling biologic mechanism, it has thus far not proved superior to standard therapy (pegylated liposomal doxorubicin) for women with recurrent disease and has not improved response rates when added to chemotherapy. It substantially prolongs progression-free survival when used as maintenance therapy, but has not improved overall survival. Definition of the role of PARP inhibitors in our armamentarium against ovarian cancer awaits results of further clinical trials.

Agents Targeting Angiogenesis

Bevacizumab, a monoclonal antibody targeting VEGF, is the most extensively tested antiangiogenic agent for ovarian cancer, and results of trials of bevacizumab in ovarian cancer are

discussed above (Table 24.14). Numerous other antiangiogenic agents are being evaluated in women with ovarian cancer, and many of them target different or multiple components of the angiogenic pathway or other pathways. Aflibercept (VEGF-TRAP) is a high-affinity soluble decoy receptor that comprises portions of the extracellular domains of both VEGFR-1 and VEGFR-2. Preliminary clinical trial reports have suggested some activity against platinum-resistant ovarian cancers. A phase 2 study randomizing ovarian cancer patients to aflibercept or placebo for the treatment of recurrent malignant ascites showed that aflibercept significantly prolonged time to first paracentesis (55 vs. 23 days) but caused a 10% gastrointestinal perforation rate, similar to that observed in heavily pretreated women receiving bevacizumab (558). Ramucirumab (IMC1121B), a monoclonal antibody to VEGFR2, produced a 5% PR rate (3 of 60) among a heavily pretreated group of patients: 75% had platinum resistant or refractory disease (534). AMG 386 is a peptide-Fc fusion protein that neutralizes the interaction between the Tie2 receptor and angiopoietin-1/2. A randomized phase II trial comparing weekly paclitaxel to weekly paclitaxel plus AMG 386 showed a statistically significant advantage in PFS to the combination, and an international phase III trial adding AMG386 to front-line therapy to ovarian cancer is underway. Toxicities reported include hypertension, peripheral edema, and hypokalemia (535).

A large number of small molecule inhibitors of VEGF receptor tyrosine kinase are in clinical development or have been approved for other cancers, particularly kidney cancer. Many of these also inhibit other kinases of relevance to angiogenic pathways, such as platelet-derived growth factor (PDGF) receptors or fibroblast growth factor (FGF) receptors. Single-agent phase 2 trials of sorafenib (536), sunitinib (537), cediranib (538), and pazopanib (539) have been reported. The best response rate reported was for pazopanib at 31%; however, this trial excluded women who did not have a complete response to primary chemotherapy, and included CA-125 responses. The response rate for women with measurable disease was only 18%. ENMD-2076 inhibits aurora kinase A as well as angiogenic kinases, and produced responses in 3 of 45 women with heavily pretreated platinum resistant disease (540). Cabozantinib (XL-184) inhibits RET, c-Met and c-kit as well as VEGFR2. A recent randomized discontinuation phase II trial of cabozantinib showed an overall response rate of 24%; it was 29% in patients with platinum sensitive ovarian cancer and 18% in patients with platinum resistant disease (541). Larger randomized trials with cediranib, nintedanib (also known as BIBF 1120) and pazopanib are underway or have been completed, and results are awaited.

Mechanisms of escape from antiangiogenic therapy continue to be studied. For example, IGF-1 activation has been described mechanism of adaptive escape during anti-VEGF therapy in ovarian cancer, which suggests that antiangiogenic therapy combined with IGF-1 blockade might be of interest (542).

Immunologic Therapies

It has long been known that immune therapies, such as Interleukin-2 (IL-2), have some activity in the treatment of ovarian cancer. In 2003 Zhang et al. made the observation that among patients in clinical complete remission the presence of intratumoral T cells was a strongly favorable prognostic factor (543). CD3⁺ tumor-infiltrating T cells were detected within tumor cell islets in 102 of 186 tumors (54.8%). The 5-year survival rate was 38% for patients whose tumors contained T cells compared to 4.5% for patients without tumor-infiltrating T cells. However, no immune therapy has yet been generally successful in the treatment of ovarian cancer.

Multiple large randomized trials have tested monoclonal antibodies targeting tumor-associated antigens, such as CA-125

and MUC-1, and these have been disappointing even in patients with the most favorable prognostic factors (optimal debulking, complete clinical response to chemotherapy) (544). Newer generations of antibodies linked to cytotoxic chemicals are emerging, and may be useful against ovarian cancer. There also remains substantial interest in vaccine-type therapies, which have used a variety of antigens, including MUC 1 carbohydrate epitope, p53 peptide, HER2/neu peptides, and the cancer-testis antigen NY-ESO-1, which are sometimes directly injected, sometimes loaded onto dendritic cells, and sometimes expressed in recombinant viral vectors. The GOG is currently conducting a randomized double-blind phase II vaccine trial in women with ovarian cancer in second or third complete remission. The agent is a polyvalent antigen-keyhole limpet hemocyanin (KLH) construct of numerous carbohydrate cell surface epitopes, which is administered with an immunological adjuvant.

Proof of principle that ovarian cancers can respond to immunologic approaches was seen in a large phase I trial of BMS-936559, an anti-programmed death ligand-1 (PDL-1) monoclonal antibody that potentiates immune responses and mediates antitumor activity in preclinical models. Seventeen patients with ovarian cancer were enrolled. One had a partial response, and 3 had stable disease lasting at least 24 weeks (545).

Other New Directions

The folate receptor is highly overexpressed in ovarian cancer, and a number of therapies have attempted to take advantage of this. Farletuzumab is an antifolate receptor antibody. A phase III randomized, double-blind, placebo-controlled study evaluating farletuzumab in combination with weekly paclitaxel in patients with platinum-resistant or refractory ovarian was closed to accrual after failure to meet predefined efficacy endpoints at interim analysis, but the phase III study evaluating this agent in combination with carboplatin and taxane in platinum-sensitive ovarian cancer in first relapse has not yet been reported (546). EC145 is a conjugate of folic acid and desacetylvinblastine that binds to the folate receptor with high affinity. A phase II trial suggested that this agent produced a significant improvement in

progression free survival when combined with PLD (21.7 weeks) compared to PLD alone (11.7 weeks) in patients with platinum-resistant ovarian cancer (547), and a phase III trial is ongoing.

As discussed above, high-grade serous cancer is characterized by near universal aberration in the *P53* tumor-suppressor gene. The *P53* gene is a cell cycle checkpoint regulator, and cells with *P53* mutations are more dependent on other cell checkpoint regulators, such as Wee-1. Inhibition of Wee-1 in *p53*-deficient tumors leads to reduced capacity for repair to damage to DNA, such as that induced by chemotherapy. MK-1777 is a Wee-1 tyrosine kinase inhibitor, and an ongoing randomized, placebo-controlled phase II study is evaluating paclitaxel and carboplatin with or without the Wee-1 tyrosine kinase inhibitor MK-1775 in women with *p53* mutation-positive platinum-sensitive recurrent ovarian cancer (546).

Aberrant DNA methylation is a frequent epigenetic event in ovarian cancer and represents an additional source of potential molecular markers. Four promoter methylation subtypes significantly associated with survival were identified in high-grade serous tumors by the Tumor Cancer Genome Atlas Project (530). Wei et al. investigated CpG island hypermethylation across stages III and intravenous ovarian tumors (548). Hierarchical clustering revealed 2 tumor groups with distinctly different methylation profiles. The duration of progression-free survival after chemotherapy was significantly shorter for patients whose tumors contained high levels of concurrent methylation compared to patients whose tumors had lower tumor methylation levels. Hypomethylating agents and histone deacetylase inhibitors are currently being studied in combination with standard chemotherapies with some interesting results. Matei et al. tested low-dose decitabine administered before carboplatin in 17 patients with heavily pretreated and platinum-resistant ovarian cancer. The regimen induced a 35% objective response rate and a progression-free survival of 10.2 months, with 9 patients (53%) free of progression at 6 months. Demethylation of *MLH1*, *RASSF1A*, *HOXA10*, and *HOXA11* in tumor biopsies after treatment positively correlated with PFS, suggesting that low-dose decitabine altered DNA methylation of genes, restoring sensitivity to carboplatin (549). A phase I/II randomized trial of carboplatin with or without SGI-110, a small molecule DNA hypomethylating agent, in patients with platinum-resistant disease is planned.

REFERENCES

1. Chan JK, Urban R, Cheung MK, et al. Ovarian cancer in younger vs older women: a population-based analysis. *Br J Cancer*. 2006;95:1314–1320.
2. Pectasides D, Fontzilas G, Aravantinos G, et al. Epithelial ovarian carcinoma in younger versus older women: is age an independent prognostic factor? The hellenic oncology cooperative group experience. *Int J Gynecol Cancer*. 2007;17:1003–1010.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10–19.
4. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*. 2010;46:765–781.
5. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New Engl J Med*. 2003;348:1625–1638.
6. Collaborative Group on Epidemiologic Studies of Ovarian Cancer. Ovarian Cancer and Body Size: Individual participant meta-analysis including 25,157 women with ovarian cancer from 47 epidemiologic studies. *PLoS Med*. 2012;9:e1001200.
7. Leitzmann MF, Koebernick C, Danforth KN, et al. Body mass index and risk of ovarian cancer. *Cancer*. 2009;115:812–822.
8. Olsen CM, Green AC, Whiteman DC, et al. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2007;43:690–709.
9. Taubes G. Epidemiology faces its limits. *Science*. 1995;269:164–169.
10. Schildkraut JM, Calingaert B, Marchbanks PA, et al. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst*. 2002;94:32–38.
11. Lacey JV, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA*. 2002;288:334–368.
12. Lacey JV, Brinton LA, Leitzmann MF, et al. Menopausal hormone therapy and ovarian cancer risk in the national institutes of health-AARP diet and health study cohort. *J Natl Cancer Inst*. 2006;98:1397–1405.
13. Whiteman D, Siskind V, Purdie D, et al. Timing of pregnancy and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2003;12:42–46.
14. Jordan S, Siskind V, Green AC, et al. Breastfeeding and risk of epithelial ovarian cancer. *Cancer Causes Control*. 2010;21:109–116.
15. Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet*. 2008;371:303–314.
16. Lengyel E. Ovarian cancer development and metastasis. *Am J Pathol*. 2010;177:1053–1064.
17. Casagrande JT, Louie E, Pike MC, et al. “Incessant ovulation” and ovarian cancer. *Lancet*. 1979;2:170–173.
18. Fredrickson TN. Ovarian tumors of the hen. *Environ Health Perspect*. 1987;73:35–51.
19. Trevino LS, Buckles EL, Johnson PA. Oral contraceptives decrease the prevalence of ovarian cancer in the hen. *Cancer Prev Res*. 2012;5:343–349.
20. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol*. 2012;55:3–23.
21. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol*. 2006;30:230–236.

22. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. *J Natl Cancer Inst.* 1998;90:1774–1786.
23. Rosenberg L, Palmer JR, Zauber AG, et al. A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am J Epidemiol.* 1994;139:654–661.
24. Rodriguez GC, Nagarsheth NP, Lee KL, et al. Progesterin-induced apoptosis in the macaque ovarian epithelium: differential regulation of transforming growth factor beta. *J Natl Cancer Inst.* 2002;94:50–60.
25. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. *JAMA.* 2003;290:1739–1748.
26. Beral V, Bull D, Green J, et al. Ovarian cancer and hormone replacement therapy in the million women study. *Lancet.* 2007;369:1703–1710.
27. Danforth KN, Tworoger SS, Hecht JL, et al. A prospective study of postmenopausal hormone use and ovarian cancer risk. *Br J Cancer.* 2007;96:151–156.
28. Morch LS, Lokkegaard E, Andreassen AH, et al. Hormone therapy and ovarian cancer. *JAMA.* 2009;302:298–305.
29. Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. *JAMA.* 1993;270:2813–2818.
30. Narod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. *The Lancet.* 2001;357:1467–1470.
31. Lin HW, Tu YY, Lin SY, et al. Risk of ovarian cancer in women with pelvic inflammatory disease: A population-based study. *Lancet Oncol.* 2011;12:900–904.
32. Hill AB. The environment and disease: Association or causation? *Proc R Soc Med.* 1965;58:295–300.
33. Pearce CL, Templeman C, Rossing MA, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol.* 2012;13:385–394.
34. Prefumo F, Todeschini F, Fulcheri E, et al. Epithelial abnormalities in cystic ovarian endometriosis. *Gynecol Oncol.* 2002;84:280–284.
35. Vecellini P, Somigliana E, Buggio L, et al. Endometriosis and ovarian cancer. *Lancet Oncol.* 2012;13:188–189.
36. Wiegand KC, Shah S, Al-Agha OM, et al. ARID1A mutations in endometriosis associated ovarian carcinomas. *N Engl J Med.* 2010;363:1532–1543.
37. Banz C, Ungethuem U, Kuban RJ, et al. The molecular signature of endometriosis-associated endometrioid ovarian cancer differs significantly from endometriosis-independent endometrioid ovarian cancer. *Fertil Steril.* 2009;94:1212–1217.
38. Shih I-M, Kurman R. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. *Am J Pathol.* 2004;164:1511–1518.
39. Schildkraut JM, Moorman PG, Halabi S, et al. Analgesic drug use and risk of ovarian cancer. *Epidemiology.* 2006;17:104–107.
40. Sorensen HT, Friis S, Norgaard B, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. *Br J Cancer.* 2003;88:1687–1692.
41. Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? a meta-analysis. *Br J Clin Pharmacol.* 2005;60:194–203.
42. Bosetti C, Negri E, Franceschi S, et al. Diet and ovarian cancer risk: a case-control study in Italy. *Int J Cancer.* 2001;93:911–915.
43. Chiang ET, Lee VS, Canchola AJ, et al. Diet and risk of ovarian cancer in the California teachers study cohort. *Am J Epidemiol.* 2007;165:802–813.
44. Chang ET, Lee VS, Canchola AJ, et al. Dietary patterns and risk of ovarian cancer in the California teachers study cohort. *Nutr Cancer.* 2008;60:285–291.
45. Prentice R, Thompson C, Caan B, et al. Low-fat dietary pattern and cancer incidence in the women's health initiative dietary modification randomized controlled trial. *J Natl Cancer Inst.* 2007;99:1534–1543.
46. Li XM, Ganmaa D, Sato A. The experience of Japan as a clue to the etiology of breast and ovarian cancers: relationship between death from both malignancies and dietary practices. *Med Hypotheses.* 2003;60:268–275.
47. Tworoger SS, Gertig DM, Gates MA, et al. Caffeine, alcohol, smoking, and the risk of incident epithelial ovarian cancer. *Cancer.* 2007;112:1169–1177.
48. Soegaard M, Jensen A, Hogdall E, et al. Different risk factor profiles for mucinous and nonmucinous ovarian cancer: results from the danish MALOVA study. *Cancer Epidemiol Biomarkers Prev.* 2007;16:1160–1166.
49. Moorman PG, Jones LW, Akushevich L, et al. Recreational physical activity and ovarian cancer risk and survival. *Ann Epidemiol.* 2011;21:178–187.
50. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian ovarian cancer study group. *J Clin Oncol.* 2012;1–11.
51. Chen S, Iversen ES, Friebe T. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. *J Clin Oncol.* 2006;24:863–871.
52. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007;25:1329–1333.
53. Mavaddat N, Barrowdale D, Andrulis IL, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the consortium of investigators and modifiers for BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev.* 2012;21:134–147.
54. Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of BRCA cancers that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. *J Clin Oncol.* 2010;28:3555–3548.
55. The Cancer Genome Atlas Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474:610–615.
56. Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. *N Engl J Med.* 1996;335:1413–1416.
57. Boyd J, Sonoda Y, Federici MG. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. *JAMA.* 2000;283:2260–2265.
58. Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA.* 2012;307:382–390.
59. ACOG Practice Bulletin. Hereditary breast and ovarian cancer syndrome. *Gynecol Oncol.* 2009;113:6–11.
60. Werness BA, Ramus SJ, DiCiccio RA. Histopathology, FIGO stage, and BRCA mutation status of ovarian cancers from the gilda radner familial ovarian cancer registry. *Int J Gynecol Pathol.* 2004;23:29–34.
61. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. *Nature.* 2012;481:287–292.
62. Quinn JE, James CR, Stewart GE. BRCA1 mRNA expression levels predict for overall survival in ovarian cancer after chemotherapy. *Clin Cancer Res.* 2007;13:7413–7420.
63. McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly (ADP-ribose) polymerase inhibition. *Cancer Res.* 2006;66:8109–8115.
64. Lucchesi JC. Synthetic lethality and semi-lethality among functionally related mutants of *Drosophila melanogaster*. *Genetics.* 1968;59:37.
65. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. *N Engl J Med.* 1998;339:424–428.
66. Modan B, Hartge P, Hirsch-Yechezel G. Oral contraceptives and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 and BRCA2 mutation. *N Engl J Med.* 2001;345:235–240.
67. McLaughlin JR, Risch HA, Lubinski J, et al. Hereditary Ovarian Cancer Clinical Study Group. Reproductive risk factors for ovarian cancer in carriers of BRCA1 and BRCA2 mutations: a case-control study. *Lancet Oncol.* 2007;8:34.
68. Kauff ND, Mitra N, Robson ME, et al. Risk of ovarian cancer in BRCA1 and BRCA2 mutation-negative hereditary breast cancer families. *J Natl Cancer Inst.* 2005;97:1382–1384.
69. Zhang Z, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1342 patients with invasive ovarian cancer. *Gynecol Oncol.* 2011;121:353–357.
70. Struwing JP, Hartge P, Wacholder S. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among ashkenazi jews. *N Engl J Med.* 1997;336:1401–1408.
71. Leib JR, Hoodfar E, Haidle JL, et al. The new genetic privacy law. *Commun Oncol.* 2008;5:351–354.
72. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality. *JAMA.* 2011;305:2295–2303.
73. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med.* 2002;346:1616–1622.
74. Kauff ND, Stagapan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med.* 2002;346:1609–1615.
75. Kauff ND, Domchek SM, Friebe TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol.* 2008;26:1331–1338.
76. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. *JAMA.* 2006;296:185–192.
77. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. *J Clin Oncol.* 2005;23:7491–7496.
78. Powell BC, Chen LM, McLennan J, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers. *Int J Gynecol Cancer.* 2011;21:846–851.

79. Domchek S, Friebe T, Garber J, et al. Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. *Breast Cancer Res.* 2010;124:195–203.
80. Muller CY, Coleman R, Adams WP. Laparoscopy in patients following transverse rectus abdominis myocutaneous flap reconstruction. *Obstet Gynecol.* 2000;96:132–135.
81. Elit L, Esplen MJ, Butler K, et al. Quality of life and psychosocial adjustment after prophylactic oophorectomy for a family history of ovarian cancer. *Familial Cancer.* 2001;1:149–156.
82. Finch A, Metcalfe KA, Chiang JK, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. *Gynecol Oncol.* 2011;121:163–168.
83. Rebbeck TR, Friebe T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the prose study group. *J Clin Oncol.* 2005;23:7804–7810.
84. Eisen A, Lubinski J, Gronwald J, et al. Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. *J Natl Cancer Inst.* 2008;100:1361–1362.
85. Colgan TJ, Murphy J, Cole D, et al. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with BRCA germline mutation status. *Am J Surg Pathol.* 2001;25:1283–1289.
86. Lynch HT, Chapelle A. Hereditary colorectal cancer. *N Engl J Med.* 2003;348:919–932.
87. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risk associated with germline mutations in MLH1, MSH2, and MSH6 genes in lynch syndrome. *JAMA.* 2011;305:2304–2310.
88. Ketabi Z, Bartuma K, Bernstein I, et al. Ovarian cancer linked to lynch syndrome typically presents as early-onset, non-serous epithelial tumors. *Gynecol Oncol.* 2011;121:462–465.
89. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the lynch syndrome. *N Engl J Med.* 2006;354:261–269.
90. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment of regimens in advanced-stage ovarian cancer: a phase III trial of the Gynecologic Cancer Intergroup. *J Clin Oncol.* 2009;27:1419–1421.
91. Zaino R, Brady MF, Lele S, et al. Advanced stage mucinous adenocarcinoma of the ovary is both rare and highly lethal. *Cancer.* 2011;117:554–562.
92. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei. *Lancet Oncol.* 2006;7:69–76.
93. Walsh C, Holschneider C, Hoang Y, et al. Coexisting ovarian malignancy in young women with endometrial cancer. *Obstet Gynecol.* 2005;106:693–699.
94. Tan D, Agarwal R, Kaye SB. Mechanisms of transcoelomic metastasis in ovarian cancer. *Lancet.* 2006;7:925–934.
95. Schouli J, Senyuya F, Fotopoulou C, et al. Intra-abdominal tumor dissemination pattern and surgical outcome in 214 patients with primary ovarian cancer. *J Surg Oncol.* 2009;99:424–427.
96. Brown PO, Palmer C. The preclinical natural history of serous ovarian cancer: defining the target for early detection. *PLoS Med.* 2009;6:1–11.
97. Bristow RE, del Carmen M, Kaufman H, et al. Radical oophorectomy with primary stapled colorectal anastomosis for resection of locally advanced epithelial ovarian cancer. *J Am College Surg.* 2003;197:565–574.
98. Aletti G, Podratz KC, Jones M, et al. Role of rectosigmoidectomy and stripping of pelvic peritoneum in outcomes of patients with advanced ovarian cancer. *J Am College Surg.* 2006;203:521–526.
99. Dauplat J, Hacker NF, Nieberg R, et al. Distant metastases in epithelial ovarian carcinoma. *Cancer.* 1987;60:1561–1566.
100. Doig T, Monaghan H. Sampling the omentum in ovarian neoplasia: when one block is enough. *Int J Gynecol Cancer.* 2006;16:36–40.
101. Tanner E, Black D, Zivanovic O, et al. Patterns of first recurrence following adjuvant intraperitoneal chemotherapy for stage IIIC ovarian cancer. *Gynecol Oncol.* 2012;124:59–62.
102. Kehoe SM, Eisenhauer EL, Chi DS. Upper abdominal surgical procedures: Liver mobilization and diaphragm peritonectomy/resection, splenectomy, and distal pancreatectomy. *Gynecol Oncol.* 2008;111:S51–S55.
103. Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol.* 2009;114:26–31.
104. Aletti G, Dowdy S, Gostout BS, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstet Gynecol.* 2006;107:77–85.
105. Ayantunde A, Parsons S. Pattern and prognostic factors in patients with malignant ascites: a retrospective study. *Ann Oncol.* 2007;18:945–949.
106. Winter WE, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecological Oncology Group study. *J Clin Oncol.* 2008;26:83–89.
107. Wimberger P, Wehling M, Lehmann N, et al. Influence of residual tumor on outcome in ovarian cancer patients with FIGO stage IV disease. *Ann Surg Oncol.* 2010;17:1642–1648.
108. McGuire WP, Hoskins WJ, Brady MF, et al. Taxol and cisplatin improves outcome in advanced ovarian cancer as compared to cyclophosphamide and cisplatin [Abstract]. *N Engl J Med.* 1996;334:1–6.
109. Ozols RF, Bundy B, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Study. *J Clin Oncol.* 2003;21:3194–3200.
110. Gershenson D, Sun CC, Lu K, et al. Clinical behavior of stage II–IV low-grade serous carcinoma of the ovary. *Obstet Gynecol.* 2006;108:361–368.
111. Schiller HM, Silverberg SG. Staging and prognosis in primary carcinoma of the fallopian tube. *Cancer.* 1971;28:389–395.
112. Peters WA, Andersen WA, Hopkins MP. Prognostic features of carcinoma of the fallopian tube. *Obstet Gynecol.* 1988;71:757–762.
113. Mangan CE, Rubin SC, Rabin DS, et al. Lymph node nomenclature in gynecologic oncology. *Gynecol Oncol.* 1986;23:222–226.
114. Morice P, Joulie F, Camatte S, et al. Lymph node involvement in epithelial ovarian cancer: analysis of 276 pelvic and paraaortic lymphadenectomies and surgical implications. *J Am Coll Surg.* 2003;197:198–205.
115. Harter P, Gnauert K, Hils R, et al. Pattern and clinical predictors of lymph node metastases in epithelial ovarian cancer. *Int J Gynecol Cancer.* 2007;17:1238–1244.
116. Benedetti P, Maggioni A, Hacker NF, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. *J Natl Cancer Inst.* 2005;97:560–566.
117. Du Bois A, Reuss A, Harter P, et al. Potential role of lymphadenectomy in advanced ovarian cancer: a combined exploratory analysis of three prospectively randomized phase III multicenter trials. *J Clin Oncol.* 2010;28:1733–1739.
118. Maggioni A, Benedetti Panici P, Dell'Anna T, et al. Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. *Br J Cancer.* 2006;95:699–704.
119. Winter WE, Maxwell L, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: A Gynecologic Oncology Group study. *J Clin Oncol.* 2007;25:3621–3627.
120. Du Bois A, Reuss A, Pujade-Lauraine E, et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of prospectively randomized phase 3 multicenter trials. *Cancer.* 2009;115:1234–1244.
121. Cormio G, Rossi C, Cazzolla A, et al. Distant metastases in ovarian carcinoma. *Int J Gynecol Cancer.* 2003;13:125–129.
122. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;354:34–43.
123. Robinson W, Beyer J, Griffin S, et al. Extraperitoneal metastases from recurrent ovarian cancer. *Int J Gynecol Cancer.* 2012;22:43–46.
124. Esselen K, Rodriguez N, Growdon W, et al. Patterns of recurrence in advanced epithelial ovarian, fallopian tube and peritoneal cancers treated with intraperitoneal chemotherapy. *Gynecol Oncol.* 2012.
125. Goff BA, Mandel LS, Melancon CH, et al. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA.* 2004;291:2705–2712.
126. Pavlik EJ, Saunders BA, Doran S, et al. The search for meaning - symptoms and transvaginal sonography screening for ovarian cancer. *Cancer.* 2012;115:3689–3698.
127. Rossing MA, Wicklund KG, Cushing-Haugen KL, et al. Predictive value of symptoms for early detection of ovarian cancer. *J Natl Cancer Inst.* 2010;102:222–229.
128. Lim AWW, Mesher D, Gentry-Maharaj A, et al. Predictive value of symptoms for ovarian cancer: comparison of symptoms reported by questionnaire, interview, and general practitioner notes. *J Natl Cancer Inst.* 2012;104:114–124.
129. Committee on Gynecologic Practice. The role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer. *Obstet Gynecol.* 2011;117:742–746.
130. Dearing A, Aletti G, McGee M, et al. How relevant are ACOG and SGO guidelines for referral of adnexal mass. *Obstet Gynecol.* 2007;110:841–848.
131. Stone RL, Nick AM, McNeish IA, et al. Paraneoplastic thrombocytosis in ovarian cancer. *N Engl J Med.* 2012;366:610–618.
132. Coll D, Meyer J, Mader M, et al. Imaging appearances of Sister Mary Joseph nodule. *Br J Radiol.* 1999;72:1230–1233.
133. Mann W, Patsner B, Coher H, et al. Preoperative serum CA-125 levels in patients with surgical stage I invasive ovarian adenocarcinoma. *J Natl Cancer Inst.* 1998;90:208–213.
134. Sassone A, Timor-Tritsch I, Artnner A, et al. Transvaginal sonographic characterization of

- ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. *Obstet Gynecol.* 1991;78:70–76.
135. Geomini P, Kruiwagen R, Bremer GL, et al. The accuracy of risk scores in predicting ovarian malignancy. *Obstet Gynecol.* 2009;113:384–394.
 136. DePriest PD, Shenson D, Fried A, et al. A morphology index based on sonographic findings in ovarian cancer. *Gynecol Oncol.* 1993;51:7–11.
 137. Jacobs IJ, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating CA-125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gyn.* 1990;97:922–929.
 138. Kinkel K, Lu Y, Mehdizade A, et al. Indeterminate ovarian mass at US: Incremental value of second imaging test for characterization – meta-analysis and Bayesian analysis. *Radiology.* 2005;236:85–94.
 139. Riccio T, Adams H, Munzing D, et al. Magnetic resonance imaging as an adjunct to sonography in the evaluation of the female pelvis. *Magnetic Resonance Imaging.* 1990;8:699–704.
 140. Medeiros L, Fretas L, Rosa D, et al. Accuracy of magnetic resonance imaging in ovarian tumor: a systematic quantitative review. *Am J Obstet Gynecol* 2011;204:e1–e10.
 141. Balan P. Ultrasonography, computed tomography and magnetic resonance imaging in the assessment of pelvic pathology. *Eur J Radiol.* 2006;58:147–155.
 142. Gadducci A, Cosio S. Surveillance of patients after initial treatment of ovarian cancer. *Crit Rev Oncol/Hematol.* 2009;71:43–52.
 143. Bristow RE, Duska L, Lambrou N, et al. A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. *Cancer.* 2000;89:1532–1540.
 144. Axtell A, Lee MH, Bristow RE, et al. Multi-Institutional reciprocal validation study of computed tomography predictors of suboptimal primary cytoreduction in patients with advanced ovarian cancer. *J Clin Oncol.* 2007;25:384–389.
 145. Fujiwara K, Yoshino K, Enomoto T, et al. Usefulness of computed tomography in predicting cytoreductive surgical outcomes for ovarian cancer. *Arch Gynecol Obstet.* 2011;284:1501–1507.
 146. Aletti G, Eisenhauer E, Santillan A, et al. Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. *Gynecol Oncol.* 2011;120:23–28.
 147. Antunovic L, Cimitan M, Borsatti E, et al. Revisiting the clinical value of 18 F-FDG PET/CT in detection of recurrent epithelial ovarian carcinomas. *Clin Nucl Med.* 2012;37:e184–e188.
 148. Risum S, Hogdall C, Loft A, et al. The diagnostic value of PET/CT for ovarian cancer – a prospective study. *Gynecol Oncol.* 2007;105:145–149.
 149. Sala E, Kataoka MY, Priest AN, et al. Advanced ovarian cancer: multiparametric MR imaging demonstrates response- and metastasis-specific effects. *Radiology.* 2012;263:149–150.
 150. Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. *Int J Gynecol Cancer.* 2008;18:414–420.
 151. Ganti S, Taylor SL, Abu Aboud O, et al. Kidney tumor biomarkers revealed by simultaneous multiple matrix metabolomics analysis. *Cancer Res.* 2012;72:3471–3479.
 152. Vergote I, Troupe CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363:943–953.
 153. Skrimisdottir I, Garmo H, Holmberg L. Non-genital tract metastases to the ovaries presented as ovarian tumors in Sweden 1990–2003: occurrence, origin and survival compared to ovarian cancer. *Gynecol Oncol.* 2007;105:166–171.
 154. Oei A, Massuger LF, Bulten J, et al. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. *Br J Cancer.* 2006;94:814–819.
 155. Ayhan A, Guvenal T, Salman MC, et al. The role of cytoreductive surgery in nongenital cancers metastatic to the ovaries. *Gynecol Oncol.* 2005;98:235–241.
 156. Alvarado-Cabrero I, Young RH, Vamvakas EC, et al. Carcinoma of the fallopian tube: a clinicopathological study of 105 cases with observations on staging and prognostic factors. *Gynecol Oncol.* 1999;72:367–379.
 157. Verleye L, Ottevanger PB, van der Graaf W, et al. EORTC-GCG process indicators for ovarian cancer surgery. *Eur J Cancer.* 2009;45:517–526.
 158. Ayhan A, Gultekin M, Celik NY, et al. Occult metastasis in early ovarian cancers: Risk factors and associated prognosis. *Am J Obstet Gynecol.* 2007;196:81.e1–81.e6.
 159. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European organisation for research and treatment of cancer – adjuvant chemotherapy in ovarian neoplasm trial. *J Natl Cancer Inst.* 2003;95:113–125.
 160. Trimbos B, Timmers P, Pecorelli S, et al. Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial. *J Natl Cancer Inst.* 2010;102:982–987.
 161. Chi DS, Abu-Rustum NR, Sonoda Y, et al. The safety and efficacy of laparoscopic surgical staging of apparent stage I ovarian and fallopian tube cancers. *Am J Obstet Gynecol.* 2005;192:1614–1619.
 162. Zivanovic O, Sonoda Y, Diaz JP, et al. The rate of port-site metastases after 2251 laparoscopic procedures in women with underlying malignant disease. *Gynecol Oncol.* 2008;111:431–437.
 163. Eichner E, Bove ER. In vivo studies on the lymphatic drainage of the human ovary. *Obstet Gynecol.* 1954;3:287–297.
 164. DiRe F, Fontanelli R, Raspagliesi F, et al. Pelvic and para-aortic lymphadenectomy in cancer of the ovary. *Bailliere's Clin Obstet Gynaecol.* 1989;3:131–138.
 165. Berek JS. Lymph node-positive stage IIIC ovarian cancer – A separate entity? *Int J Gynecol Cancer.* 2009;19:18–20.
 166. Rungtuan B, Miller A, Richard SD, et al. Should stage IIIC ovarian cancer be further stratified by intraperitoneal vs. retroperitoneal only disease? A gynecologic oncology group study. *Gynecol Oncol.* 2012;124:53–58.
 167. Schmeler KM, Frumovitz M, Deavers M, et al. Prevalence of lymph node metastasis in primary mucinous carcinoma of the ovary. *Obstet Gynecol.* 2010;116:269–273.
 168. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol.* 2002;20:1248–1259.
 169. Eisenkop SM, Spirtos NM, Friedman RL, et al. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. *Gynecol Oncol.* 2003;90:390–396.
 170. Prefontaine M, Gelfand A, Donovan J, et al. Reproducibility of tumor measurements in ovarian cancer: a study of interobserver variability. *Gynecol Oncol.* 1994;55:87–90.
 171. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr.* 1975;42:101–104.
 172. Olive KP, Jacobetz MA, Davidson CJ, et al. Inhibition of hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science.* 2009;324:1457–1461.
 173. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol.* 1994;170:974–979.
 174. Hoskins WJ, Bundy BN, Thigpen JT, et al. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a gynecologic oncology group study. *Gynecol Oncol.* 1992;47:159–166.
 175. Magtibay PM, Adams PB, Silverman MB, et al. Splenectomy as part of cytoreductive surgery in ovarian cancer. *Gynecol Oncol.* 2006;102:369–374.
 176. Chi DS, Bristow RE, Armstrong DK, et al. Is the easier way ever the better way. *J Clin Oncol.* 2011;29:4073–4075.
 177. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy is the better treatment option in some patients with stage IIIC to IV ovarian cancer. *J Clin Oncol.* 2011;29:4076–4078.
 178. Wright J, Lewin SN, Deutsch I, et al. Defining the limits of radical cytoreductive surgery for ovarian cancer. *Gynecol Oncol.* 2011;123:467–473.
 179. Aletti G, Dowdy S, Podratz KC, et al. Analysis of factors impacting operability in stage IV ovarian cancer: rationale use of a triage system. *Gynecol Oncol.* 2007;105:84–89.
 180. Angioli R, Palaia I, Angelo Zullo M, et al. Diagnostic open laparoscopy in the management of advanced ovarian cancer. *Gynecol Oncol.* 2006;100:455–461.
 181. Van Der Burg MEL, Van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. *N Engl J Med.* 1995;332:629–634.
 182. Rose PG, Nerenstone S, Brady MF, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med.* 2004;351:2489–2497.
 183. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;353:34–43.
 184. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase3, open-label, randomised controlled trial. *Lancet.* 2009;9698:1331–1338.
 185. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365:2473–2483.
 186. Jänicke F, Hölscher M, Kuhn W, et al. Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. *Cancer.* 1992;70:2129–2136.
 187. Chi DS, McCaughy K, Diaz JP, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. *Cancer.* 2006;106:1933–1939.
 188. Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian cancer. *Cancer.* 2000;88:144–153.
 189. Harter P, Hahmann M, Lueck HJ, et al. Surgery for recurrent ovarian cancer: role of peritoneal carcinomatosis. Exploratory analysis of the DESKTOP I trial about risk factors, surgical implications, and prognostic value of peritoneal

- carcinomatosis. *Ann Surg Oncol.* 2009;13:1702–1710.
190. Harter P, Schouli J, Reuss A, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer. *Int J Gynecol Cancer.* 2011;21:289–295.
 191. Güngör M, Ortac F, Arvas M, et al. The role of secondary cytoreductive surgery of recurrent ovarian cancer. *Gynecol Oncol.* 2005;97:74–79.
 192. Díaz-Montes TP, Bristow RE. Secondary cytoreduction for patients with recurrent ovarian cancer. *Curr Oncol Rep.* 2012;7:451–458.
 193. Radwany SM, von Gruenigen VE. Palliative and end-of-life care for patients with ovarian cancer. *Clin Obstet Gynecol.* 2012;55:173–184.
 194. Pothuri B, Vaidya A, Aghajanian C, et al. Palliative surgery for bowel obstruction in recurrent ovarian cancer: an updated series. *Gynecol Oncol.* 2003;89:306–313.
 195. Kobel M, Kalloger S, Huntsman DG, et al. On behalf of the Cheryl Brown Ovarian Cancer Outcomes Unit of the British Columbia Cancer Agency, Vancouver, B.C. Differences in tumor cell type in low versus high stage ovarian carcinomas. *Int J Gynecol Pathol.* 2010;29:203–211.
 196. Akeson M, Jakobsen A-M, Zetterqvist BM, et al. A population-based 5-year cohort study including all cases of epithelial ovarian cancer in western Sweden: 10-year survival and prognostic factors. *Int J Gynecol Cancer.* 2009;19:116–123.
 197. Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. *Am J Surg Pathol.* 2003;27:985–993.
 198. Kurman RJ, Shih IM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer: shifting the paradigm. *Hum Pathol.* 2011;42:918–31.
 199. Levanon K, Crum C, Drapkin R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. *J Clin Oncol.* 2008;26:5284–93.
 200. Salvador S, Gilks B, Kobel M, et al. The fallopian tube: primary site of most pelvic high grade serous carcinomas. *Int J Gynecol Cancer.* 2009;19:58–64.
 201. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol.* 2010;34:433–443.
 202. Steffenson KD, Waldstrom M, Grove A, et al. Improved classification of epithelial ovarian cancer: results of 3 Danish cohorts. *Int J Gynecol Cancer.* 2011;21:1592–1600.
 203. Yemelyanova AV, Cosin JA, Bidus MA, et al. Pathology of stage I versus stage III ovarian carcinoma with implications for pathogenesis and screening. *Int J Gynecol Cancer.* 2008;18:465–469.
 204. Guth U, Huang DJ, Bauer G, et al. Metastatic patterns at autopsy in patients with ovarian carcinoma. *Cancer.* 2007;110:1272–1280.
 205. Seidman JD, Cho KR, Ronnett BM, et al. Surface epithelial tumors of the ovary. In: Kurman RJ, Ellenson LH, Ronnett BM, eds. *Blaustein's Pathology of the Female Genital Tract.* 6th ed. New York, NY: Springer; 2011:679–784.
 206. Seidman JD, Wang B. Evaluation of normal-sized ovaries associated with primary peritoneal serous carcinoma for possible precursors of ovarian serous carcinoma. *Gynecol Oncol.* 2007;106:201–206.
 207. Stern RC, Dash R, Bentley RC, et al. Malignancy in endometriosis: frequency and comparison of ovarian and extraovarian types. *Int J Gynecol Pathol.* 2001;20:133–139.
 208. Brinton LA, Gridley G, Persson I, et al. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol.* 1997;176:572–579.
 209. Kobayashi H, Sumimoto K, Moniwa N, et al. Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka, Japan. *Int J Gynecol Cancer.* 2007;17:37–43.
 210. Ronnett BM, Kajdacsy-Balla A, Gilks CB, et al. Mucinous borderline ovarian tumors: points of general agreement and persistent controversies regarding nomenclature, diagnostic criteria, and behavior. *Hum Pathol.* 2004;35:949–960.
 211. Seidman JD, Sherman ME, Bell KA, et al. Salpingitis, salpingoliths and serous tumors of the ovaries: is there a connection? *Int J Gynecol Pathol.* 2002;21:101–107.
 212. Demopoulos RI, Aronov R, Mesia A. Clues to the pathogenesis of fallopian tube carcinoma: a morphological and immunohistochemical case control study. *Int J Gynecol Pathol.* 2001;20:128–132.
 213. Piek MJ, Kenemans P, Verheijen RHM. Intra-peritoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. *Am J Obstet Gynecol.* 2004;191:718–732.
 214. Vang R, Wheeler JE. Diseases of the fallopian tube and paratubal region. In: Kurman RJ, Ellenson LK, Ronnett BM, eds. *Blaustein's Pathology of the Female Genital Tract.* 6th ed. New York, NY: Springer; 2011:529–78.
 215. Carcangiu ML, Peissel B, Pasini B, et al. Incidental carcinomas in prophylactic specimens in BRCA1 and BRCA2 germ-line mutation carriers with emphasis on fallopian tube lesions: report of 6 cases and review of the literature. *Am J Surg Pathol.* 2006;30:1222–1230.
 216. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol.* 2006;30:230–236.
 217. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. *Am J Surg Pathol.* 2007;31:161–169.
 218. Klaren HM, van't Veer LJ, van Leeuwen FE, et al. Potential for bias in studies on efficacy of prophylactic surgery for BRCA1 and BRCA2 mutation. *J Natl Cancer Inst.* 2003;95:941–947.
 219. Visvanathan K, Vang R, Shaw P, et al. Diagnosis of serous tubal intraepithelial carcinoma based on morphologic and immunohistochemical features: a reproducibility study. *Am J Surg Pathol.* 2011;35:1766–1775.
 220. Lee Y, Medeiros F, Kindelberger D, et al. Advances in the recognition of tubal intraepithelial carcinoma: applications to cancer screening and the pathogenesis of ovarian cancer. *Adv Anat Pathol.* 2006;13:1–7.
 221. Seidman JD, Yemelyanova A, Zaino RJ, et al. The tubal-peritoneal junction: a potential site of carcinogenesis. *Int J Gynecol Pathol.* 2011;30:4–11.
 222. Tornos C, Soslow RA. Frozen section of ovarian lesions. In: Soslow RA, Tornos C, eds. *Diagnostic Pathology of Ovarian Tumors.* New York, NY: Springer; 2011:15–36.
 223. Heatley MK. A systematic review of papers examining use of intraoperative frozen section in predicting the final diagnosis of ovarian lesions. *Int J Gynecol Pathol.* 2012;31:111–115.
 224. Shih KK, Garg K, Soslow RA, et al. Accuracy of frozen section diagnosis of ovarian borderline tumor. *Gynecol Oncol.* 2011;123:517–521.
 225. Storms A-A, Sukumvanich P, Monaco SE, et al. Mucinous tumors of the ovary: diagnostic challenges at frozen section and clinical implications. *Gynecol Oncol.* 2012;125:75–79.
 226. Yemelyanova AV, Vang R, Judson K, et al. Distinction of primary and metastatic mucinous tumors involving the ovary: analysis of size and laterality data by primary site with reevaluation of an algorithm for tumor classification. *Am J Surg Pathol.* 2008;32:128–138.
 227. Pongsuaveeyakul T, Khunamornpong S, Settakorn J, et al. Accuracy of frozen section diagnosis of ovarian mucinous tumors. *Int J Gynecol Cancer.* 2012;22:400–406.
 228. Movahedi-Lankarani S, Baker PM, Gilks B, et al. Protocol for the examination of specimens from patients with carcinoma of the ovary. College of American Pathologists, 2011. http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/Ovary_11protocol.pdf. Accessed March 18, 2012.
 229. Tam KF, Cheung ANY, Liu KL, et al. A retrospective review on atypical glandular cells of undetermined significance (AGUS) using the Bethesda 2001 classification. *Gynecol Oncol.* 2003;91:603–607.
 230. Ayhan A, Gultekin M, Taskiran C, et al. Ascites and epithelial ovarian cancers: a reappraisal with respect to different aspects. *Int J Gynecol Cancer.* 2007;17:68–75.
 231. Colgan TJ, Boerner SL, Murphy J, et al. Peritoneal lavage cytology: an assessment of its value during prophylactic oophorectomy. *Gynecol Oncol.* 2002;85:397–403.
 232. Agoff SN, Mendelin JE, Grieco VS, et al. Unexpected gynecologic neoplasms in patients with proven or suspected BRCA-1 or -2 mutations: implications for gross examination, cytology, and clinical follow-up. *Am J Surg Pathol.* 2002;26:171–178.
 233. Seidman JD, Soslow RA, Vang R, et al. Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. *Hum Pathol.* 2004;35:918–33.
 234. Khunamornpong S, Settakorn J, Sukpan K, et al. Mucinous tumor of low malignant potential (“borderline” or “atypical proliferative” tumor) of the ovary: a study of 171 cases with the assessment of intraepithelial carcinoma and microinvasion. *Int J Gynecol Pathol.* 2011;30:218–230.
 235. Seidman JD, Mehrotra A. Benign ovarian serous tumors: a re-evaluation and proposed reclassification of serous “cystadenomas” and “cystadenofibromas.” *Gynecol Oncol.* 2005;96:395–401.
 236. Cheng E, Kurman RJ, Wang M, et al. Molecular genetic analysis of ovarian serous cystadenomas. *Lab Invest.* 2004;84:778–784.
 237. Hunter SM, Anglesio MS, Sharma R, et al. Copy number aberrations in benign serous ovarian tumors: a case for reclassification? *Clin Cancer Res.* 2011;17:7273–7282.
 238. Longacre TA, McKenney JK, Tazelaar HD, et al. Ovarian serous tumors of low malignant potential (borderline tumors): outcome-based study of 276 patients with long-term (>5-year) follow-up. *Am J Surg Pathol.* 2005;29:707–723.
 239. Seidman JD, Kraus JA, Yemelyanova A, et al. Ovarian low grade serous neoplasms: evaluation of sampling recommendations based on tumors expected to have invasion (those with peritoneal invasive low grade serous carcinoma (invasive implants)). *Modern Pathol.* 2009;22 (Suppl. 1):236A (abstract).
 240. Seidman JD, Kurman RJ. Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. *Hum Pathol.* 2000;31:539–557.

241. Kraus J, Seidman JD. The relationship between papillary infarction and microinvasion in ovarian atypical proliferative ("borderline") serous and seromucinous tumors. *Int J Gynecol Pathol.* 2010;29:303–309.
242. McKenney JK, Balzer BL, Longacre TA. Patterns of stromal invasion in ovarian serous tumors of low malignant potential (borderline tumors): a reevaluation of the concept of stromal microinvasion. *Am J Surg Pathol.* 2006;30:1209–1221.
243. Longacre TA, McKenney JK, Tazelaar HD, et al. Ovarian serous tumors of low malignant potential (borderline tumors): outcome-based study of 276 patients with long-term (>5-year) follow-up. *Am J Surg Pathol.* 2005;29:707–723.
244. Gilks CB, Alkushi A, Yue JJW, et al. Advanced-stage serous borderline tumors of the ovary: a clinicopathological study of 49 cases. *Int J Gynecol Pathol.* 2003;22:29–36.
245. Bell KA, Sehdev AES, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumors (borderline) and micropapillary serous carcinomas. *Am J Surg Pathol.* 2001;25:419–432.
246. McKenney JK, Balzer BL, Longacre TA. Lymph node involvement in ovarian serous tumors of low malignant potential (borderline tumors): pathology, prognosis, and proposed classification. *Am J Surg Pathol.* 2006;30:614–624.
247. Sherman ME, Mink PJ, Curtis R, et al. Survival among women with borderline ovarian tumors and ovarian carcinoma: a population-based analysis. *Cancer.* 2004;100:1045–1052.
248. Akesson M, Zetterqvist BM, Dahllof K, et al. Population-based cohort follow-up study of all patients operated for borderline ovarian tumor in western Sweden during an 11-year period. *Int J Gynecol Cancer.* 2008;18:453–459.
249. Park JY, Kim DY, Kim JH, et al. Surgical management of borderline ovarian tumors: the role of fertility sparing surgery. *Gynecol Oncol.* 2009;113:75–82.
250. Kurman RJ, Trimble CL. The behavior of serous tumors of low malignant potential: are they ever malignant? *Int J Gynecol Pathol.* 1993;12:120–127.
251. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II–IV low-grade serous carcinoma of the ovary. *Obstet Gynecol.* 2006;108:361–368.
252. Gilks CB, Ionescu DN, Kallinger SE, et al. Tumor cell type can be reproducibly diagnosed and is of independent prognostic significance in patients with maximally debulked ovarian carcinoma. *Hum Pathol.* 2008;39:1239–1251.
253. Prat J, de Nictolis M. Serous borderline tumors of the ovary: a long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. *Am J Surg Pathol.* 2002;26:1111–1128.
254. Deavers MT, Gershenson DM, Tortolero-Luna G, et al. Micropapillary and cribriform patterns in ovarian serous tumors of low malignant potential: a study of 99 advanced stage cases. *Am J Surg Pathol.* 2002;26:1129–1141.
255. Shvartsman HS, Sun CC, Bodurka DC, et al. Comparison of the clinical behavior of newly diagnosed stages II–IV low-grade serous carcinoma of the ovary with that of serous ovarian tumors of low malignant potential that recur as low grade serous carcinoma. *Gynecol Oncol.* 2007;105:625–629.
256. Smith-Sehdev AE, Sehdev PS, Kurman RJ. Non-invasive and invasive micropapillary (low grade) serous carcinoma of the ovary: a clinicopathologic analysis of 135 cases. *Am J Surg Pathol.* 2003;27:725–736.
257. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II–IV low-grade serous carcinoma of the ovary. *Obstet Gynecol.* 2006;108:361–368.
258. Seidman JD, Yemelyanova A, Cosin JA, et al. Survival rates for FIGO stage III ovarian carcinoma by cell type: a study of 262 unselected patients with uniform pathologic review. *Int J Gynecol Cancer.* 2012;22:367–371.
259. Carlson JW, Miron A, Jarboe EA, et al. Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention. *J Clin Oncol.* 2008;26:4160–4165.
260. Tang S, Onuma K, Deb P, et al. Frequency of serous tubal intraepithelial carcinoma in various gynecologic malignancies: a study of 300 consecutive cases. *Int J Gynecol Pathol.* 2012;31:103–110.
261. Seidman JD, Zhao P, Yemelyanova A. "Primary peritoneal" high grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. *Gynecol Oncol.* 2011;120:470–473.
262. Leonhardt K, Eienkel J, Sohr S, et al. P53 signature and serous tubal in-situ carcinoma in cases of primary tubal and peritoneal carcinomas and serous borderline tumors of the ovary. *Int J Gynecol Pathol.* 2011;30:417–24.
263. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. *Am J Surg Pathol.* 2004;28:496–504.
264. Plaxe SC. Epidemiology of low-grade serous ovarian cancer. *Am J Obstet Gynecol.* 2008;198:459.e1–459.e9.
265. Malpica A, Deavers MT, Tornos C, et al. Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma. *Am J Surg Pathol.* 2007;31:1168–1174.
266. Riopel MA, Ronnett BM, Kurman RJ. Evaluation of diagnostic criteria and behavior of ovarian intestinal-type mucinous tumors: atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive, and metastatic carcinomas. *Am J Surg Pathol.* 1999;23:617–635.
267. McKenney JK, Soslow RA, Longacre TA. Ovarian mature teratomas with mucinous epithelial neoplasms: morphologic heterogeneity and association with pseudomyxoma peritonei. *Am J Surg Pathol.* 2008;32:645–655.
268. Chen S, Leitao MM, Tornos C, et al. Invasion patterns in stage I endometrioid and mucinous ovarian carcinomas: a clinicopathologic analysis emphasizing favorable outcomes in carcinomas without destructive stromal invasion and the occasional malignant course of carcinomas with limited destructive stromal invasion. *Mod Pathol.* 2005;18:903–911.
269. Yemelyanova A, Seidman JD. Metastatic tumors. In: Soslow RA, Tornos C, eds. *Diagnostic Pathology of Ovarian Tumors.* New York, NY: Springer; 2011:133–144.
270. Zaino RJ, Brady MF, Lele SM, et al. Advanced stage mucinous adenocarcinoma of the ovary is both rare and highly lethal. *Cancer.* 2011;117:554–562.
271. Roth LM, Emerson RE, Ulbright TM. Ovarian endometrioid tumors of low malignant potential: a clinicopathologic study of 30 cases with comparison to well-differentiated endometrioid adenocarcinoma. *Am J Surg Pathol.* 2003;27:1253–1259.
272. Storey DJ, Rush R, Stewart M, et al. Endometrioid epithelial ovarian cancer: 20 years of prospectively collected data from a single center. *Cancer.* 2008;112:2211–2220.
273. Soslow RA. Histologic subtypes of ovarian carcinoma: an overview. *Int J Gynecol Pathol.* 2008;27:161–174.
274. McCluggage WG. My approach to and thoughts on the typing of ovarian carcinomas. *J Clin Pathol.* 2008;61:152–163.
275. Silva EG, Deavers MT, Bodurka DC, et al. Association of low grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? *Int J Gynecol Pathol.* 2006;25:52–58.
276. Murray MP, Park KJ. Pathology of endometrioid tumors. In: Soslow RA, Tornos C, eds. *Diagnostic Pathology of Ovarian Tumors.* New York, NY: Springer; 2011:75–90.
277. Zaino R, Whitney C, Brady MF, et al. Simultaneously detected endometrial and ovarian carcinomas – a prospective clinicopathologic study of 74 cases – a Gynecologic Oncology Group study. *Gynecol Oncol.* 2001;83:355–362.
278. Cho KR, Shih IM. Ovarian cancer. *Annu Rev Pathol Mech Dis.* 2009;4:287–313.
279. Han G, Gilks CB, Leung S, et al. Mixed ovarian epithelial carcinomas with clear cell and serous components are variants of high-grade serous carcinoma: an interobserver correlative and immunohistochemical study of 32 cases. *Am J Surg Pathol.* 2008;32:955–964.
280. Veras E, Mao T-L, Ayhan A, et al. Cystic and adenofibromatous clear cell carcinomas of the ovary: distinctive tumors that differ in their pathogenesis and behavior: a clinicopathologic analysis of 122 cases. *Am J Surg Pathol.* 2009;33:844–853.
281. Timmers PJ, Zwinderman AH, Teodorovic I, et al. Clear cell carcinoma compared to serous carcinoma in early ovarian cancer: same prognosis in a large randomized trial. *Int J Gynecol Cancer.* 2009;19:88–93.
282. Suzuki S, Kajiyama H, Shibata K, et al. Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients? *Ann Oncol.* 2008;19:1284–1287.
283. Takano M, Kikuchi Y, Yaegashi N, et al. Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging. *Br J Cancer.* 2006;94:1369–1374.
284. Magazzino F, Katsaros D, Ottaiano A, et al. Surgical and medical treatment of clear cell ovarian cancer: results from the multicenter Italian trials in ovarian cancer (MITO) 9 retrospective study. *Int J Gynecol Cancer.* 2011;21:1063–1070.
285. Seidman JD, Khedmati F. Exploring the histogenesis of ovarian mucinous and transitional cell (Brenner) tumors: a study of 120 tumors. *Arch Pathol Lab Med.* 2008;132:1753–1760.
286. Khedmati F, Chirolas C, Seidman JD. Ovarian and paraovarian squamous-lined cysts (epidermoid cysts): a clinicopathologic study of 18 cases with comparison to mature cystic teratomas. *Int J Gynecol Pathol.* 2009;28:193–196.
287. Khunamornpong S, Suprasert P, Na Chiangmai W, et al. Metastatic tumors to the ovaries: a study of 170 cases in Northern Thailand. *Int J Gynecol Cancer.* 2006;16(suppl. 1):132–138.
288. Leiser AL, Chi DS, Ishill NM, et al. Carcinosarcoma of the ovary treated with platinum and taxane: the memorial Sloan-Kettering Cancer Center experience. *Gynecol Oncol.* 2007;105:657–661.
289. Eichorn JH, Young RH, Clement PB, et al. Mesodermal (mullerian) adenocarcinoma of the

- ovary: a clinicopathologic analysis of 40 cases and a review of the literature. *Am J Surg Pathol*. 2002;26:1243–1258.
290. Maeda D, Ota S, Takazawa Y, et al. Mucosal carcinoma of the fallopian tube coexists with ovarian cancer of serous subtype only: a study of Japanese cases. *Virch Arch*. 2010;457:597–608.
 291. Gilks CB, Ionescu DN, Kallger SE, et al. Tumor cell type can be reproducibly diagnosed and is of independent prognostic significance in patients with maximally debulked ovarian carcinoma. *Hum Pathol*. 2008;39(8):1239–1251.
 292. Kosary CL. Cancer of the ovary. In: *SEER Survival Monograph: Cancer Survival Among Adults: US SEER Program, 1998–2001*. Available at: http://seer.cancer.gov/publications/survival/surv_ovary.pdf (Accessed September 19, 2012.).
 293. Vergote I, De Brabanter J, Fyles A, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. *Lancet*. 2001;357(9251):176–182.
 294. Vergote I. Prognostic factors in stage I ovarian carcinoma. *Verh K Acad Geneesk Belg*. 2001;63(3):257–271; discussion 272–256.
 295. Chan JK, Tian C, Monk BJ, et al. Prognostic factors for high-risk early-stage epithelial ovarian cancer: a Gynecologic Oncology Group study. *Cancer*. 2008;112(10):2202–2210.
 296. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet*. 2006;95 (Suppl. 1):S161–S192.
 297. Seidman JD, Yemelyanova AV, Khedmati F, et al. Prognostic factors for stage I ovarian carcinoma. *Int J Gynecol Pathol*. 2010;29(1):1–7.
 298. Leita MM, Soslow RA, Baergen RN, et al. Mutation and expression of the TP53 gene in early stage epithelial ovarian carcinoma. *Gynecol Oncol*. 2004;93(2):301–306.
 299. Timmers PJ, Zwinderman AH, Teodorovic I, et al. Clear cell carcinoma compared to serous carcinoma in early ovarian cancer: same prognosis in a large randomized trial. *Int J Gynecol Cancer*. 2009;19(1):88–93.
 300. Winter WE 3rd, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007;25(24):3621–3627.
 301. Malpica A, Deavers MT, Tornos C, et al. Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma. *Am J Surg Pathol*. 2007;31(8):1168–1174.
 302. Dembo AJ, Davy M, Stenwig AE, et al. Prognostic factors in patients with stage I epithelial ovarian cancer. *Obstet Gynecol*. 1990;75(2):263–273.
 303. Paulsen T, Kaern J, Trope C. Improved 5-year disease-free survival for FIGO stage I epithelial ovarian cancer patients without tumor rupture during surgery. *Gynecol Oncol*. 2011;122(1):83–88.
 304. Seidman JD, Cosin JA, Wang BG, et al. Upstaging pathologic stage I ovarian carcinoma based on dense adhesions is not warranted: a clinicopathologic study of 84 patients originally classified as FIGO stage II. *Gynecol Oncol*. 2010;119(2):250–254.
 305. Obermair A, Fuller A, Lopez-Varela E, et al. A new prognostic model for FIGO stage 1 epithelial ovarian cancer. *Gynecol Oncol*. 2007;104(3):607–611.
 306. Makar AP, Baekelandt M, Trope CG, et al. The prognostic significance of residual disease, FIGO substage, tumor histology, and grade in patients with FIGO stage III ovarian cancer. *Gynecol Oncol*. 1995;56(2):175–180.
 307. Rungruang B, Miller A, Richard SD, et al. Should stage IIIC ovarian cancer be further stratified by intraperitoneal vs. retroperitoneal only disease? A Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;124(1):53–58.
 308. Bamias A, Sotiropoulos M, Zagouri F, et al. Prognostic evaluation of tumour type and other histopathological characteristics in advanced epithelial ovarian cancer, treated with surgery and paclitaxel/carboplatin chemotherapy: Cell type is the most useful prognostic factor. *Eur J Cancer*. 2012;48(10):1476–1483.
 309. Seidman JD, Horkayne-Szakaly I, Cosin JA, et al. Testing of two binary grading systems for FIGO stage III serous carcinoma of the ovary and peritoneum. *Gynecol Oncol*. 2006;103(2):703–708.
 310. Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system: A Gynecologic Oncology Group Study. *Cancer*. 2012;118(12):3087–3094.
 311. Seidman JD, Yemelyanova A, Cosin JA, et al. Survival rates for international federation of gynecology and obstetrics stage III ovarian carcinoma by cell type: a study of 262 unselected patients with uniform pathologic review. *Int J Gynecol Cancer*. 2012;22(3):367–371.
 312. Gershenson DM, Sun CC, Bodurka D, et al. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. *Gynecol Oncol*. 2009;114(1):48–52.
 313. Steffensen KD, Waldstrom M, Brandslund I, et al. Prognostic impact of prechemotherapy serum levels of HER2, CA125, and HE4 in ovarian cancer patients. *Int J Gynecol Cancer*. 2011;21(6):1040–1047.
 314. Skaznik-Wikiel ME, Sukumvanich P, Beriwal S, et al. Possible use of CA-125 level normalization after the third chemotherapy cycle in deciding on chemotherapy regimen in patients with epithelial ovarian cancer: brief report. *Int J Gynecol Cancer*. 2011;21(6):1013–1017.
 315. Matsuo K, Ahn EH, Prather CP, et al. Patient-reported symptoms and survival in ovarian cancer. *Int J Gynecol Cancer*. 2011;21(9):1555–1565.
 316. Matsuo K, Prather CP, Ahn EH, et al. Significance of perioperative infection in survival of patients with ovarian cancer. *Int J Gynecol Cancer*. 2012;22(2):245–253.
 317. Nakamura K, Hongo A, Kodama J, et al. The pretreatment of maximum standardized uptake values (SUVmax) of the primary tumor is predictor for poor prognosis for patients with epithelial ovarian cancer. *Acta Med Okayama*. 2012;66(1):53–60.
 318. Stone RL, Nick AM, McNeish IA, et al. Paraneoplastic thrombocytosis in ovarian cancer. *N Engl J Med*. 2012;366(7):610–618.
 319. Terplan M, Temkin S, Tergas A, et al. Does equal treatment yield equal outcomes? The impact of race on survival in epithelial ovarian cancer. *Gynecol Oncol*. 2008;111(2):173–178.
 320. Terplan M, Schluterman N, McNamara EJ, et al. Have racial disparities in ovarian cancer increased over time? An analysis of SEER data. *Gynecol Oncol*. 2012;125(1):19–24.
 321. Terplan M, Smith EJ, Temkin SM. Race in ovarian cancer treatment and survival: a systematic review with meta-analysis. *Cancer Causes Control*. 2009;20(7):1139–1150.
 322. Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. *N Engl J Med*. 1996;335(19):1413–1416.
 323. Boyd J, Sonoda Y, Federici MG, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. *JAMA*. 2000;283(17):2260–2265.
 324. Lacour RA, Euscher E, Atkinson EN, et al. A phase II trial of paclitaxel and carboplatin in women with advanced or recurrent uterine carcinosarcoma. *Int J Gynecol Cancer*. 2011;21(3):517–522.
 325. Yang D, Khan S, Sun Y, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. *JAMA*. 2011;306(14):1557–1565.
 326. Kang J, D'Andrea AD, Kozono D. A DNA repair pathway-focused score for prediction of outcomes in ovarian cancer treated with platinum-based chemotherapy. *J Natl Cancer Inst*. 2012;104(9):670–681.
 327. Pils D, Hager G, Tong D, et al. Validating the impact of a molecular subtype in ovarian cancer on outcomes: a study of the OVCAD Consortium. *Cancer Sci*. 2012.
 328. Kleppe M, Wang T, Van Gorp T, et al. Lymph node metastasis in stages I and II ovarian cancer: a review. *Gynecol Oncol*. 2011;123(3):610–614.
 329. Schmeler KM, Tao X, Frumovitz M, et al. Prevalence of lymph node metastasis in primary mucinous carcinoma of the ovary. *Obstet Gynecol*. 2010;116(2 Pt. 1):269–273.
 330. Satoh T, Hatae M, Watanabe Y, et al. Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: a proposal for patient selection. *J Clin Oncol*. 2010;28(10):1727–1732.
 331. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. *N Engl J Med*. 1990;322(15):1021–1027.
 332. Dembo AJ. Radiotherapeutic management of ovarian cancer. *Semin Oncol*. 1984;11(3):238–250.
 333. Dembo AJ. The role of radiotherapy in ovarian cancer. *Bull Cancer*. 1982;69(3):275–283.
 334. Klaassen D, Shelley W, Starreveld A, et al. Early stage ovarian cancer: a randomized clinical trial comparing whole abdominal radiotherapy, melphalan, and intraperitoneal chronic phosphate: a National Cancer Institute of Canada Clinical Trials Group report. *J Clin Oncol*. 1988;6(8):1254–1263.
 335. Sell A, Bertelsen K, Andersen JE, et al. Randomized study of whole-abdomen irradiation versus pelvic irradiation plus cyclophosphamide in treatment of early ovarian cancer. *Gynecol Oncol*. 1990;37(3):367–373.
 336. Smith JP. Chemotherapy in gynecologic cancer. *Clin Obstet Gynecol*. 1975;18(4):109–124.
 337. Chiara S, Conte P, Franzoni P, et al. High-risk early-stage ovarian cancer. Randomized clinical trial comparing cisplatin plus cyclophosphamide versus whole abdominal radiotherapy. *Am J Clin Oncol*. 1994;17(1):72–76.
 338. Swenerton KD, Santos JL, Gilks CB, et al. Histotype predicts the curative potential of radiotherapy: the example of ovarian cancers. *Ann Oncol*. 2011;22(2):341–347.
 339. Hoskins PJ, Le N, Gilks B, et al. Low-stage ovarian clear cell carcinoma: population-based outcomes in British Columbia, Canada, with evidence for a survival benefit as a result of irradiation. *J Clin Oncol*. 2012;30(14):1656–1662.
 340. Varia MA, Stehman FB, Bundy BN, et al. Intraperitoneal radioactive phosphorus (32P) versus observation after negative second-look laparotomy for stage III ovarian carcinoma: a randomized trial of the Gynecologic Oncology Group. *J Clin Oncol*. 2003;21(15):2849–2855.
 341. Trimpos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1

- and Adjuvant ChemoTherapy in Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst.* 2003;95(2):105–112.
342. Colombo N, Guthrie D, Chiari S, et al. International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer Inst.* 2003;95(2):125–132.
 343. Bolis G, Villa A, Ferraris C, et al. Survival of advanced ovarian cancer patients with microscopic partial response after surgery and first-line chemotherapy. *Eur J Cancer.* 1995;31A(6):1019–1020.
 344. Ahmed FY, Wiltshaw E, A'Hern RP, et al. Natural history and prognosis of untreated stage I epithelial ovarian carcinoma. *J Clin Oncol.* 1996;14(11):2968–2975.
 345. Kolomainen DE, A'Hern R, Coxon FY, et al. Can patients with relapsed, previously untreated, stage I epithelial ovarian cancer be successfully treated with salvage therapy? *J Clin Oncol.* 2003;21(16):3113–3118.
 346. Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2006;102(3):432–439.
 347. Chan JK, Tian C, Fleming GF, et al. The potential benefit of 6 vs.3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010;116(3):301–306.
 348. Bamias A, Bamia C, Karadimou A, et al. A risk-adapted strategy of adjuvant paclitaxel/carboplatin in early-stage ovarian cancer: time-dependent effect of 4 versus 6 cycles on outcome. *Oncology.* 2011;81(5–6):365–371.
 349. Mannel RS, Brady MF, Kohn EC, et al. A randomized phase III trial of IV carboplatin and paclitaxel $\times$ 3 courses followed by observation versus weekly maintenance low-dose paclitaxel in patients with early-stage ovarian carcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 2011;122(1):89–94.
 350. Takada T, Iwase H, Iitsuka C, et al. Adjuvant chemotherapy for stage I clear cell carcinoma of the ovary: an analysis of fully staged patients. *Int J Gynecol Cancer.* 2012;22(4):573–578.
 351. Del Carmen MG, Birrer M, Schorge JO. Clear cell carcinoma of the ovary: a review of the literature. *Gynecol Oncol.* 2012.
 352. Ditto A, Martinelli F, Reato C, et al. Systematic Para-aortic and pelvic lymphadenectomy in early stage epithelial ovarian cancer: a prospective study. *Ann Surg Oncol.* 2012.
 353. Vayssie C, Touboul C, Filleron T, et al. Early stage (IA-IB) primary carcinoma of the fallopian tube: case-control comparison to adenocarcinoma of the ovary. *J Gynecol Oncol.* 2011;22(1):9–17.
 354. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the fallopian tube. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet.* 2006;95(Suppl. 1):S145–S160.
 355. Morice P, Uzan C, Fauvet R, et al. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. *Lancet Oncol.* 2012;13(3):e103–e115.
 356. Trimble CL, Kosary C, Trimble EL. Long-term survival and patterns of care in women with ovarian tumors of low malignant potential. *Gynecol Oncol.* 2002;86(1):34–37.
 357. Song T, Choi CH, Kim HJ, et al. Accuracy of frozen section diagnosis of borderline ovarian tumors. *Gynecol Oncol.* 2011;122(1):127–131.
 358. Ramirez PT, Slomovitz BM, McQuinn L, et al. Role of appendectomy at the time of primary surgery in patients with early-stage ovarian cancer. *Gynecol Oncol.* 2006;103(3):888–890.
 359. Rao GG, Skinner E, Gehrig PA, et al. Surgical staging of ovarian low malignant potential tumors. *Obstet Gynecol.* 2004;104(2):261–266.
 360. Suh-Burgmann E. Long-term outcomes following conservative surgery for borderline tumor of the ovary: a large population-based study. *Gynecol Oncol.* 2006;103(3):841–847.
 361. Silva EG, Tornos C, Zhuang Z, et al. Tumor recurrence in stage I ovarian serous neoplasms of low malignant potential. *Int J Gynecol Pathol.* 1998;17(1):1–6.
 362. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II–IV low-grade serous carcinoma of the ovary. *Obstet Gynecol.* 2006;108(2):361–368.
 363. Morice P, Uzan C, Gouy S, et al. Gynaecological cancers in pregnancy. *Lancet.* 2012;379(9815):558–569.
 364. Shih KK, Zhou Q, Huh J, et al. Risk factors for recurrence of ovarian borderline tumors. *Gynecol Oncol.* 2011;120(3):480–484.
 365. Seidman JD, Soslow RA, Vang R, et al. Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. *Hum Pathol.* 2004;35(8):918–933.
 366. Gershenson DM, Silva EG, Levy L, et al. Ovarian serous borderline tumors with invasive peritoneal implants. *Cancer.* 1998;82(6):1096–1103.
 367. Shvartsman HS, Sun CC, Bodurka DC, et al. Comparison of the clinical behavior of newly diagnosed stages II–IV low-grade serous carcinoma of the ovary with that of serous ovarian tumors of low malignant potential that recur as low-grade serous carcinoma. *Gynecol Oncol.* 2007;105(3):625–629.
 368. Shih KK, Zhou QC, Aghajanian C, et al. Patterns of recurrence and role of adjuvant chemotherapy in stage II–IV serous ovarian borderline tumors. *Gynecol Oncol.* 2010;119(2):270–273.
 369. Faluyi O, Mackean M, Gourley C, et al. Interventions for the treatment of borderline ovarian tumours. *Cochrane Database Syst Rev.* 2010. (9):CD007696.
 370. Bristow RE, Gossett DR, Shook DR, et al. Recurrent micropapillary serous ovarian carcinoma. *Cancer.* 2002;95(4):791–800.
 371. Abu-Jawdeh GM, Jacobs TW, Niloff J, et al. Estrogen receptor expression is a common feature of ovarian borderline tumors. *Gynecol Oncol.* 1996;60(2):301–307.
 372. Gershenson DM, Sun CC, Iyer RB, et al. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. *Gynecol Oncol.* 2012;125(3):661–666.
 373. Bidus MA, Webb JC, Seidman JD, et al. Sustained response to bevacizumab in refractory well-differentiated ovarian neoplasms. *Gynecol Oncol.* 2006;102(1):5–7.
 374. Diaz-Padilla I, Malpica AL, Minig L, et al. Ovarian low-grade serous carcinoma: a comprehensive update. *Gynecol Oncol.* 2012;126(2):279–285.
 375. Wong KK, Tsang YT, Deavers MT, et al. BRAF mutation is rare in advanced-stage low-grade ovarian serous carcinomas. *Am J Pathol.* 2010;177(4):1611–1617.
 376. van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med.* 1995;332(10):629–634.
 377. Hakes TB, Chalas E, Hoskins WJ, et al. Randomized prospective trial of 5 versus 10 cycles of cyclophosphamide, doxorubicin, and cisplatin in advanced ovarian carcinoma. *Gynecol Oncol.* 1992;45(3):284–289.
 378. Bertelsen K, Jakobsen A, Stroyer J, et al. A prospective randomized comparison of 6 and 12 cycles of cyclophosphamide, adriamycin, and cisplatin in advanced epithelial ovarian cancer: a Danish Ovarian Study Group trial (DACOVA). *Gynecol Oncol.* 1993;49(1):30–36.
 379. Lambert HE, Rustin GJ, Gregory WM, et al. A randomized trial of five versus eight courses of cisplatin or carboplatin in advanced epithelial ovarian carcinoma. A North Thames Ovary Group Study. *Ann Oncol.* 1997;8(4):327–333.
 380. Muggia FM, Braly PS, Brady MF, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol.* 2000;18(1):106–115.
 381. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011;365(26):2484–2496.
 382. Omura G, Blessing JA, Ehrlich CE, et al. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group Study. *Cancer.* 1986;57(9):1725–1730.
 383. Aabo K, Adams M, Adniti P, et al. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. Advanced Ovarian Cancer Trialists' Group. *Br J Cancer.* 1998;78(11):1479–1487.
 384. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. *J Clin Oncol.* 1987;5(5):756–767.
 385. Fracasso PM, Blessing JA, Morgan MA, et al. Phase II study of oxaliplatin in platinum-resistant and refractory ovarian cancer: a gynecologic group study. *J Clin Oncol.* 2003;21(15):2856–2859.
 386. Misset JL, Vennin P, Chollet PH, et al. Multitenter phase II–III study of oxaliplatin plus cyclophosphamide vs. cisplatin plus cyclophosphamide in chemonaive advanced ovarian cancer patients. *Ann Oncol.* 2001;12(10):1411–1415.
 387. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996;334(1):1–6.
 388. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst.* 2000;92(9):699–708.
 389. Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet.* 2003;361(9375):2099–2106.
 390. Spriggs DR, Brady MF, Vaccarello L, et al. Phase III randomized trial of intravenous cisplatin plus a 24- or 96-hour infusion of paclitaxel in epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2007;25(28):4466–4471.

391. Bolis G, Scarfone G, Polverino G, et al. Paclitaxel 175 or 225 mg per meters squared with carboplatin in advanced ovarian cancer: a randomized trial. *J Clin Oncol*. 2004;22(4):686–690.
392. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet*. 2009;374(9698):1331–1338.
393. Katsumata N, Yasuda M, Isonishi S, et al. Long-term follow-up of a randomized trial comparing conventional paclitaxel and carboplatin with dose-dense weekly paclitaxel and carboplatin in women with advanced epithelial ovarian, Fallopian tube, or primary peritoneal cancer: JGOG 3016 trial. ASCO. 2012. Abstract #5003 (*J Clin Oncol*. June 2012).
394. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004;96(22):1682–1691.
395. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol*. 2009;27(9):1419–1425.
396. Gordon AN, Teneriello M, Janicek MF, et al. Phase III trial of induction gemcitabine or paclitaxel plus carboplatin followed by paclitaxel consolidation in ovarian cancer. *Gynecol Oncol*. 2011;123(3):479–485.
397. Pignata S, Scambia G, Ferrandina G, et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. *J Clin Oncol*. 2011;29(27):3628–3635.
398. Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007;25(33):5165–5171.
399. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol*. 2007;25(33):5180–5186.
400. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol*. 2008;26(1):76–82.
401. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365(26):2473–2483.
402. Los G, Mutsaers PH, van der Vijgh WJ, et al. Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res*. 1989;49(12):3380–3384.
403. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335(26):1950–1955.
404. Miyagi Y, Fujiwara K, Kigawa J, et al. Intraperitoneal carboplatin infusion may be a pharmacologically more reasonable route than intravenous administration as a systemic chemotherapy. A comparative pharmacokinetic analysis of platinum using a new mathematical model after intraperitoneal vs. intravenous infusion of carboplatin—a Sankai Gynecology Study Group (SGSG) study. *Gynecol Oncol*. 2005;99(3):591–596.
405. Fujiwara K, Armstrong D, Morgan M, et al. Principles and practice of intraperitoneal chemotherapy for ovarian cancer. *Int J Gynecol Cancer*. 2007;17(1):1–20.
406. Trimble EL. <http://ctep.cancer.gov/highlights/20060105ovarian.htm>. Accessed July 22, 2012.
407. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354(1):34–43.
408. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol*. 2001;19(4):1001–1007.
409. Helm CW. Ports and complications for intraperitoneal chemotherapy delivery. *BJOG*. 2012;119(2):150–159.
410. Piccart MJ, Floquet A, Scarfone G, et al. Intraperitoneal cisplatin versus no further treatment: 8-year results of EORTC 55875, a randomized phase III study in ovarian cancer patients with a pathologically complete remission after platinum-based intravenous chemotherapy. *Int J Gynecol Cancer*. 2003;13(suppl. 2):196–203.
411. Sorbe B. Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: a randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment. *Int J Gynecol Cancer*. 2003;13(3):278–286.
412. Pfisterer J, Weber B, Reuss A, et al. Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a gynecologic cancer intergroup trial of the AGO-OVAR and GINECO. *J Natl Cancer Inst*. 2006;98(15):1036–1045.
413. De Placido S, Scambia G, Di Vagno G, et al. Topotecan compared with no therapy after response to surgery and carboplatin/paclitaxel in patients with ovarian cancer: multicenter Italian Trials in Ovarian Cancer (MITO-1) randomized study. *J Clin Oncol*. 2004;22(13):2635–2642.
414. Bolis G, Danese S, Tateo S, et al. Epidoxorubicin versus no treatment as consolidation therapy in advanced ovarian cancer: results from a phase II study. *Int J Gynecol Cancer*. 2006;16(suppl. 1):74–78.
415. Papadimitriou C, Dafni U, Anagnostopoulos A, et al. High-dose melphalan and autologous stem cell transplantation as consolidation treatment in patients with chemosensitive ovarian cancer: results of a single-institution randomized trial. *Bone Marrow Transplant*. 2008;41(6):547–554.
416. Pujade-Lauraine E, Cure H, Battista C, et al. High dose chemotherapy in ovarian cancer. *Int J Gynecol Cancer*. 2001;11(suppl. 1):64–67.
417. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol*. 2003;21(13):2460–2465.
418. Markman M, Liu PY, Moon J, et al. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m²) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. *Gynecol Oncol*. 2009;114(2):195–198.
419. Pecorelli S, Favalli G, Gadducci A, et al. Phase III trial of observation versus six courses of paclitaxel in patients with advanced epithelial ovarian cancer in complete response after six courses of paclitaxel/platinum-based chemotherapy: final results of the After-6 protocol 1. *J Clin Oncol*. 2009;27(28):4642–4648.
420. Hall GD, Brown JM, Coleman RE, et al. Maintenance treatment with interferon for advanced ovarian cancer: results of the Northern and Yorkshire gynaecology group randomised phase III study. *Br J Cancer*. 2004;91(4):621–626.
421. Berek JS, Taylor PT, Gordon A, et al. Randomized, placebo-controlled study of oregovomab for consolidation of clinical remission in patients with advanced ovarian cancer. *J Clin Oncol*. 2004;22(17):3507–3516.
422. Verheijen RH, Massuger LF, Benigno BB, et al. Phase III trial of intraperitoneal therapy with yttrium-90-labeled HMFG1 murine monoclonal antibody in patients with epithelial ovarian cancer after a surgically defined complete remission. *J Clin Oncol*. 2006;24(4):571–578.
423. Vergote IB, Joly F, Katsaros D, et al. Randomized phase III study of erlotinib versus observation in patients with no evidence of disease progression after first-line platinum-based chemotherapy for ovarian carcinoma: A GCG and EORTC-GCG study. *J Clin Oncol*. 2012;30(suppl; abstr LBA5000).
424. Tothill RW, Tinker AV, George J, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. *Clin Cancer Res*. 2008;14(16):5198–5208.
425. Omura GA, Brady MF, Homesley HD, et al. Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience. *J Clin Oncol*. 1991;9(7):1138–1150.
426. Takano M, Kikuchi Y, Yaegashi N, et al. Clear cell carcinoma of the ovary: a retrospective multicenter experience of 254 patients with complete surgical staging. *Br J Cancer*. May 22 2006;94(10):1369–1374.
427. Anglesio MS, Carey MS, Kobel M, et al. Clear cell carcinoma of the ovary: a report from the first ovarian clear cell symposium, June 24th, 2010. *Gynecol Oncol*. 2011;121(2):407–415.
428. Takano M, Sugiyama T, Yaegashi N, et al. Less impact of adjuvant chemotherapy for stage I clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study. *Int J Gynecol Cancer*. 2010;20(9):1506–1510.
429. Goff BA, Sainz de la Cuesta R, Muntz HG, et al. Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. *Gynecol Oncol*. 1996;60(3):412–417.
430. Mackay HJ, Brady MF, Oza AM, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. *Int J Gynecol Cancer*. 2010;20(6):945–952.
431. Crotzer DR, Sun CC, Coleman RL, et al. Lack of effective systemic therapy for recurrent clear cell carcinoma of the ovary. *Gynecol Oncol*. 2007;105(2):404–408.
432. Takakura S, Takano M, Takahashi F, et al. Randomized phase II trial of paclitaxel plus carboplatin therapy versus irinotecan plus cisplatin therapy as first-line chemotherapy for clear cell

- adenocarcinoma of the ovary: a JGOG study. *Int J Gynecol Cancer*. 2010;20(2):240–247.
433. Takano M, Kikuchi Y, Kudoh K, et al. Weekly administration of temsirolimus for heavily pretreated patients with clear cell carcinoma of the ovary: a report of six cases. *Int J Clin Oncol*. 2011;16(5):605–609.
 434. Yoshino K, Enomoto T, Fujita M, et al. Salvage chemotherapy for recurrent or persistent clear cell carcinoma of the ovary: a single-institution experience for a series of 20 patients. *Int J Clin Oncol*. 2011.
 435. Duska LR, Garrett L, Henretta M, et al. When ‘never-events’ occur despite adherence to clinical guidelines: the case of venous thromboembolism in clear cell cancer of the ovary compared with other epithelial histologic subtypes. *Gynecol Oncol*. 2010;116(3):374–377.
 436. Savvari P, Peitsidis P, Alevizaki M, et al. Paraneoplastic humoral mediated hypercalcemia induced by parathyroid hormone-related protein in gynecologic malignancies: a systematic review. *Onkologie*. 2009;32(8–9):517–523.
 437. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. *Virchows Arch*. 2012;460(3):237–249.
 438. Winter WE 3rd, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2008;26(1):83–89.
 439. Zaino RJ, Brady MF, Lele SM, et al. Advanced stage mucinous adenocarcinoma of the ovary is both rare and highly lethal: a Gynecologic Oncology Group study. *Cancer*. 2011;117(3):554–562.
 440. del Carmen MG, Birrer M, Schorge JO. Carcinosarcoma of the ovary: a review of the literature. *Gynecol Oncol*. 2012;125(1):271–277.
 441. Rauh-Hain JA, Growdon WB, Rodriguez N, et al. Carcinosarcoma of the ovary: a case-control study. *Gynecol Oncol*. 2011;121(3):477–481.
 442. Chun KC, Kim JJ, Kim DY, et al. Optimal debulking surgery followed by paclitaxel/platinum chemotherapy is very effective in treating ovarian carcinosarcomas: a single center experience. *Gynecol Obstet Invest*. 2011;72(3):208–214.
 443. Stavrou C, Ford A, Ghaem-Maghani S, et al. A study of symptoms described by ovarian cancer survivors. *Gynecol Oncol*. 2012;125(1):59–64.
 444. Arriba LN, Fader AN, Frasure HE, et al. A review of issues surrounding quality of life among women with ovarian cancer. *Gynecol Oncol*. 2010;119(2):390–396.
 445. Grover S, Hill-Kayser CE, Vachani C, et al. Patient reported late effects of gynecological cancer treatment. *Gynecol Oncol*. 2012;124(3):399–403.
 446. Matulonis UA, Kornblith A, Lee H, et al. Long-term adjustment of early-stage ovarian cancer survivors. *Int J Gynecol Cancer*. 2008;18(6):1183–1193.
 447. Guidozzi F, Daponte A. Estrogen replacement therapy for ovarian carcinoma survivors: A randomized controlled trial. *Cancer*. 1999;86(6):1013–1018.
 448. Pignata S, De Placido S, Biamonte R, et al. Residual neurotoxicity in ovarian cancer patients in clinical remission after first-line chemotherapy with carboplatin and paclitaxel: the Multi-center Italian Trial in Ovarian cancer (MITO-4) retrospective study. *BMC Cancer*. 2006;6:5.
 449. Lavoie-Smith EM, Pang H, Cirrincione C, et al. CALGB 170601: a phase III double blind trial of duloxetine to treat painful chemotherapy-induced peripheral neuropathy (CIPN). *ASCO* 2012. abstract #CRA 9013.
 450. National Comprehensive Cancer Network (NCCN). <http://www.NCCN.org>. Accessed 4/2/2012, version 3.2012.
 451. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized controlled trial. *JAMA*. 2011;305(22):2295–2303.
 452. Rustin GJ, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet*. 2010;376(9747):1155–1163.
 453. Skates SJ. Ovarian cancer screening: development of the risk of ovarian cancer algorithm (ROCA) and ROCA screening trials. *Int J Gynecol Cancer*. 2012;22(Suppl. 1):S24–S26.
 454. Granato T, Midulla C, Longo F, et al. Role of HE4, CA72.4, and CA125 in monitoring ovarian cancer. *Tumour Biol*. 2012.
 455. Duffy MJ, Bonfrer JM, Kulpa J, et al. CA125 in ovarian cancer: European Group on Tumor Markers guidelines for clinical use. *Int J Gynecol Cancer*. 2005;15(5):679–691.
 456. Rustin GJ, Quinn M, Thigpen T, et al. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst*. 2004;96(6):487–488.
 457. Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCGI). *Int J Gynecol Cancer*. 2011;21(2):419–423.
 458. Herzog TJ, Vermorken JB, Pujade-Lauraine E, et al. Correlation between CA-125 serum level and response by RECIST in a phase III recurrent ovarian cancer study. *Gynecol Oncol*. 2011;122(2):350–355.
 459. Sabbatini P, Mooney D, Iasonos A, et al. Early CA-125 fluctuations in patients with recurrent ovarian cancer receiving chemotherapy. *Int J Gynecol Cancer*. 2007;17(3):589–594.
 460. Azad NS, Annunziata CM, Steinberg SM, et al. Lack of reliability of CA125 response criteria with anti-VEGF molecularly targeted therapy. *Cancer*. 2008;112(8):1726–1732.
 461. Menzin AW, Kobrin S, Pollak E, et al. The effect of renal function on serum levels of CA 125. *Gynecol Oncol*. 1995;58(3):375–377.
 462. Yap TA, Carden CP, Kaye SB. Beyond chemotherapy: targeted therapies in ovarian cancer. *Nat Rev Cancer*. 2009;9(3):167–181.
 463. Herzog TJ. The current treatment of recurrent ovarian cancer. *Curr Oncol Rep*. 2006;8(6):448–454.
 464. Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. *Oncologist*. 2002;7(suppl. 5):20–28.
 465. Markman M, Rothman M, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol*. 1991;9(3):389–393.
 466. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: overall survival analysis. *Eur J Cancer*. 2012.
 467. Eisenhauer EA, Vermorken JB, van Glabbeke M. Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients [see comments]. *Ann Oncol*. 1997;8(10):963–968.
 468. Lee CK, Simes RJ, Brown C, et al. Prognostic nomogram to predict progression-free survival in patients with platinum-sensitive recurrent ovarian cancer. *Br J Cancer*. 2011;105(8):1144–1150.
 469. Markman M, Markman J, Webster K, et al. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. *J Clin Oncol*. 2004;22(15):3120–3125.
 470. Hoskins PJ, Le N. Identifying patients unlikely to benefit from further chemotherapy: a descriptive study of outcome at each relapse in ovarian cancer. *Gynecol Oncol*. 2005;97(3):862–869.
 471. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol*. 2012;30(14):1715–1724.
 472. Gonzalez-Martin AJ, Calvo E, Bover I, et al. Randomized phase II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma: a GEICO (Grupo Espanol de Investigacion en Cancer de Ovario) study. *Ann Oncol*. 2005;16(5):749–755.
 473. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol*. 2006;24(29):4699–4707.
 474. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001;19(14):3312–3322.
 475. Piccart MJ, Green JA, Lacave AJ, et al. Oxaliplatin or paclitaxel in patients with platinum-pretreated advanced ovarian cancer: a randomized phase II study of the European Organization for Research and Treatment of Cancer Gynecology Group. *J Clin Oncol*. 2000;18(6):1193–1202.
 476. Dizon DS, Dupont J, Anderson S, et al. Treatment of recurrent ovarian cancer: a retrospective analysis of women treated with single-agent carboplatin originally treated with carboplatin and paclitaxel. The Memorial Sloan-Kettering Cancer Center experience. *Gynecol Oncol*. 2003;91(3):584–590.
 477. Gronlund B, Høgdall C, Hansen HH, et al. Results of reinduction therapy with paclitaxel and carboplatin in recurrent epithelial ovarian cancer. *Gynecol Oncol*. 2001;83(1):128–134.
 478. Cantù MG, Buda A, Parma G, et al. Randomized controlled trial of single-agent paclitaxel versus cyclophosphamide, doxorubicin, and cisplatin in patients with recurrent ovarian cancer who responded to first-line platinum-based regimens. *J Clin Oncol*. 2002;20(5):1232–1237.
 479. Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCGI CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs. paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. *Br J Cancer*. 2012;107(4):588–591. doi: 10.1038/bjc.2012.307. Epub 2012 Jul 26.
 480. Schouli J, Meier W, Wimberger P, et al. Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or carboplatin plus pegylated doxorubicin (PLDC): A randomized phase III trial of the NOGGO-AGO-Germany-AGO Austria and GEICO-GCGI intergroup study (HECTOR). 2012 ASCO Annual Meeting Abstract.
 481. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*. 1997;15(6):2183–2193.
 482. Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared

- with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. *J Clin Oncol.* 2007;25(19):2811–2818.
483. Buda A, Floriani I, Rossi R, et al. Randomised controlled trial comparing single agent paclitaxel vs. epidoxorubicin plus paclitaxel in patients with advanced ovarian cancer in early progression after platinum-based chemotherapy: an Italian Collaborative Study from the Mario Negri Institute, Milan, G.O.N.O. (Gruppo Oncologico Nord Ovest) group and I.O.R. (Istituto Oncologico Romagnolo) group. *Br J Cancer.* 2004;90(11):2112–2117.
 484. Lortholary A, Largillier R, Weber B, et al. Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomized phase II trial from Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO). *Ann Oncol.* 2012;23(2):346–352.
 485. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. *J Clin Oncol.* 2010;28(19):3107–3114.
 486. Markman M, Blessing JA, Moore D, et al. Al-tretamine (hexamethylmelamine) in platinum-resistant and platinum-refractory ovarian cancer: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol.* 1998;69(3):226–229.
 487. Markman M, Hakes T, Reichman B, et al. Ifosfamide and mesna in previously treated advanced epithelial ovarian cancer: activity in platinum-resistant disease. *J Clin Oncol.* 1992;10(2):243–248.
 488. Morotti M, Valenzano Menada M, Venturini PL, Mammoliti S, Ferrero S. Pemetrexed disodium in ovarian cancer treatment. *Expert Opin Investig Drugs.* 2012;21(4):437–449.
 489. Kaern J, Baekelandt M, Tropé CG. A phase II study of weekly paclitaxel in platinum and paclitaxel-resistant ovarian cancer patients. *Eur J Gynaecol Oncol.* 2002;23(5):383–389.
 490. Markman M, Hall J, Spitz D, et al. Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. *J Clin Oncol.* 2002;20(9):2365–2369.
 491. Markman M, Zanotti K, Webster K, et al. Phase 2 trial of single agent docetaxel in platinum and paclitaxel-refractory ovarian cancer, fallopian tube cancer, and primary carcinoma of the peritoneum. *Gynecol Oncol.* 2003;91(3):573–576.
 492. Coleman RL, Brady WE, McMeekin DS, et al. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011;122(1):111–115.
 493. Gore M, Oza A, Rustin G, et al. A randomised trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer. *Eur J Cancer.* 2002;38(1):57–63.
 494. Homesley HD, Hall DJ, Martin DA, et al. A dose-escalating study of weekly bolus topotecan in previously treated ovarian cancer patients. *Gynecol Oncol.* 2001;83(2):394–399.
 495. Schouli J, Stengel D, Harter P, et al. Topotecan weekly versus conventional 5-Day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol.* 2011;29(2):242–248.
 496. Herzog TJ, Sill MW, Walker JL, et al. A phase II study of two topotecan regimens evaluated in recurrent platinum-sensitive ovarian, fallopian tube or primary peritoneal cancer: a Gynecologic Oncology Group Study (GOG 146Q). *Gynecol Oncol.* 2011;120(3):454–458.
 497. Markman M, Kennedy A, Webster K, et al. Phase 2 trial of liposomal doxorubicin (40 mg/m²) in platinum/paclitaxel-refractory ovarian and fallopian tube cancers and primary carcinoma of the peritoneum. *Gynecol Oncol.* 2000;78(3 Pt. 1):369–372.
 498. Brewer CA, Blessing JA, Nagourney RA, et al. Cisplatin plus gemcitabine in platinum-refractory ovarian or primary peritoneal cancer: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol.* 2006;103(2):446–450.
 499. Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2007;25(33):5165–5171.
 500. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol.* 2007;25(33):5180–5186. Erratum in: *J Clin Oncol.* 2008;26(10):1773.
 501. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol.* 2008;26(1):76–82.
 502. Kummam S, Oza AM, Fleming GF, et al. Randomized trial of oral cyclophosphamide (C) with or without veliparib (V), an oral poly (ADP-ribose) polymerase (PARP) inhibitor, in patients with recurrent BRCA-positive ovarian, or primary peritoneal or high-grade serous ovarian carcinoma. (Abstract #5020). *ASCO Proc.* 2012.
 503. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: A randomized, double-blind, placebo-controlled Phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30(17):2039–2045.
 504. Pujade-Lauraine E, Hilpert F, Weber B, et al. AURELIA: a randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC) (Abstract #LBA5002[^]). *ASCO Proc.* 2012.
 505. McAlpine JN, Kelly MG, O'Malley DM, et al. Atypical presentations of carboplatin hypersensitivity reactions: characterization and management in patients with gynecologic malignancies. *Gynecol Oncol.* 2006;103(1):288–292.
 506. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol.* 2005;99(2):393–399.
 507. Joly F, Ray-Coquard I, Fabbro M, et al. Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin compared to carboplatin-paclitaxel combination: analysis from the GCG CALYPSO relapsing ovarian cancer trial. *Gynecol Oncol.* 2011;122(2):226–232.
 508. Kurtz JE, Kaminsky MC, Floquet A, et al. Ovarian cancer in elderly patients: carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in late relapse: a Gynecologic Cancer Intergroup (GCG) CALYPSO sub-study. *Ann Oncol.* 2011;22(11):2417–2423.
 509. Kushner DM, Connor JP, Sanchez F, et al. Weekly docetaxel and carboplatin for recurrent ovarian and peritoneal cancer: a phase II trial. *Gynecol Oncol.* 2007;105(2):358–364.
 510. Zheng H, Kavanagh JJ, Hu W, et al. Hormonal therapy in ovarian cancer. *Int J Gynecol Cancer.* 2007;17:325–338.
 511. Rendina GM, Donadio C, Giovannini M. Steroid receptors and prognostic therapy in ovarian endometrioid carcinoma. *Eur J Gynaecol Oncol.* 1982;3:241–246.
 512. Wilailak S, Linasmita V, Srisupundit S. Phase II study of high-dose megestrol acetate in platinum-refractory epithelial ovarian cancer. *Anticancer Drugs.* 2001;12:719–724.
 513. Freedman RS, Saul PB, Edwards CL, et al. Ethinyl estradiol and medroxyprogesterone acetate in patients with epithelial ovarian carcinoma: a phase II study. *Cancer Treat Rep.* 1986;70(3):369–373.
 514. Fromm GL, Freedman RS, Fritsche HA, et al. Sequentially administered ethinyl estradiol and medroxyprogesterone acetate in the treatment of refractory epithelial ovarian carcinoma in patients with positive estrogen receptors. *Cancer.* 1991;68(9):1885–1889.
 515. Perez-Gracia JL, Carrasco EM. Tamoxifen therapy for ovarian cancer in the adjuvant and advanced settings: systematic review of the literature and implications for future research. *Gynecol Oncol.* 2002;84:201–209.
 516. Jager W, Sauerbrei W, Beck E, et al. A randomized comparison of triptorelin and tamoxifen as treatment of progressive ovarian cancer. *Anticancer Res.* 1995;15(6B):2639–2642.
 517. Markman M, Iseminger KA, Hatch KD, et al. Tamoxifen in platinum-refractory ovarian cancer: a Gynecologic Oncology Group Ancillary Report. *Gynecol Oncol.* 1996;62:4–6.
 518. Hurteau JA, Brady MF, Darcy KM, et al. Randomized phase III trial of tamoxifen versus thalidomide in women with biochemical-recurrent-only epithelial ovarian, fallopian tube or primary peritoneal carcinoma after a complete response to first-line platinum/taxane chemotherapy with an evaluation of serum vascular endothelial growth factor (VEGF): A Gynecologic Oncology Group Study. *Gynecol Oncol.* 2010;119(3):444–450.
 519. Engel JB, Schally AV, Buchholz S, et al. Targeted chemotherapy of endometrial, ovarian, and breast cancers with cytotoxic analogs of luteinizing hormone-releasing hormone (LHRH). *Arch Gynecol Oncol.* 2012;286:437–442.
 520. Verschraegen CF, Westphalen S, Hu W, et al. Phase II study of cetrorelix, a luteinizing hormone-releasing hormone antagonist in patients with platinum-resistant ovarian cancer. *Gynecol Oncol.* 2003;90(3):552–559.
 521. Gordon AN, Finkler N, Edwards RP, et al. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. *Int J Gynecol Cancer.* 2005;15(5):785–792.
 522. Schilder RJ, Pathak HB, Lokshin AE, et al. Phase II trial of single agent cetuximab in patients with persistent or recurrent epithelial ovarian or primary peritoneal carcinoma with the potential for dose escalation to rash. *Gynecol Oncol.* 2009;113(1):21–27.
 523. Seiden MV, Burris HA, Matulonis U, et al. A phase II trial of EMD72000 (matuzumab), a humanized anti-EGFR monoclonal antibody, in patients with platinum-resistant ovarian and primary peritoneal malignancies. *Gynecol Oncol.* 2007;104(3):727–731.

524. Gordon AN, Finkler N, Edwards RP, et al. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. *Int J Gynecol Cancer*. 2005;15(5):785–792.
525. Posadas EM, Liel MS, Kwitkowski V, et al. A phase II and pharmacodynamic study of gefitinib in patients with refractory or recurrent epithelial ovarian cancer. *Cancer*. 2007;109(7):1323–1330.
526. Wagner U, du Bois A, Pfisterer J, et al. Gefitinib in combination with tamoxifen in patients with ovarian cancer refractory or resistant to platinum-taxane based therapy—a phase II trial of the AGO Ovarian Cancer Study Group (AGO-OVAR 2.6). *Gynecol Oncol*. 2007;105(1):132–137.
527. Bookman MA, Darcy KM, Clarke-Pearson D, et al. Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: a phase II trial of the Gynecologic Oncology Group. *J Clin Oncol*. 2003;21(2):283–290.
528. Gordon MS, Matei D, Aghajanian C, et al. Clinical activity of pertuzumab (rhuMab 2C4), a HER dimerization inhibitor, in advanced ovarian cancer: potential predictive relationship with tumor HER2 activation status. *J Clin Oncol*. 2006;24(26):4324–4332.
529. Makhija S, Amler LC, Glenn D, et al. Clinical activity of gemcitabine plus pertuzumab in platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. *J Clin Oncol*. 2010;28(7):1215–1223.
530. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011;474:609–615.
531. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol*. 2012;30(4):372–379.
532. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382–1392.
533. Oza AM, Cibula D, Oaknin A, et al. Olaparib plus paclitaxel plus carboplatin (P/C) followed by olaparib maintenance treatment in patients (pts) with platinum-sensitive recurrent serous ovarian cancer (PSR SOC): a randomized, open-label phase II study. *ASCO Proc*. 2012;(Abstract #5001).
534. Penson RT, Moore KN, Fleming GF, et al. A phase II, open-label, multicenter study of IMC-1121B (ramucirumab; RAM) monotherapy in the treatment of persistent or recurrent epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) carcinoma (CP12-0711/NCT00721162). *ASCO Proc*. 2012;(Abstract #5012).
535. Karlan BY, Oza AM, Richardson GE, et al. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer. *J Clin Oncol*. 2012;30(4):362–371.
536. Matei D, Sill MW, Lankes HA, et al. Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: a gynecologic oncology group trial. *J Clin Oncol*. 2011;29(1):69–75.
537. Baumann KH, du Bois A, Meier W, et al. A phase II trial (AGO 2.11) in platinum-resistant ovarian cancer: a randomized multicenter trial with sunitinib (SU11248) to evaluate dosage, schedule, tolerability, toxicity, and effectiveness of a multitargeted receptor tyrosine kinase inhibitor monotherapy. *Ann Oncol*. 2012;e pub.
538. Matulonis UA, Berlin S, Ivy P, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. *J Clin Oncol*. 2009;27(33):5601–5606.
539. Friedlander M, Hancock KC, Rischin D, et al. A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. *Gynecol Oncol*. 2010;119(1):32–37.
540. Matulonis U, Tew WP, Matei D, et al. A phase II study of ENMD-2076 in platinum-resistant ovarian cancer. *J Clin Oncol*. 2011;29(suppl; abstr 5021).
541. Buckanovich RJ, Berger R, Sella A, et al. Activity of cabozantinib (XL184) in advanced ovarian cancer patients (pts): Results from a phase II randomized discontinuation trial (RDT). *J Clin Oncol*. 2011;29(suppl; abstr 5008).
542. Shao M, Hollar S, Chambliss D, et al. Targeting the insulin growth factor and the vascular endothelial growth factor pathways in ovarian cancer. *Mol Cancer Ther*. 2012;11:1576–1586.
543. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003;348:203–213.
544. Berek J, Taylor P, McGuire W, Smith LM, Schultes B, Nicodemus CF. Oregovomab maintenance monoimmunotherapy does not improve outcomes in advanced ovarian cancer. *J Clin Oncol*. 2009;27(3):418–425.
545. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455–2465.
546. Westin SN, Herzog TJ, Coleman RL. Investigational agents in development for the treatment of ovarian cancer. *Invest New Drugs*. e pub June 4, 2012.
547. Naumann RW, Coleman RL, Burger RA, et al. PRECEDENT: A randomized phase II trial comparing EC145 and pegylated liposomal doxorubicin (PLD) in combination, versus PLD alone, in subjects with platinum-resistant ovarian cancer. *J Clin Oncol*. 2011;29 (suppl; abstr 5045).
548. Wei SH, Chen CM, Strathdee G, et al. Methylation microarray analysis of late-stage ovarian carcinomas distinguishes progression-free survival in patients and identifies candidate epigenetic markers. *Clin Cancer Res*. 2002;8:2246–2252.
549. Matei D, Fang F, Shen C, et al. Epigenetic resensitization to platinum in ovarian cancer. *Cancer Res*. 2012;72:2197–2205.
550. Vergote IB, Vergote-De Vos LN, Abeler VM, et al. Randomized trial comparing cisplatin with radioactive phosphorus or whole-abdomen irradiation as adjuvant treatment of ovarian cancer. *Cancer*. 1992;69:741–749.
551. Bolis G, Colombo N, Pecorelli S, et al. Adjuvant treatment for early epithelial ovarian cancer: results of two randomised clinical trials comparing cisplatin to no further treatment or chromic phosphate (³²P). GICO: Gruppo Interregionale Collaborativo in Ginecologia Oncologica. *Ann Oncol*. 1995;6:887–893.
552. Trope C, Kaern J, Hogberg T, et al. Randomized study on adjuvant chemotherapy in stage I high-risk ovarian cancer with evaluation of DNA-ploidy as prognostic instrument. *Ann Oncol*. 2000;11:281–288.
553. Young RC, Brady ME, Nieberg RK, et al. Adjuvant treatment for early epithelial ovarian cancer: a randomized phase III trial of intraperitoneal 32P or intravenous cyclophosphamide and cisplatin—a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21:4350–4355.
554. Bolis G, Scarfone G, Giardina G, et al. Carboplatin alone vs carboplatin plus epidoxorubicin as second-line therapy for cisplatin- or carboplatin-sensitive ovarian cancer. *Gynecol Oncol*. 2001;81(1):3–9.
555. Cantù MG, Buda A, Parma G, et al. Randomized controlled trial of single-agent paclitaxel versus cyclophosphamide, doxorubicin, and cisplatin in patients with recurrent ovarian cancer who responded to first-line platinum-based regimens. *J Clin Oncol*. 2002;20(5):1232–1237.
556. Alberts DS, Liu PY, Wilczynski SP, et al. Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). *Gynecol Oncol*. 2008;108(1):90–94.
557. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol*. 2010;28(20):3323–3329.
558. Gotlieb WH, Amant F, Advani S, et al. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Oncol*. 2010;13:154–62.
559. Shimzu Y, Kamoi S, universal S, et al. Toward the development of a universal grading system for ovarian epithelial carcinoma. I. Prognostic significance of histopathological features: problems involved in the architectural grading system. *Gynecol Oncol*. 1998;70:2–12.
560. Farley J, Brady WE, Vathipadiekal V, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. *Lancet Oncol*. Dec 20, 2012. [Epub ahead of print].
561. International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet*. 2002 Aug 17;360(9332):505–15.

INTRODUCTION

Significant improvement in the management of ovarian germ cell tumors (OGCT) has been achieved during the past 3 decades. The development of more effective chemotherapy regimens is the leading cause for improved outcome in this rare group of patients. Other advancements in the field include the development of a more precise surgical staging system, improved radiographic imaging, more sophisticated pathology techniques, as well as improved supportive care and symptom control that has enabled safe delivery of treatment. A substantial majority of patients with OGCT are long-term survivors and suffer minimal morbidity from treatment. Fertility-sparing surgical procedures enable young women with OGCT to preserve their reproductive potential. These positive results in clinical outcome reflect a collaborative effort between different specialties (surgery, medical oncology, pathology, and radiology).

PATHOLOGY

The current World Health Organization (WHO) classification of OGCTs includes dysgerminoma, yolk sac tumor, embryonal carcinoma, polyembryoma, nongestational choriocarcinoma, mixed germ cell tumors, and teratomas (immature, mature, and monodermal types) (1). Primitive germ cell tumors account for 2% to 3% of all ovarian cancers and occur usually in young women. The peak age incidence for development of these tumors is the early twenties. The pathology of these neoplasms is discussed here in the same order as the listing in the current WHO classification.

Dysgerminoma

Dysgerminoma represents the most common ovarian malignant germ cell tumor (2). Most dysgerminomas are seen in patients with a normal karyotype, but it is the most frequent ovarian neoplasm in patients with gonadal dysgenesis. About 5% to 10% are associated with gonadoblastomas in sexually maldeveloped patients. Most dysgerminomas occur in normal females who usually present with abdominal enlargement, a mass, or pain due to torsion. About 10% of dysgerminomas are bilateral on gross examination and another 10% have microscopic involvement of the contralateral ovary. Association with gonadoblastoma increases the risk of bilateral involvement by dysgerminoma.

On gross examination, dysgerminomas are usually large, white to gray, fleshy lobulated masses that have no more than

very focal areas of hemorrhage or necrosis on cut section. Abundant hemorrhage, necrosis, or cystic areas in a well-fixed tumor should raise the question of a mixed germ cell tumor. Microscopically, dysgerminomas display nests and cords of primitive-appearing germ cells with clear to eosinophilic cytoplasm and prominent cytoplasmic borders (Fig. 25.1). Nuclei are enlarged but they are not pleomorphic. Mitoses may be numerous, and the number of mitotic figures does not have any therapeutic or prognostic significance. Nests of tumor cells are separated by fibrous trabeculae that contain lymphocytes and, sometimes, granulomas. Syncytiotrophoblast cells are present in about 3% of dysgerminomas.

Dysgerminomas contain cytoplasmic glycogen that can be demonstrated with periodic acid Schiff (PAS) stain. These tumors display diffuse staining for placenta-like alkaline phosphatase (PLAP), usually with accentuation of the cytoplasmic membrane. Positive staining for c-kit (3) and the nuclear transcription factor OCT 3/4 (4) are helpful in confirming this diagnosis, dysgerminoma being the only OGCT that displays c-kit staining (5). Approximately one-third of dysgerminomas harbor c-kit amplifications or activating mutations, and these molecular alterations correlate with advanced stage (6). Both dysgerminoma and embryonal carcinoma stain for OCT 3/4. In contrast to embryonal carcinoma, dysgerminoma does not stain for CD30. Syncytiotrophoblast cells present in dysgerminomas display human chorionic gonadotropin (HCG) staining. In contrast to choriocarcinoma, the syncytiotrophoblast cells in dysgerminomas are not admixed with cytotrophoblast cells. Dysgerminomas do not produce alpha-fetoprotein (AFP), a finding that may be helpful in distinguishing them from the solid variant of yolk sac tumor. Optimal and prompt fixation of the surgical specimen facilitates the correct diagnosis. Poor fixation can result in artifacts that mimic embryonal carcinoma and yolk sac tumor histology.

Yolk Sac Tumor

Yolk sac tumor (endodermal sinus tumor) is the second most common OGCT, accounting for 22% of cases studied at the Armed Forces Institute of Pathology (AFIP) (2,7). These tumors grow very rapidly, often becoming clinically evident in less than 1 month.

Ovarian yolk sac tumors are typically large and unilateral, although metastasis to the opposite ovary may occur. These tumors have a smooth external surface unless rupture or invasion into surrounding structures has occurred. On cut section, these neoplasms are tan to gray, with abundant hemorrhage and necrosis. They may be partially solid, but they usually contain cysts that vary in size from a few millimeters to several centimeters in diameter. The cut surface appears mucoid, slimy,

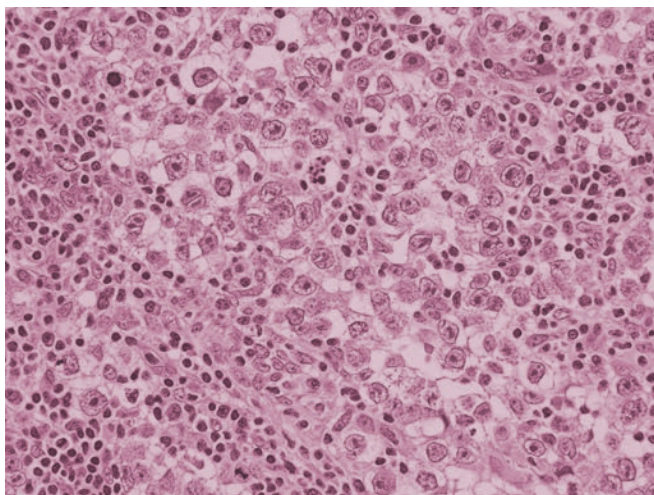


FIGURE 25.1. Dysgerminoma. This neoplasm has nests of cells with clear cytoplasm and enlarged hyperchromatic nuclei. Fibrous septae containing lymphocytes separate nests of tumor.

or gelatinous. Yolk sac tumor (7) display many different histologic patterns (8). The most common microscopic pattern in primary ovarian tumors is the reticular or microcystic pattern (Fig. 25.2). The tumor has a mesh-like pattern and it displays a network of flattened or cuboidal epithelial cells with varying degrees of atypia. The endodermal sinus (festoon) pattern contains Schiller-Duval bodies (Fig. 25.3) that have a central capillary surrounded by connective tissue and a peripheral layer of columnar cells. These structures are situated in cavities lined by yolk sac tumor cells. When present, Schiller-Duval bodies are diagnostic of yolk sac tumor. Other less common variants of yolk sac tumor include hepatoid, polyvesicular vitelline, enteric, endometrioid, solid, parietal, and mesenchymal patterns. Most patterns of yolk sac tumor may contain eosinophilic hyaline globules that are PAS positive and diastase resistant. These globules may be seen in non-germ cell tumors and they are not specific for yolk sac tumor. They do not contain AFP. Yolk sac tumors generally display cytoplasmic staining for cytokeratin and AFP, although the parietal pattern of yolk sac tumor typically does not contain AFP. Therefore, serum AFP is a useful marker for yolk sac tumor, although a negative serum AFP

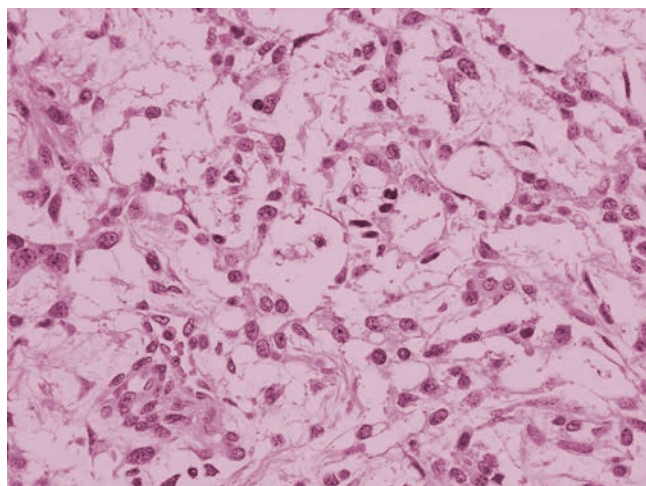


FIGURE 25.2. Reticular pattern of yolk sac tumor. There is a mesh-like arrangement of cuboidal tumor cells.

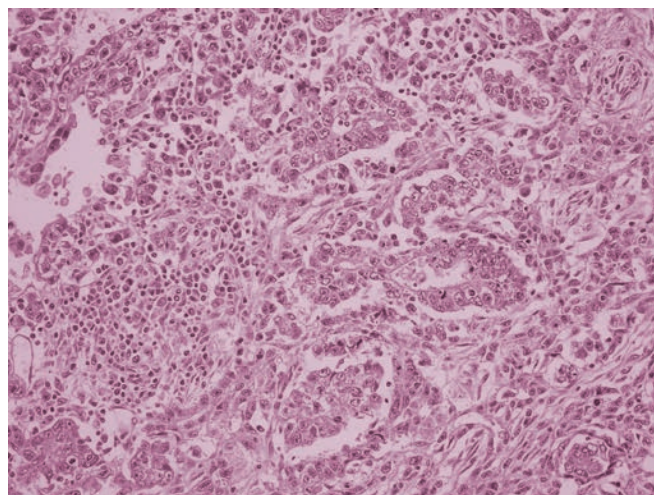


FIGURE 25.3. Schiller-Duval bodies, papillary structures with central blood vessels, are seen in the endodermal sinus pattern of yolk sac tumor.

does not exclude the disease. Chemotherapy has resulted in the appearance of AFP-negative parietal yolk sac tumor after eradication of AFP-positive patterns of the tumor (9). Enteric glands in yolk sac tumor may be carcinoembryonic antigen (CEA)-positive. Some types of yolk sac tumor need to be differentiated from endometrioid and clear cell tumors of the ovary. Germ cell tumors usually occur in younger patients than epithelial ovarian tumors, but the lack of staining for cytokeratin 7 and epithelial membrane antigen supports a diagnosis of yolk sac tumor (10) in controversial neoplasms.

Embryonal Carcinoma

Embryonal carcinoma is rarely seen in the ovary, in contrast to its frequent occurrence in the testis. Only 14 cases were identified during a period of 30 years at the AFIP (11), and there have been no recent large series of these tumors. Embryonal carcinoma of the ovary is usually associated with yolk sac tumor in mixed germ cell tumors. On gross examination, embryonal carcinoma characteristically displays areas of hemorrhage and necrosis. Microscopically, this tumor is composed of very crowded cells that display overlapping nuclei in paraffin sections. The nuclei are very pleomorphic and they contain large, prominent nucleoli. The mitotic rate is high in these tumors. Glandular, solid, and papillary patterns may be seen. Vascular invasion is common. Embryonal carcinoma stains positively for PLAP, pan-cytokeratin (AE1/AE3 and CAM 5.2), CD30, and OCT3/4. In contrast to seminoma, embryonal carcinoma does not display c-kit staining. Some embryonal carcinomas display focal AFP positivity that may represent partial transformation to yolk sac tumor. Syncytiotrophoblast cells may be present. They produce hCG, but they are not accompanied by admixed cytotrophoblast cells unless choriocarcinoma is also present.

Polyembryoma

Polyembryoma is a very rare malignant ovarian tumor (2). In the few cases reported, the embryoid bodies characteristic of this germ cell tumor have coexisted with other germ cell tumor types. The microscopic appearance of embryoid bodies (12), with an embryonic disc separating a yolk sac and an amniotic cavity, may actually be due to an admixture of yolk sac tumor and embryonal carcinoma.

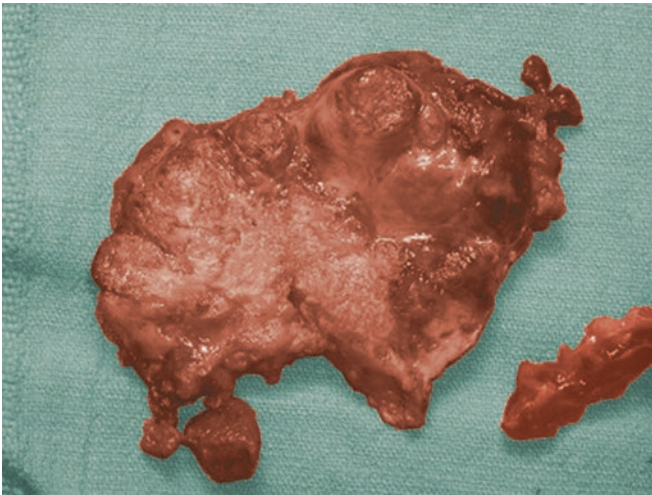


FIGURE 25.4. Choriocarcinoma. This ovarian neoplasm is extremely hemorrhagic.

Choriocarcinoma

Primary nongestational ovarian choriocarcinoma is rare (13). It is most often seen as a component of mixed germ cell tumors of the ovary (14,15). Choriocarcinomas display abundant hemorrhage and necrosis on gross examination (Fig. 25.4). Microscopically, these neoplasms show a plexiform pattern composed of an admixture of syncytiotrophoblast and cytotrophoblast cells (Fig. 25.5). Syncytiotrophoblastic giant cells have abundant eosinophilic to amphophilic cytoplasm that contains multiple atypical, hyperchromatic nuclei. Cytotrophoblast cells are round and often have well-defined cell borders, clear to lightly eosinophilic cytoplasm, and single, atypical nuclei. Numerous mitoses are present. Choriocarcinoma spreads by blood vessel invasion that is easy to identify in these tumors. Cytotrophoblast cells do not produce hCG. Syncytiotrophoblast cells are formed from cytotrophoblast cells, and syncytiotrophoblast does produce hCG. Choriocarcinoma may also stain for cytokeratins, epithelial membrane antigen, and carcinoembryonic antigen. Nongestational choriocarcinoma must be distinguished

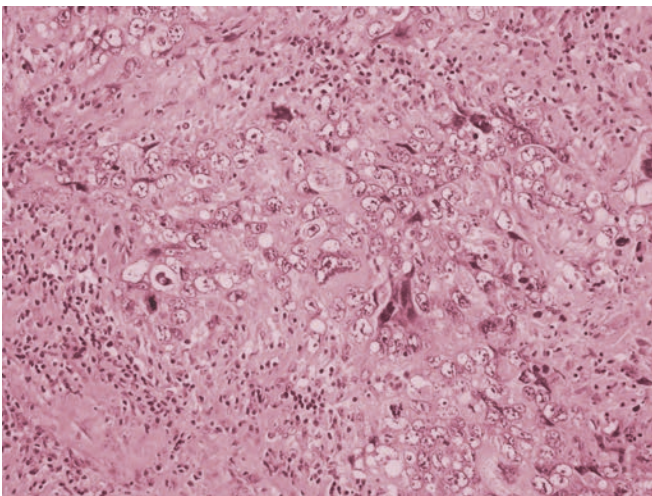


FIGURE 25.5. Choriocarcinoma. Syncytiotrophoblastic cells have dark cytoplasm and multiple atypical nuclei. Cytotrophoblastic cells have lighter cytoplasm and single atypical nuclei. Both cell types are admixed in choriocarcinoma. Areas of hemorrhage and necrosis are common.

from gestational choriocarcinoma because the former has a worse prognosis and requires more aggressive therapy. Identification of paternal genetic material indicates that the tumor is of gestational origin (16).

Mixed Germ Cell Tumors

Mixed germ cell tumors of the ovary contain 2 or more different types of germ cell neoplasm, either intimately admixed or as separate foci within the tumor (14,15). They are much less common in the ovary than in the testis. They accounted for only 8% of malignant ovarian germ cell tumors accessioned at the AFIP over a period of 30 years (14).

Malignant mixed germ cell tumors are large, unilateral neoplasms, but the gross appearance on the cut surface depends on the particular types of germ cell tumor present. The most common germ cell tumor element in the AFIP series was dysgerminoma (80%), followed by yolk sac tumor (70%), teratoma (53%), choriocarcinoma (20%), and embryonal carcinoma (13%) (14). The most frequent combination has been dysgerminoma and yolk sac tumor. Syncytiotrophoblast may occur either as a component of choriocarcinoma or as isolated cells in other germ cell tumor elements. The diagnosis and prognosis of malignant mixed germ cell tumors depend on adequate tumor sampling to detect small areas of different types of germ cell tumor. Thorough sampling is essential because the types of tumor identified may affect therapy and prognosis.

Teratomas

Teratomas are germ cell tumors that contain tissue derived from 2 or 3 embryonic layers. Teratomas are subclassified according to whether the tumor elements represent mature or immature tissue types. In addition, monodermal and highly specialized teratomas are composed of a predominance of one tissue type such as thyroid tissue (struma ovarii). This discussion of the pathology of ovarian tumors will address predominantly mature and immature teratomas in adult women. In contrast to other ovarian germ cell tumor types, ovarian teratomas do not contain 12p amplification (17,18). Ovarian teratomas apparently arise by parthenogenesis.

Most teratomas are mature cystic teratomas that contain differentiated tissue components such as skin, cartilage, glia, glandular elements, and bone. Any tissue type present in adults may be represented in teratomas. The widest variety of tissue types is characteristically identified in a nodule in the wall of the cystic neoplasms. Mature cystic teratomas represent benign neoplasms unless they contain a somatic malignancy such as squamous carcinoma, papillary thyroid carcinoma, or other non-germ cell tumors arising in differentiated elements of the teratoma.

Immature teratomas in adult women, in contrast to mature cystic teratomas, are uncommon tumors. They represent about 3% of all ovarian teratomas, but immature teratomas are the third most common form of malignant ovarian germ cell tumors. Very limited amounts of immature tissue occurring in mature cystic teratomas do not seem to alter the prognosis of those tumors (19), but immature tissue in solid teratomas represents a malignant tumor that can disseminate and metastasize.

Most immature ovarian teratomas are unilateral neoplasms, although they can metastasize to the opposite ovary and they can also be associated with mature teratoma in the opposite ovary. Immature teratomas are predominantly solid tumors, but they may contain some cystic areas. The cut surface of immature teratomas is soft and fleshy or encephaloid in appearance (Fig. 25.6). Areas of hemorrhage and necrosis are common. Microscopically, these tumors contain a variety of mature and immature tissue components. The immature elements almost

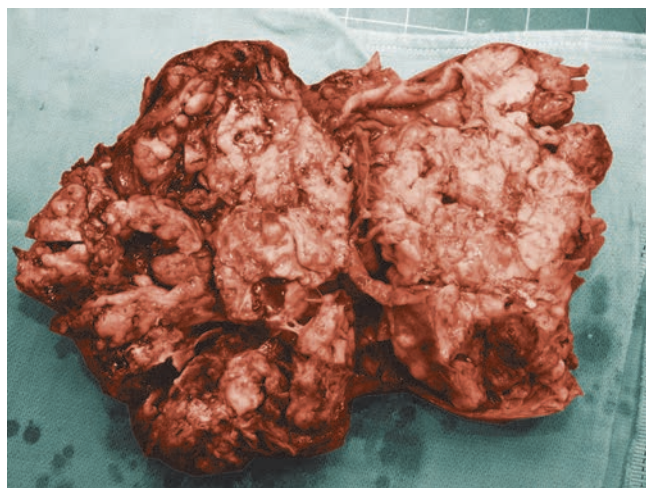


FIGURE 25.6. Ovarian immature teratoma. The neoplasm is predominantly solid and has a soft, encephaloid appearance.

always consist of immature neural tissue in the form of small round blue cells focally organized into rosettes and tubules (Fig. 25.7). There is a correlation between disease prognosis and the degree of immaturity in the teratoma. The 3-tiered grading system is still the one most often used (20). Grade 1 neoplasms display some immaturity, but the immature neural tissue does not exceed, in aggregate, the area of one low-power field (40X) in any slide. Grade 2 teratomas contain more immaturity, but immature neural tissue occupies no more than an area equal to 3 low-power fields in any slide. Grade 3 neoplasms contain immature neural tissue that occupies an area greater than 3 low-power fields in at least one slide (21). Mature tissue is easily identified in grade 1 tumors. It is present to a lesser extent in grade 2 neoplasms and may be absent altogether in grade 3 immature teratomas. The amount of mitotic activity and immature neural tissue with rosettes and tubules also increases with increasing tumor grade. Some authors prefer classifying immature teratomas as either low (grade 1) or high (grades 2 and 3) grade teratomas. In patients whose neoplasm has disseminated beyond the ovary, the grade of the tumor metastasis is important in predicting survival and determining treatment. Occasionally, patients may have peritoneal implants that contain only mature

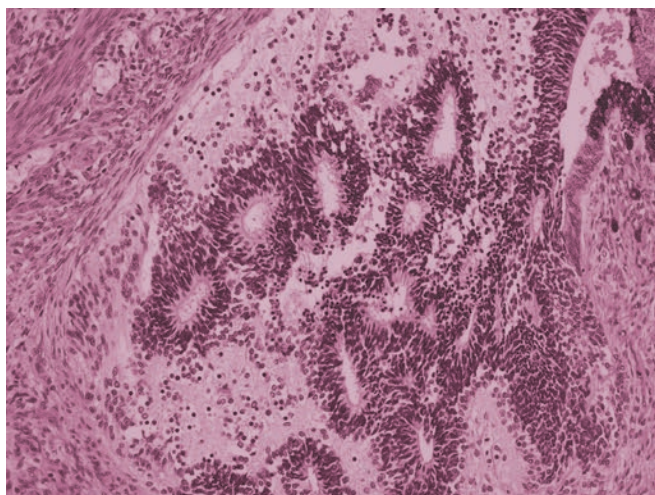


FIGURE 25.7. Ovarian immature teratoma. Immature neural tissue forms tubules.

tissue, but these mature glial implants may represent host tissue and not actual tumor implants (22). It is extremely important to sample peritoneal disease thoroughly in order to identify foci of immature teratoma.

A rare, but distinct entity deserves mention. The **poorly differentiated small cell carcinoma of the ovary**, classically associated with hypercalcemia (23) may have germ cell origin, as suggested by immunostaining for α -1-antitrypsin, presence of PAS-positive intracellular globules, presence of foci of intercellular basement membrane material, and focal laminin immunoreactivity (24). Microscopically, the small cell carcinoma of the ovary has similar features to that of the lung. Neuroendocrine differentiation is present with typical growth pattern, evidence of secretory granules, and expression of neuroendocrine markers; synaptophysin and chromogranin (25). These tumors occur usually in young women and are invariably associated with a dismal prognosis (26,27). Rapidly enlarging abdominal or pelvic mass is a common manifestation. Hypercalcemia is present in two-thirds of cases and small cell carcinoma is the most common cause of ovarian tumor-associated hypercalcemia. Because of its aggressive course, some women have symptoms of overt metastatic disease at presentation. Treatment with germ cell type chemotherapy regimen is probably justified, although data are scant and inconclusive, given the rarity of such tumors.

Biologically, ovarian germ cell tumors, like testis cancer, are derived from primordial germ cells, which undergo defective meiosis. Karyotypic abnormalities are common and include aneuploidy or chromosomal rearrangements. In contrast, benign teratomas have a normal karyotype. One report notes chromosomal abnormalities in 7% of mature teratomas (28,29). Analysis of centromeric heteromorphism suggests that 65% to 70% of benign teratomas result from a post-meiosis I type error (homozygotes), while the remaining 30% to 35% are caused by defective meiosis I, as demonstrated by heterozygosity of centromeric markers (28). Among malignant ovarian germ cell tumors, aneuploidy and chromosomal translocations or truncations similar to those encountered in testicular carcinoma have been widely reported (30,31). The presence of an isochromosome 12p (i12p) has been noted in ovarian tumors (32), albeit less commonly than in testis cancer. Other chromosomal aberrations such as loss or gain in chromosomes 1, 11, 12, 16, and X can be identified (33). The association between dysgerminoma and dysgenetic gonads (34) is well recognized and should be managed accordingly, as will be discussed.

Clinical Features

Malignant germ cell tumors of the ovary occur mainly in girls and young women.

In the University of Texas M.D. Anderson Cancer Center (UTMDACC) series, the age of the patients ranged from 6 to 40 years, with a median age of 16 to 20 years, depending upon histological type (35). There are ethnic and racial differences in the incidence of germ cell tumors, as shown in an analysis based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, with increased incidence of OGCTs among pediatric Black females compared to Black males and among Hispanic girls aged 10 to 19 years, as compared to non-Hispanics (36). Interestingly, a case-cohort study from the Children Oncology Group, including 274 cases (195 OGCTs and 79 testicular cancers), showed that a family history of cancer was inversely correlated with the risk of developing germ cell tumors (37).

Signs and symptoms in these patients are rather consistent. Abdominal pain associated with a palpable pelvic-abdominal mass is present in approximately 85% of patients (15,38,39). Ten percent of patients present with acute abdominal pain,

usually caused by rupture, hemorrhage, or ovarian torsion. This finding is somewhat more common in patients with endodermal sinus tumor or mixed germ cell tumors and is frequently misdiagnosed as acute appendicitis. Less common signs and symptoms include abdominal distention (35%), fever (10%), and vaginal bleeding (10%). A few patients exhibit isosexual precocity, presumably due to hCG production by tumor cells.

In a small percentage of cases, ovarian germ cell tumors occur during pregnancy or in the immediate postpartum period (38). In the series reported by Gordon, 20 of 158 patients with dysgerminoma were diagnosed during pregnancy or after delivery (40). Nondysgerminomatous ovarian tumors occur less frequently during pregnancy, but rare cases have been reported (41–44). Marked increase in AFP heralds the presence of a germ cell tumor with yolk sac component. By and large, patients with ovarian tumors diagnosed during pregnancy can be treated successfully, without compromising the health of the fetus. Surgical resection of tumors and chemotherapy have been performed safely in mid and third trimesters. However, rapid disease progression and/or pregnancy termination/miscarriage have been recorded, especially for nondysgerminomatous tumors (45).

Many germ cell tumors possess the unique property of producing biologic markers that are detectable in serum. The development of specific and sensitive radioimmunoassay techniques to measure hCG and AFP led to dramatic improvements in patient monitoring. Serial measurements of serum markers aid the diagnosis and, more importantly, are useful for monitoring response to treatment and detection of subclinical recurrences. Table 25.1 illustrates typical findings in the sera of patients with various tumor histologic types. Endodermal sinus tumor and choriocarcinoma are prototypes for AFP and hCG production, respectively. Embryonal carcinoma can secrete both hCG and AFP, but most commonly produces hCG. Mixed tumors may produce either, both, or none of the markers, depending on the type and quantity of elements present. Dysgerminoma is commonly devoid of hormonal production, although a small percentage of tumors produces low levels of hCG, if multinucleated syncytiotrophoblastic giant cells are present. The presence of an elevated level of AFP or high level of hCG (>100 Units/mL) denotes the presence of tumor elements other than dysgerminoma. Therapy should be adjusted accordingly (see below). Although immature teratomas are associated with negative markers, a few tumors can produce AFP. A third tumor marker is lactic dehydrogenase (LDH), which is frequently elevated in patients with dysgerminoma or other germ cell tumors. Unfortunately, it is less specific than hCG or AFP, which limits its usefulness. CA-125 also can be nonspecifically elevated in patients with ovarian germ cell tumors (46). Age over 45 years, stage

greater than I, and yolk sac tumor histology have been identified as prognostic factors that affect survival (47).

SURGERY

Operative Findings

Malignant germ cell tumors of the ovary tend to be quite large. In the UTMDACC series, these tumors ranged in size from 7 to 40 cm, with a median size of 16 cm (15). Predominance of right-sided over left-sided involvement was noted. Bilaterality of tumor involvement (especially true stage IB disease) is exceedingly rare, except for dysgerminoma. Bilateral involvement occurs in 10% to 15% of dysgerminoma patients (40,48–51). For nondysgerminomatous tumors, bilateral involvement signifies either advanced disease with metastatic spread to the contralateral ovary or the presence of a mixed germ cell tumor with prominent dysgerminoma component.

Ascites may be noted in approximately 20% of cases. Rupture of tumors, either preoperatively or intraoperatively, can occur in approximately 20% of cases. Torsion of the ovarian pedicle was documented in 5% of patients in the UTMDACC series.

Benign cystic teratoma is associated with malignant germ cell tumors in 5% to 10% of cases. These coexistent teratomas may occur in the ipsilateral ovary, in the contralateral ovary, or bilaterally. Likewise, a preexisting gonadoblastoma may be noted in association with dysgerminoma and dysgenetic gonads related to a 46,XY karyotype (34,52–54).

Malignant germ cell tumors generally spread in 1 of 2 ways: along the peritoneal surface or through lymphatic dissemination. Although the relative frequency of these 2 principal mechanisms is difficult to discern, it is generally accepted that these neoplasms more commonly metastasize to lymph nodes than epithelial tumors. The high prevalence of inadequate staging procedures makes the true incidence of lymph node involvement uncertain. It is our impression that although still uncommon, malignant germ cell tumors have a somewhat greater predilection than epithelial tumors to metastasize hematogenously to parenchyma of liver or lung. The stage distribution is also very different from that of epithelial tumors. In most large series, approximately 60% to 70% of tumors will be stage I (40). The next most common stage is III, accounting for 25% to 30% of tumors. Stages II and IV are relatively uncommon.

Extent of Primary Surgery

The initial treatment approach for a patient suspected of having a malignant ovarian germ cell tumor is surgery, both for diagnosis and for therapy. After an adequate vertical midline incision, a thorough determination of the disease extent by inspection and palpation should be made. If the disease is confined to one or both ovaries, it is imperative that proper staging biopsies be performed (see below).

The type of primary operative procedure depends upon the surgical findings. Because many of these patients are young women, for whom preservation of fertility is a priority, minimizing the surgical resection while ensuring removal of tumor bulk must be thoughtfully balanced. As noted previously, bilateral ovarian involvement is rare, except for the case of pure dysgerminoma. Bilateral involvement may be found in cases of advanced disease (stages II–IV), in which there is metastasis from one ovary to the opposite gonad, or in cases of mixed germ cell tumors with dysgerminoma component. Therefore, fertility-sparing unilateral salpingo-oophorectomy with preservation of the contralateral ovary and of the uterus can be performed in

Table 25.1 Serum Tumor Markers in Malignant Germ Cell Tumors of the Ovary

Histology	AFP	hCG
Dysgerminoma	–	±
Endodermal sinus tumor	+	–
Immature teratoma	±	–
Mixed germ cell tumor	±	±
Choriocarcinoma	–	+
Embryonal carcinoma	±	+
Polyembryoma	±	+

most patients (55–57). If the contralateral ovary appears grossly normal on careful inspection, it should be left undisturbed. However, in the case of pure dysgerminoma, biopsy may be considered, because occult or microscopic tumor involvement occurs in a small percentage of patients. Unnecessary biopsy, however, may result in future infertility due to peritoneal adhesions or ovarian failure. If the contralateral ovary appears abnormally enlarged, a biopsy or ovarian cystectomy should be performed. If frozen examination reveals a dysgenetic gonad, or if there are clinical indications suggesting a hermaphrodite phenotype, then bilateral salpingo-oophorectomy is indicated. However, it is difficult to establish this diagnosis on frozen section. This determination should preferably be made by determining a normal female karyotype preoperatively. If benign cystic teratoma is found in the contralateral ovary, an event that can occur in 5% to 10% of patients, then ovarian cystectomy with preservation of remaining normal ovarian tissue is recommended.

An important problem, albeit rare, is bilateral gonadal involvement in a patient who desires to preserve fertility and who is a candidate for postoperative chemotherapy. There are no data regarding the ability of chemotherapy to eradicate a primary ovarian tumor. In testis cancer, there are presumptive data suggesting that tumor may persist after chemotherapy in the gonad and that the testis may be a drug sanctuary. In exceptional situations, it may be reasonable to preserve an involved ovary in a patient who will be receiving chemotherapy. However, it is conceivable that ovarian preservation could increase the risk for recurrence in these selected cases. The decision to preserve an involved ovary is difficult and must be made carefully considering patient's wishes.

The advent of *in vitro* fertilization technology also has an impact on operative management (58). Convention has dictated that if a bilateral salpingo-oophorectomy is necessary, a hysterectomy should also be performed. However, with current assisted reproduction technologies (ART) involving donor oocyte and hormonal support, a woman without ovaries could potentially sustain a normal intrauterine pregnancy. Similarly, if the uterus and one ovary are resected because of tumor involvement, current techniques provide the opportunity for oocyte retrieval from the remaining ovary, *in vitro* fertilization with sperm from her male partner, and embryo implantation into a surrogate's uterus. As the field of ARTs is evolving, traditional guidelines concerning surgical treatment in young patients with gynecologic tumors have to be thoughtfully adapted to individual circumstances.

Surgical Staging

Surgical staging information is essential for determining extent of disease, providing prognostic information, and guiding postoperative management. A meticulous approach is important for every patient, but is of critical importance for those patients with early clinical disease to detect the presence of occult or microscopic metastases. Staging of ovarian germ cell tumors follows the same principles applicable to epithelial ovarian tumors, as described by the International Federation of Gynecologists and Obstetricians (FIGO); see Table 25.2. Proper staging procedures consist of the following:

1. Although a transverse incision is cosmetically superior, a vertical midline incision is usually necessary for adequate exposure, appropriate staging biopsies, and resection of large pelvic tumors or metastatic disease in the upper abdomen.
2. Ascites, if present, should be evacuated and submitted for cytologic analysis. If no peritoneal fluid is noted, cytologic washings of the pelvis and bilateral paracolic gutters should be performed prior to manipulation of the intraperitoneal contents.

Table 25.2 FIGO Staging of Ovarian Germ Cell Tumors

Stage	Description
I	Tumor limited to ovaries.
IA	Tumor limited to one ovary, no ascites, intact capsule.
IB	Tumor limited to both ovaries, no ascites, intact capsule.
IC	Tumor either stage IA or IB, but with ascites present containing malignant cells or with ovarian capsule involvement or rupture or with positive peritoneal washings.
II	Tumor involving one or both ovaries with extension to the pelvis.
IIA	Extension to uterus or tubes.
IIB	Involvement of both ovaries with pelvic extension.
IIC	Tumor either stage IIA or IIB, but with ascites present containing malignant cells or with ovarian capsule involvement or rupture or with positive peritoneal washings.
III	Tumor involving one or both ovaries with tumor implants outside the pelvis or with positive retroperitoneal or inguinal lymph nodes. Superficial liver metastases qualify as stage III.
IIIA	Tumor limited to the pelvis with negative nodes but with microscopic seeding of the abdominal peritoneal surface.
IIIB	Negative nodes, tumor implants in the abdominal cavity <2 cm.
IIIC	Positive nodes or tumor implants in the abdominal cavity >2 cm.
IV	Distant metastases present.

3. The entire peritoneal cavity and its structures should be carefully inspected and palpated in a methodical manner. We generally prefer to start with the subphrenic spaces and move caudad toward the pelvis. The subdiaphragmatic areas, omentum, colon, all peritoneal surfaces, the entire retroperitoneum, and small intestinal serosa and mesentery should be checked. If any suspicious areas are noted, they should be submitted for biopsy or excised.
4. Next, the primary ovarian tumor and pelvis should be examined. Both ovaries should carefully be assessed for size, presence of obvious tumor involvement, capsular rupture, external excrescences, or adherence to surrounding structures.
5. If disease seems to be limited, that is, confined to the ovary or localized to the pelvis, then random staging biopsies of structures at risk should be performed. These sites should include the omentum (with generous biopsies from multiple areas) and the peritoneal surfaces of the following sites: bilateral paracolic gutters, cul-de-sac, lateral pelvic walls, vesicouterine reflection, and subdiaphragmatic areas. Any adhesions should also be generously sampled.
6. The paraaortic and bilateral pelvic lymph node-bearing areas should be carefully palpated. Any suspicious nodes should be excised or sampled. If no suspicious areas are detected, these areas should be sampled. There is no evidence that a complete paraaortic and/or pelvic lymphadenectomy is advantageous.
7. If obvious gross metastatic disease is present, it should be excised if feasible, or at least sampled to document disease extent. The concept of cytoreductive surgery is discussed below.

The gynecologic literature is replete with examples of inadequate surgical staging. The assumption that surgical staging in the 1990s is superior to that of several years ago may be erroneous. Most patients still undergo initial surgery in community hospitals and are inadequately staged. Upon referral of such a patient to a university or tertiary care center, the oncologist is faced with the dilemma of inadequate staging information. In such cases, postoperative studies including computed tomography of the abdomen are recommended. If histopathologic and limited anatomic information from the first surgery clearly indicates the use of systemic chemotherapy, it is generally inadvisable to consider re-exploration solely for the purpose of precise staging information. Reoperation to complete comprehensive staging may be appropriate under clinical circumstances where careful surveillance observation after complete staging is a sensible alternative to chemotherapy.

Cytoreductive Surgery

If widely spread tumor is encountered at initial surgery, it is recommended that the same principles concerning cytoreductive surgery applied in the surgical management of advanced epithelial ovarian cancer be followed. Specifically, as much tumor as is technically feasible and safe should be resected. However, because of their rarity, there is scant information in the literature on the impact of cytoreductive surgery of malignant germ cell tumors.

In a study of the Gynecologic Oncology Group (GOG), Slayton et al. found that 15 of 54 (28%) patients with completely resected disease at primary surgery failed chemotherapy with a combination of vincristine, dactinomycin, and cyclophosphamide (VAC), as opposed to 15 of 22 (68%) patients with incompletely resected disease treated with the same regimen (59). Furthermore, a higher percentage of patients with bulky postoperative residual disease (82%) failed chemotherapy compared to those with minimal residual disease (55%). In a subsequent GOG study reported by Williams, patients received the combination regimen of cisplatin, vinblastine, and bleomycin (PVB). In this study, patients with nondysgerminomatous tumors and clinically nonmeasurable disease after surgery, had a greater likelihood of remaining progression-free than those with measurable disease (65% vs. 34%) (60). In addition, patients who had been surgically debulked to optimal disease had an outcome intermediate between patients with suboptimal disease and those with optimal disease without debulking.

Even with epithelial tumors, the relative influence of tumor biology, surgical skill, and aggressiveness remains uncertain. Germ cell tumors, especially dysgerminomas, are generally much more chemosensitive than epithelial ovarian tumors. Therefore, aggressive resection of metastatic disease in these cases, especially resection of bulky retroperitoneal nodes, is questionable. The surgeon must exercise thoughtful and mature intraoperative judgment when encountering such situations, carefully weighing the risks of cytoreductive maneuvers in the setting of chemosensitive tumors. There is no substitute for surgical experience and a clear understanding of the biological behavior of these neoplasms. Even in the face of extensive metastatic disease, it is possible to perform a fertility-sparing procedure with preservation of a normal contralateral ovary.

The value of secondary cytoreductive surgery in the management of malignant ovarian germ cell tumors is even less clear than that of primary cytoreductive surgery. Although secondary cytoreduction is of questionable benefit for patients with refractory epithelial ovarian cancer (61,62), germ cell tumors are relatively more chemosensitive than epithelial tumors and more likely to respond to second-line therapy. Therefore, if a patient has an isolated focus of persistent tumor after first-line chemotherapy in an area such as the lung, liver, retroperitoneum, or

brain, then surgical extirpation should be considered before changing chemotherapy regimens. Although this clinical situation is extremely rare, it has been observed in other situations involving chemosensitive tumors, such as gestational trophoblastic disease and testicular cancer.

Unlike testicular cancer, the finding of a residual mass after completion of chemotherapy is less common in patients with ovarian germ cell tumors because these women are likely to have considerable tumor debulking at the time of the diagnostic surgical procedure and thus enter chemotherapy with significantly less tumor burden. At completion of chemotherapy, men with nonseminomatous tumors or seminoma may have persistent mature teratoma or desmoplastic fibrosis. In patients with bulky dysgerminoma, residual masses after chemotherapy are very likely to represent desmoplastic fibrosis. Although a number of patients with pure ovarian immature teratomas or mixed germ cell tumors have persistent mature teratoma at the completion of chemotherapy, as documented by second-look laparotomy (63), the majority are left with multiple small peritoneal implants rather than with a dominant mass. However, it is now recognized that occasional patients who have received chemotherapy for immature teratoma or mixed germ cell tumor containing teratoma will have bulky residual teratoma after chemotherapy. The natural history or biologic implications of this finding are not clear. In testicular cancer, patients with bulky residual teratoma may experience slow progression of tumor (64) or may develop overtly malignant tumors over time (65–68). There are similar anecdotal reports of progressive mature teratoma in ovarian germ cell tumor patients after chemotherapy (69–71). Considering this information, it seems appropriate to resect persistent masses in patients with negative markers after chemotherapy for germ cell tumors containing immature teratoma. If viable neoplasm is found, additional chemotherapy should be considered. However, if only mature teratoma is resected, observation is generally recommended.

Second-Look Laparotomy

Since 1960, second-look laparotomy was included in the routine management of patients with epithelial ovarian cancer to assess disease status after a fixed interval of chemotherapy. It was only natural that such an approach would be extrapolated to the management of patients with malignant ovarian germ cell tumors. In a review of the experience with second-look laparotomy at UTMDACC, findings were negative in 52 of 53 patients (72). The one patient with positive findings at second-look laparotomy had an elevated AFP level prior to surgery, which accurately predicted residual disease. This patient received subsequent chemotherapy with PVB, entering prolonged remission. Of the patients with negative findings, one woman relapsed 9 months after the negative second look surgery and subsequently died. Thirteen patients in this series had biopsy-proven evidence of residual mature teratoma (so-called “chemotherapeutic retroconversion”) at second-look laparotomy; treatment was discontinued in all patients and none developed recurrence. Thus, in this series, second-look surgery did not add prognostic information or alter the therapeutic management of patients. The role of second-look surgery is further obscured in the setting of advancement in imaging techniques (CT scanning, PET, and MRI) and in an era where tumor marker measurements are part of routine care of patients with germ cell tumors.

The GOG experience with second-look laparotomy in ovarian germ cell tumors has been reviewed (63). One hundred seventeen patients enrolled prospectively on 1 of 3 GOG protocols using cisplatin-based chemotherapy after initial surgical staging and cytoreduction (GOG protocols #45, 78, and 90) underwent

second-look surgical procedures. Of these, 45 surgical procedures were performed in patients who received 3 courses of cisplatin, etoposide, and bleomycin (BEP) after complete tumor resection. In this subgroup, 38 patients had negative findings, 2 patients had immature teratoma, and 5 patients had mature teratoma. One of the patients with residual immature teratoma received further chemotherapy and one did not. Both these and the rest of patients were disease-free. One patient with negative second-look surgery findings subsequently relapsed and succumbed to disease. Hence, in the subgroup of patients with completely resected primary ovarian germ cell tumors, the benefit of second-look surgery is nil. In contrast, 72 patients in this series treated with similar chemotherapy had advanced incompletely resected tumor before beginning adjuvant treatment. In this subgroup, 48 patients did not have teratoma elements in their primary tumor. At second-look surgery, 45 patients had no residual tumor and 3 patients displayed persistent endodermal sinus tumor or embryonal carcinoma. All 3 of the latter patients died despite further treatment. Five patients with negative second laparotomies recurred, of which only one was salvaged with chemotherapy. Thus, the value of second look surgery in patients with incompletely resected germ cell tumors, not containing teratoma is arguably minimal. However, in the subgroup of patients with incompletely resected tumors containing teratoma elements (total of 24 patients), second-look surgery had an impact on subsequent management. Of these patients, 16 were found to have mature teratoma at second look, which was bulky or progressive in 7 cases. Four additional patients were found to have residual immature teratoma. Fourteen of the total 16 patients with teratoma and 6 of the 7 women with bulky residual tumor remained disease free after surgical resection. Therefore, while second-look laparotomy is not necessary in patients with tumor completely resected primarily or in those patients with initially incompletely resected tumor not containing teratoma, clinical benefit can be derived in those patients with incompletely resected **primary** tumor that contains elements of teratoma (see Table 25.3).

Advances in imaging technology, including the advent of positron emission tomography (PET scanning) may further obviate the need for surgical re-exploration. While PET scan is sensitive for detecting active (malignant) tumor, its usefulness in evaluating residual mature teratoma is more limited (73–76). A positive PET scan in the setting of a residual mass after treatment is

highly indicative of viable tumor and when used in conjunction with traditional radiographic techniques (CT scan, MRI) and tumor marker determinations, can predict relapses with accuracy (77). A recent series demonstrates that in patients with residual masses after treatment for seminoma, a positive PET scan is strong evidence that the residual mass contains persistent tumor. In contrast, if the PET scan is negative, residual masses are unlikely to contain active tumor. The specificity of the PET scan in this situation was 100%, the sensitivity was 80%, and the positive and negative predictive values were 100% and 95%, respectively (78). Although studies using PET scanning in OGCT are scant (79,80), the concepts are very similar and can be extrapolated from the testis cancer literature.

CHEMOTHERAPY FOR OVARIAN GERM CELL TUMORS

Chemotherapy: From VAC to PEB

One of the great triumphs of cancer treatment in the 1970s and 1980s has been the development of effective chemotherapy for testicular cancer (81,82). The lessons learned from prospective, randomized trials in testicular cancer subsequently have been applied to OGCTs. Presently, the overwhelming majority of patients with ovarian germ cell tumors survive their disease with the judicious use of surgery and cisplatin-based combination chemotherapy. There are many similarities, but a few important differences between testicular cancer and OGCTs.

Historically, the first regimens used successfully for women with OGCTs were VAC (vincristine, dactinomycin, and cyclophosphamide) or VAC-type regimens. Such treatment had curative potential, especially in early-stage disease. However, among patients with advanced disease, the number of long-term survivors after VAC therapy remained under 50%. In the series reported from UTMDACC, although 86% of patients with stage I tumors were cured with VAC, the efficacy of the regimen was significantly lower for patients with advanced disease (35). Only 57% of stage II patients and 50% of patients with stage III achieved long-term control. The 2 patients with stage IV tumors in this series succumbed to disease. Similarly, in a GOG study, only 7 out of 22 patients with incompletely resected OGCTs achieved long-term disease control after VAC, as compared to 39 of 54 patients with completely resected tumors (83). In that report, 11 of 15 patients with stage III and both patients with stage IV disease progressed within 12 months. These data suggest that VAC chemotherapy was insufficient for the treatment of advanced stage and/or incompletely resected OGCTs.

Because of the experience gained from the treatment of testicular germ cell tumors demonstrating the superiority of cisplatin-based regimens, new platinum-based regimens were tested in patients with ovarian germ cell tumors. Gershenson reported the efficacy of PVB in a small series of patients treated at UTMDACC (84). Among 15 patients, 7 received PVB in the adjuvant setting and 9 received the combination at the time of recurrence. Six of 7 patients treated with PVB upfront became long-term survivors. Among them, 3 women had optimally debulked stage III disease.

Subsequently, the PVB combination was evaluated prospectively in GOG protocol #45 (60). In this study, 47 of 89 patients with nondysgerminomatous ovarian tumors (53%) were disease-free with a median follow-up of 52 months. The latest treatment failure occurred at 28 months. Eight other patients had durable remissions with second-line therapy and a few other patients had nonprogressive or slowly progressive immature teratoma. Thus, the 4-year overall survival was approximately 70%. Of note, 29% of patients enrolled in this trial had received prior radiation or chemotherapy, which might

Table 25.3 Results of Second-Look Surgery in Patients Enrolled on GOG Protocols

Primary Surgery	Total Number	Positive Second-Look: Progression-Free/Total Number	Negative Second-Look: Progression-Free/Total Number
Completely resected tumor	45	7/7 ^a	37/38
Incompletely resected tumor	24	16/20 ^b	4/4
Teratoma present Teratoma absent	48	0/3 ^c	41/45

^a Five mature teratomas and 2 immature teratomas.

^b Sixteen mature teratomas and 4 immature teratomas.

^c Three embryonal carcinoma and yolk sac tumors.

Source: Reprinted with permission from Williams SD, Blessing JA, DiSaia PJ, et al. Second-look laparotomy in ovarian germ cell tumors: the Gynecologic Oncology Group experience. *Gynecol Oncol*. 1994;52(3):287–291.

Table 25.4 The BEP Regimen^a

Cisplatin	20 mg/m ² days 1–5
Etoposide (VP-16)	100 mg/m ² days 1–5
Bleomycin	30 units IV weekly

^aThree to 4 courses given at 21-day intervals.

have affected negatively the overall outcome. As discussed previously, patients who were debulked to optimal disease fared better than those who were not. Histological type and marker elevation before treatment were not associated with adverse outcome. However, even among patients with nonmeasurable, and presumably small volume disease, and without prior treatment, 8 of 30 patients treated with PVB ultimately failed.

In testicular cancer, subsequent experience has documented that etoposide is at least equivalent to vinblastine and produces improved survival in patients with high tumor volume (82). Furthermore, the use of etoposide in place of vinblastine led to reduced neurologic toxicity, abdominal pain, and constipation. The latter 2 adverse effects are particularly important for patients with OGCTs, as many would have had recent abdominal surgery. These observations led to the evaluation of the combination of BEP (Table 25.4) in patients with ovarian germ cell tumors. In a series from UTMACC, long-term remissions were recorded in 25 of 26 patients treated with BEP (85). The only patient who succumbed to disease had been noncompliant with treatment, monitoring, and follow-up. In this series, 4 patients with measurable disease after surgery had complete remissions after BEP treatment. This led to a prospective GOG study evaluating BEP in patients with ovarian germ cell tumors (86). The regimen was highly effective, 91 of 93 enrolled patients being free of disease at follow-up. On the basis of these data, although BEP and VAC have not been prospectively compared, BEP emerged as the preferred regimen for patients with OGCTs. The inclusion of cisplatin in the treatment of ovarian tumors resulted indisputably in an improvement in survival and disease control, as shown by the results of GOG studies, as well as by other clinical series (87–89). These results of therapy are summarized in Table 25.5.

Differences in Outcome for Patients with Completely Resected Tumors Versus Advanced Stage Disease

It is clear that several prognostic factors impact the outcome of patients with OGCTs and that there are important differences

between testicular and ovarian germ cell neoplasms. Debulking surgery plays a central role in the management of ovarian tumors, but has a less important role in testicular cancer. In the hands of an experienced surgeon, the majority of women with ovarian tumors are debulked to minimal and often clinically undetectable disease before starting chemotherapy. Therefore, unlike patients with testicular cancer, most women who are candidates for chemotherapy have minimal or no residual disease. However, even in this circumstance, there seems to be little doubt that adjuvant therapy is appropriate in the majority of cases. The anticipated risk of relapse with surgery alone in patients with advanced disease is as high as 75% to 80%. Particularly, patients with embryonal carcinoma, endodermal sinus tumors, and mixed tumors containing these elements are considered to be at very high risk of recurrence without postoperative therapy. This risk can be minimized by the use of adjuvant chemotherapy. In GOG protocol #78, 50 of 51 patients with completely resected OGCTs remained free of disease when 3 cycles of BEP were given adjutantly. Other studies using cisplatin-based therapy have given similar results (Table 25.6). The recommended treatment for most patients (with the exception of patients with grade 1, stage IA immature teratoma, or stage IA dysgerminoma) is adjuvant chemotherapy with 3 courses of BEP. Virtually all patients with early stage or completely resected disease will survive after careful surgical staging and cisplatin-based adjuvant chemotherapy. More recently, clinical series and observations are beginning to suggest that surveillance with careful follow-up after surgery may be an acceptable alternative for carefully selected patients, as discussed below. Given the fact that surgery followed by chemotherapy is curative for most patients, this course of action should be taken only after very careful consideration. Further studies are needed in this area.

In contrast, most clinical series have shown worse clinical outcome for patients with metastatic disease or with incompletely resected tumors (see Table 25.7). Current clinical trials in testicular cancer separate patients with small tumor volume and a resultant excellent prognosis from those with bulky tumor or liver and brain involvement (90). Patients in the former group are usually complete responders to chemotherapy and long-term survivors, whereas only about 50% to 60% of the latter patients are cured. Hence, clinical trials for patients with good prognostic factors investigate shorter or less toxic chemotherapy aiming at minimizing toxicity (91), while preserving efficacy. In contrast, clinical trials for patients with high-risk disease have evaluated more intensive chemotherapy regimens with the goal of improving the likelihood of cure (92,93). For instance, high-dose chemotherapy (HDCT) with stem cell rescue was tested for patients with high-risk testicular cancer in a multi-institutional clinical protocol (ECOG protocol 3894).

Table 25.5 Adjuvant Chemotherapy

Institution	Regimen	Progression-free/Total (%)
GOG (66)	BEP	89/93 (96)
Australia (51)	Multiple	9/10 (90)
Hospital 12 de Octubre (32)	PVB or BEP	9/9 (100)
M.D. Anderson (18)	PVB	4/4 (100)
Instituto Nazionale Tumori (3)	PVB	9/10 (90)
M.D. Anderson (19)	BEP	20/20 (100)

Abbreviations: GOG, Gynecologic Oncology Group; BEP, cisplatin, etoposide, bleomycin; PVB, cisplatin, vinblastine, bleomycin.

Table 25.6 Chemotherapy of Advanced Disease

Institution	Regimen	Progression-Free/Total (%)
GOG (67)	PVB	47/89 (53)
Australia (51)	Multiple	42/46 (91)
Hospital 12 de Octubre (32)	PVB or BEP	15/19 (79)
M.D. Anderson (18)	PVB	7/11 (64)
Instituto Nazionale Tumori (13)	PVB	7/14 (50)
M.D. Anderson (19)	BEP	5/6 (83)

Note: BEP, bleomycin, etoposide, and cisplatin; GOG, Gynecologic Oncology Group; PVB, cisplatin, vinblastine, bleomycin.

Patients considered to have high risk for relapse were randomized to receive 4 cycles of BEP (control arm) versus 2 cycles of BEP followed by HDCT with autologous stem cell rescue in the form of 2 (tandem) courses using carboplatin, etoposide, and cyclophosphamide as a conditioning regimen (experimental arm). The 1-year durable complete response rate was 52% after BEP + HDCT and 48% after BEP alone ($p = 0.53$) (94). The results of the trial disproved the concept that more aggressive chemotherapy in the first-line setting improves outcome of high-risk testicular cancer patients when compared to standard dose BEP (95).

Dependable risk stratification, as the one used for testicular tumors, is not currently in use for OGCTs. The only clinical prognosticators for outcome of OGCTs remain stage at diagnosis and increase in tumor marker levels (96). Whether this reflects an inherent biologic difference between ovarian germ cell tumors and testis cancer or merely an underestimation of tumor volume because of intraperitoneal spread is not clear. In summary, with the exception of patients with grade 1, stage IA immature teratoma, or stage IA dysgerminoma, the available evidence supports that women with OGCT should receive 3 to 4 cycles of BEP chemotherapy after cytoreductive surgery. Therapy courses longer than 4 cycles are not supported, regardless of tumor volume.

Management of Residual or Recurrent Disease

The large majority of patients with OGCTs are cured with surgery and platinum-based chemotherapy. However, a small percentage of patients have persistent or progressive disease during treatment or recur after completion of treatment. Like in testicular cancer, these treatment failures are categorized as platinum-resistant (progression during or within 4 to 6 weeks of completing treatment) or platinum-sensitive (recurrence beyond 6 weeks from platinum-based therapy).

Most recurrences occur within 24 months from primary treatment. In a series from UTMDACC, 42 treatment failures were identified among 160 patients with ovarian germ cell tumors treated between 1970 and 1990 (97). Treatment failure in these patients was attributed to inadequate surgery in 14 patients, inadequate radiation in 5 patients, inadequate chemotherapy in 16 patients (underdosing and noncompliance), treatment-related toxicity in 1 patient, and unidentifiable causes in 6 patients. A significant number of patients included in this series had received VAC-based chemotherapy, which accounted for the higher than expected rate of recurrence.

Given the high curability rate of OGCTs with primary treatment, the management of recurrent disease represents a complex and often difficult issue, and preferably should be performed in a specialized center. Data to guide the management of patients with recurrent OGCTs are scant and largely extrapolated from the clinical experience with testicular cancer. The single most important prognostic factor in patients with testicular cancer is whether or not they are refractory to cisplatin. The likelihood of cure with high-dose salvage therapy in patients who relapse from a complete remission after initial therapy is as high as 60% or more. On the other hand, in patients who are truly cisplatin-refractory, the likelihood of long-term survival and cure is significantly less. However, up to 30% to 40% of these patients can become long-term survivors. Approximately 30% of patients with recurrent platinum-sensitive testicular cancer can be salvaged with second-line chemotherapy (VeIP: vinblastine, ifosfamide, platinum) (92). However, there is now strong evidence that high-dose therapy with carboplatin, etoposide with or without cyclophosphamide or ifosfamide, and stem cell rescue is superior to standard dose salvage therapy for these patients (98,99). Generally, in patients who are not cisplatin-refractory

one course of standard dose therapy, usually cisplatin, vinblastine, and ifosfamide, is given. If an initial response is seen, then 2 subsequent courses of high-dose chemotherapy (carboplatin and etoposide) with stem cell rescue are given (100). A recent report from Indiana University describes this approach among 184 patients with recurrent testicular cancer. At a median follow-up of 48 months, 116 patients were in complete remission. Remarkably, of the subgroup of 40 patients who were platinum refractory, 18 are disease-free after high-dose chemotherapy (101). While this approach has not been prospectively tested in women with recurrent platinum-sensitive OGCTs, because of the small numbers of patients, the concepts are very similar and support the use of high-dose therapy in this setting. Referral to a specialized center for management of recurrent disease is desirable.

Active agents in the setting of recurrence after high-dose chemotherapy include ifosfamide, taxanes, gemcitabine, and oxaliplatin (102–105). In a phase II trial from Indiana University, the combination of gemcitabine and paclitaxel induced objective responses in 10 of 31 patients who had recurred after high-dose chemotherapy. Of those, 5 patients were free of disease 2 years after treatment (105). The combination of gemcitabine and oxaliplatin (GemOx) induced a 46% response rate in a group of 31 patients with recurrent germ cell tumors. Over 60% of these patients were platinum-resistant or refractory (106). Referral for treatment with investigational agents for recurrent, refractory OGCTs is appropriate.

Immediate Toxicity of Chemotherapy

Acute adverse effects of chemotherapy can be substantial and these patients should be treated by physicians experienced in their management. About 25% of patients develop febrile neutropenic episodes during chemotherapy and require hospitalization and broad-spectrum antibiotics (107). Cisplatin can be associated with nephrotoxicity. This can be avoided by ensuring adequate hydration during and immediately after chemotherapy and by avoidance of aminoglycoside antibiotics. Bleomycin can cause pulmonary fibrosis (107). Pulmonary function testing is frequently used to follow these patients. However, the value of carbon monoxide diffusion capacity to predict early lung disease has been challenged (108). The most effective method for monitoring patients with germ cell tumors is careful physical examination of the chest. Findings of early bleomycin lung disease are a lag or diminished expansion of one hemithorax or fine basilar rales that do not clear with cough. These findings can be very subtle but if present immediate discontinuation of bleomycin should be mandated. It is important to note that randomized trials in good prognosis testicular cancer have suggested that bleomycin is an important component of the treatment regimen, particularly if only 3 courses of therapy are given (109,110). Other randomized trials have shown that carboplatin is inferior to cisplatin and cannot be substituted for cisplatin without worsening therapeutic outcome (111,112).

Patients with advanced OGCTs should receive 3 to 4 courses of treatment given in full dose and on schedule. There is presumptive evidence in testicular cancer that the timeliness of chemotherapy may be associated with outcome. Thus, treatment is given regardless of hematological parameters on the scheduled day of treatment. The impact of the hematopoietic growth factors (G-CSF, GM-CSF) on the management of the myelosuppressive complications of this chemotherapy has not been precisely defined. As most patients will not develop neutropenic fever or infection, hematopoietic growth factors are not routinely necessary (113). It is reasonable to use hematopoietic growth factors to avoid dose reductions for patients with previous episodes of neutropenic fever or in unusually ill patients who are at a higher risk of myelosuppressive complications, or those who received

Table 25.7 A Typical Antiemetic Regimen

Granisetron 1 mg IV 30 min prior to cisplatin daily for 5 days

or

Ondanesetron 0.15 mg/kg IV 30 min prior and 4 h after cisplatin daily for 5 days

plus

Dexamethasone 20 mg IV 30 min prior to cisplatin on days 1 and 2

plus

Aprepitant 125 mg PO on day 1 and 80 mg PO on days 2 and 3, prior to cisplatin infusion

prior radiotherapy. Modern antiemetic therapy, an example of which is shown in Table 25.7, has greatly lessened chemotherapy-induced emesis. By following these guidelines and providing supportive care as indicated, virtually all patients can be treated on schedule, in full or nearly full dose. Chemotherapy-related mortality should be less than 1%. Indeed in GOG protocol #78, there were no toxic deaths among 93 patients treated. Late effects of chemotherapy are discussed below.

Immature Teratoma

The situation of patients with immature teratoma (IT) is more complex. Immature teratomas are categorized as grade 1, 2, or 3 depending on the amount of immature neuroepithelium in the tumor, based on Thurlbeck and Scully's system, which was modified by Norris (2). Our current appreciation of recurrence risk in these patients is based on an early study by Norris (3). This report demonstrated that prognosis of patients with IT directly relates to tumor grade. Specifically, only 1 of 14 patients with grade 1 IT recurred, while 13 of 26 patients with grade 2 and 3 tumors recurred. This study set the current standard of care for women with stage I teratoma, which is surveillance for grade 1 immature teratoma and adjuvant chemotherapy with 3 courses of BEP for patients with grade 2 and 3 tumors (4). However, a significant limitation of the Norris report is the probable underestimation of tumor stage. Hence, in the modern era of complete surgical staging of ovarian neoplasms, it might be appropriate to reconsider the role of routine adjuvant therapy in these patients. Obviously, such an approach must be done with great caution, as surgery followed by adjuvant therapy cures virtually all patients with localized high-grade teratoma. However, it is possible that the risk of relapse is sufficiently low in a defined population of well-staged patients, to warrant clinical observation. This could be accomplished with careful follow-up, such that relapsing patients would be diagnosed with small volume tumor and cured with subsequent salvage chemotherapy. While some issues are different in testicular cancer, a deferral of chemotherapy has been shown to be an appropriate therapeutic alternative for resected stage II tumors and clinical stage I disease. Surveillance for stage I ovarian IT is supported by experience from several groups.

First, an Intergroup study of the Pediatric Oncology Group and the Children's Cancer Group reported that surveillance after complete surgical resection in 41 girls with ovarian immature teratoma was sufficient (114,115). Only one recurrence (which was salvaged with BEP) was noted during 24 months of follow-up. Of note is that in this series, 13 patients had grade 2 and 3 IT, and 10 patients had mixed tumors containing IT plus yolk sac tumor (5).

Second, investigators at Mount Vernon and Charing Cross Hospitals in England have observed 15 patients with stage IA tumors after initial surgical treatment (116). Of these, 9 patients had grade 2 or 3 immature teratoma and 6 had elements of endodermal sinus tumor. There were 3 recurrences in this series, 1 of 9 in the pure immature teratoma group and 2 of 6 in the mixed histology group. Two of these patients were salvaged with chemotherapy and one patient died of pulmonary embolus. Of note is that the patient who died became pregnant 4 months after diagnosis and could not be followed adequately due to her pregnancy.

Third, investigators at the University of Milan reported the clinical outcome in a group of 32 patients with pure ovarian IT followed prospectively (117). In this group, 9 patients had grade 2 and 3 stage IA immature teratomas and were treated with surgery and intensive surveillance. Only 2 recurrences were noted in this group. They consisted of 1 case of mature teratoma and 1 case of gliosis. The mature teratoma was resected and the patient with gliosis was followed without treatment. Both patients are alive and well, and never received chemotherapy. Furthermore, among 4 patients with stage IC tumors treated with surgical resection and surveillance, there was one case of gliosis and one recurrence with mature tissue, which was resected (no chemotherapy). All patients are currently free of disease.

When considering these issues, it is important to not overstate the toxicities of adjuvant therapy. In earlier times, chemotherapy-induced emesis was a very significant problem. However, with modern antiemetics such as the 5HT₃ antagonists, emesis is greatly reduced and, while unpleasant, rarely is a major complication of chemotherapy. Acute treatment-related mortality, particularly from bleomycin-related lung disease, is also rare. Nonetheless, chemotherapy is certainly unpleasant, produces universal alopecia, occasionally severe emesis, and has a remote risk of serious acute toxicity and drug-induced mortality. Considering this information, it may be appropriate to consider surveillance with careful follow-up in well-staged adult patients with ovarian stage IA immature teratoma. While this concept is supported by evidence derived from the pediatric literature and 2 small clinical series as discussed, this hypothesis has not been tested prospectively and should be approached with caution.

DYSGERMINOMA

Dysgerminoma is the female equivalent of seminoma. This disease differs from its nondysgerminomatous counterparts in several respects. First, it is more likely to be localized to the ovary at the time of diagnosis (stage I). Bilateral involvement is more common, as is its spread to retroperitoneal lymph nodes. While less relevant now than before the era of modern chemotherapy, dysgerminoma is very sensitive to radiation (40,50,118).

Observation for Stage I Tumors

As many as 75% to 80% of dysgerminoma patients used to be considered stage I at diagnosis (49,119). However, with more precise surgical staging, as done currently, the true figure is probably somewhat less. Traditionally, most of these women received postoperative radiotherapy. Given the fact that pelvic radiotherapy is associated with high incidence of gonadal dysfunction and sterility, an alternative option for low-risk patients who desire to maintain fertility is postsurgical clinical surveillance (120). In a previous era, clinical observation was deemed appropriate for women with tumors less than 10 cm and without contralateral ovarian involvement; while adjuvant radiotherapy was

recommended for larger tumors (121). The size-based distinction was subsequently called into question (119,122). In a series reported by LaPolla et al., 7 of 9 patients with stage IA dysgerminoma followed without postoperative radiotherapy remained disease-free (119). All but 1 had tumors greater than 10 cm. In another report, among 14 patients with stage IA dysgerminoma treated with surveillance, 5 recurred. Of those, 4 patients were salvaged with radiation and 1 was salvaged with radiation followed by chemotherapy. All stage IA patients are alive, free of disease (118). Similarly, Gordon reported that the 5-year survival among 72 patients with stage IA pure dysgerminoma treated conservatively was 95% (40). The recurrence rate in this case series was 17%, with 4 deaths attributable to disease. However, in this series salvage chemotherapy was offered to only 1 patient, which may explain the unfavorable outcomes. A report from Mount Vernon and Charing Cross Hospitals quoted 2 relapses among 9 patients with stage IA dysgerminoma treated with observation. Both were cured with salvage chemotherapy (123). A summary of reports using observation after surgery in stage I dysgerminoma is presented in Table 25.8.

Currently, patients with stage IA dysgerminoma can be observed after unilateral salpingo-oophorectomy, regardless of the size of the primary tumor, if preservation of fertility is an issue. Careful follow-up is required, because as many as 15% to 25% of patients will experience a recurrence. However, because of the tumor's chemosensitivity, virtually all patients can be salvaged successfully at the time of recurrence, if adequate follow-up and early detection have been accomplished.

Radiation Therapy

In the past, many stage I patients and all patients with higher stage tumors received radiotherapy. DePalo and associates recommended radiation therapy for all stage I–III patients (49). Radiation therapy was delivered to the ipsilateral hemipelvis (with shielding of the contralateral ovary and the head of the femur) and to the paraaortic nodes. A single field with the upper limit at T10–T11 and the lower limit at L4–L5 level was used. For stage III retroperitoneal disease, curative radiation therapy was set up in the same fashion as for stage I, with the addition of a prophylactic field including the mediastinum and supraclavicular nodes. In the presence of peritoneal involvement, the whole abdomen and pelvis, mediastinum and supraclavicular

Table 25.8 Results of Clinical Surveillance after Surgery in Patients with Stage IA Dysgerminoma

Institution	Period	Progression-Free/Total Number (%)	Overall Survival/Total Number (%)
AFIP (38)	–1969	46/57 (80)	52/57 (91)
Hopkins (40)	1930–1981	58/72 (80)	67/72 (94)
Mayo Clinic (118)	1950–1984	9/14 (64)	14/14 (100)
Iowa Hospitals (119)	1935–1985	7/7 (100)	7/7 (100)
M.D. Anderson (121)	–1976	5/5 (100)	5/5 (100)
Mount Vernon Hospital (116)	1973–1995	6/9 (66)	9/9 (100)

Abbreviation: AFIP, Armed Forces Institute of Pathology.

nodes were irradiated. Typically, 30 Gy (7.5 to 9 Gy/week) were given as prophylactic irradiation. For curative irradiation, 35 to 40 Gy total dose was given and a boost (10 Gy) was delivered to involved nodes. When irradiating above the diaphragm, DePalo gave 30 additional Gy 3 to 6 weeks after completion of irradiation below the diaphragm. When irradiating the entire abdominal cavity, the fields were similar to those used for epithelial tumors. They gave a total dose of 25 Gy (6 to 7.5 Gy/week). The kidneys were shielded. Similar techniques were reported by Lawson and Adler (124) and others (121,125,126).

Currently, most investigators consider this form of treatment obsolete because of the small number of patients who would derive a potential benefit and because of the subsequent reduced tolerance for chemotherapy in this population. Furthermore, considering the recent developments in the field of chemotherapy, it is accepted that primary chemotherapy is equally or more effective than irradiation of extensive normal tissue volumes, and is substantially less likely to compromise salvage therapy when patients relapse after primary therapy. Given that most patients will be cured of their ovarian tumors, and that most patients are young at the time of diagnosis, some consideration should also be given to the delayed carcinogenic effects of intermediate dose radiation. Although this issue has not been specifically addressed in women with OGCTs, it is logical to extrapolate from the experience of younger women who are frequently successfully treated with radiation for cancer of the uterine cervix, and in whom the risk of second malignancies (both within and remote from the primary radiation fields) is increased 2 or 3 decades following successful initial treatment (127).

Results of radiation therapy are reasonably good. DePalo et al. reported that all 13 stage I patients (12 stage IA and 1 with stage IB) treated with radiotherapy were alive and free of disease with a median follow-up of 77 months (49). The 5-year relapse-free survival for 12 stage III patients was 61.4% and the overall survival was 89.5%. Median follow-up was 67 months. Only 1 death was reported in this group. Earlier, DePalo et al. reported 100% overall 5-year survival and 90% recurrence-free 5-year survival in 31 stage IA, IB, and IC patients (49). At 4 years, the overall survival was 80% and the recurrence-free survival was 57% in stage III patients. Lawson and Adler reported that 10 of 14 stage I–III patients were alive with a median follow-up of 54 months (124). In this small series there was no correlation between survival and the stage of disease or the size of the primary tumor. Others reported similar results, with overall progression-free rates varying between 70% to 90% (see Table 25.9) (50,51). However, despite the remarkable radiosensitivity of dysgerminoma, radiotherapy is rarely performed nowadays, since chemotherapy is equally or more effective, less toxic, and less likely to compromise gonadal function.

Chemotherapy

There is an increasing amount of information available about chemotherapy for patients with advanced ovarian dysgerminoma. Dysgerminoma is very responsive to cisplatin-based chemotherapy, even more so than tumors other than dysgerminoma (85,128). Since 1984, patients with advanced dysgerminoma were eligible for GOG protocols. Patients enrolled on these studies received 3 to 4 courses of PVB or BEP. In a combined analysis, 20 patients were evaluated (129). All had stage III or IV disease and most of them had suboptimal (greater than 2 cm) residual tumor. Overall, with a median follow-up of 26 months, 19 of the 20 women were disease-free. Among 11 patients with clinically measurable tumor, 10 had complete responses to chemotherapy. Fourteen patients who underwent second-look laparotomy had completely negative results. Thus, it appears that

Table 25.9 Effects of Radiotherapy in Women with Pure Dysgerminoma

Institution	Period	Stage	Progression-Free/Total Number of Patients (%)
AFIP (38)	–1969	I–III	12/14 (85)
Mayo Clinic (118)	1950–1984	I–IV	16/20 (80)
M.D. Anderson (121)	–1976	I–III	26/31 (84)
Florence (51)	1960–1983	Ic–III	21/26 (80)
NCI Milan (49)	1970–1982	I–III	21/25 (84)
Iowa Hospitals (119)	1935–1985	I–III	12/13 (92)
Sweden (50)	1927–1984	I–IV	49/60 (83)
Egypt (155)	1978–1989	II–III	10/15 (66)
Prince of Whales Hospital (124)	1969–1983	II–III	10/14 (72)

Abbreviation: AFIP, Armed Forces Institute of Pathology.

nearly all patients with advanced dysgerminoma treated with chemotherapy will be durable complete responders.

Considering that patients with stage III dysgerminoma would require extensive radiation and still carry a risk of failure and that such patients probably fare worse with subsequent chemotherapy, it is clear that these patients should be treated primarily with chemotherapy. For most, the preferred adjuvant therapy is BEP. This regimen almost invariably prevents recurrence in nondysgerminomatous tumors and certainly will do so in dysgerminoma. Most patients treated with BEP will retain fertility. An alternative regimen tested by the GOG consists of a 3-day regimen with carboplatin and etoposide. On this protocol, all 39 patients with pure dysgerminoma remained free of disease at a median follow-up of 7.8 years (130). Although highly active, this regimen is not recommended for routine use due to significantly less experience accumulated with its use and the concern that this regimen is not as effective in tumors containing nondysgerminomatous elements.

The implications of elevated hCG or AFP levels in patients with dysgerminoma should be emphasized. These tumor markers are usually increased in patients with nondysgerminomatous tumors. Therefore, AFP elevation denotes the presence of elements other than dysgerminoma and treatment should be tailored accordingly. An elevated hCG level can be occasionally seen in pure dysgerminoma. This finding should not alter therapy, but it should prompt reexamination of the tumor specimen to determine whether syncytiotrophoblastic cells are present or if the tumor contains nondysgerminomatous elements.

In summary, the majority of dysgerminoma patients have stage I disease at diagnosis. These patients can be treated with unilateral salpingo-oophorectomy and if fertility is an issue, they can be observed carefully with regular pelvic examinations, abdominal computerized tomography, and tumor markers including LDH. Fifteen percent to 25% of patients observed will experience recurrence and will require chemotherapy. In patients with more advanced disease, the risk of recurrence is significant enough to warrant adjuvant treatment. Alternatives

are chemotherapy or radiation. For the majority of patients, chemotherapy is the clear choice because of ease of administration, predictable and minimal toxicity, and fertility-sparing properties. Chemotherapy is also recommended for patients with metastatic or incompletely resected tumor and for patients who recur after previous radiotherapy. Radiation might be considered as initial treatment in unusual circumstances, such as older patients or in those with serious concomitant illness that would preclude the use of systemic chemotherapy.

LATE EFFECTS OF TREATMENT

As the prognosis of patients with OGCTs has dramatically improved with the evolution of modern combination chemotherapy, attention is focused on late effects of therapy. There is a considerable body of literature on the late effects of treatment in testicular cancer patients, yet the information available for women with OGCTs remains scant. However, many analogies can be drawn.

Sequelae of Surgery

Young patients with OGCTs undergo at least one, if not multiple, surgical procedures. Although there is no available information on the long-term effects of surgery on these patients, future infertility related to pelvic surgery with subsequent peritoneal and tubal adhesions is well described. Therefore, meticulous surgical technique and avoidance of unnecessary operative maneuvers (e.g., biopsy of a normal contralateral ovary) are required for preventing future complications (55,131,132). Another cause of infertility in this population is unnecessary bilateral salpingo-oophorectomy and hysterectomy. The M.D. Anderson series included several patients who underwent surgical sterilization without a good indication before referral to their center. It is expected that this phenomenon will become less frequent, as information concerning the outcome of treated patients with OGCTs is more widely disseminated. In a series from Milan, among 55 patients treated with fertility-sparing surgery, without further chemotherapy, 12 out of 12 patients who attempted conception became pregnant and 12 normal deliveries were recorded (133). Two additional pregnancies occurred in this group and resulted in termination, one of which was due to in-uterus detection of fetal malformation. Recently, Gershenson reported the findings of GOG protocol 9901 (134). Among 132 survivors of ovarian germ cell tumors, treated with surgery and platinum-based chemotherapy, 71 patients had fertility-sparing procedures. Of those fertile survivors, 62 (87.3%) maintained menstrual periods and 24 survivors reported 37 successful pregnancies. Although the survivors reported increased incidence of gynecological problems and diminished sexual pleasure, they also tended to have stronger, more positive relationships with their significant others (134).

As with any group of patients with a history of pelvic surgery, patients with OGCTs may develop functional cysts in the residual ovary. Muram et al. reported his experience with 27 patients with ovarian germ cell tumors who underwent unilateral salpingo-oophorectomy and were followed for 12 to 215 months after completion of therapy (135). Of the 18 patients who maintained ovarian function, 13 (72%) developed functional cysts during follow-up. A trial of oral contraceptives and serial ovarian surveillance with sonography is helpful in distinguishing functional cysts from tumor recurrence.

Sequelae of Radiation Therapy

There is limited information about the late effects of radiotherapy in dysgerminoma patients. In a review of the late effects of

radiotherapy in patients receiving abdominal therapy for ovarian dysgerminoma at UTMDACC, there was a small increase in reported dyspareunia and the number of bowel movements (120). Somewhat surprisingly, at a median follow-up of 12 years, none of the 43 patients treated with radiotherapy developed small bowel obstruction. No other significant intestinal or bladder problems were recorded. As expected none of the patients treated with radiation conceived. Although the late effects of radiotherapy in this population seem to be few with the notable exception of gonadal failure (136), these observations may soon be of only historical interest. As discussed earlier, there has been a strong trend away from radiotherapy and toward chemotherapy as the preferred postoperative therapy of dysgerminoma patients. Concern over preservation of gonadal function has been the driving force behind this transition (48,137).

Sequelae of Chemotherapy

The evolutionary development and refinement of combination chemotherapy have resulted in the cure of a high percentage of patients with chemosensitive tumors, such as lymphomas, testicular cancer, gestational trophoblastic disease, and malignant ovarian germ cell tumors. Within the last few years, several reports have described the long-term effects of chemotherapy in cancer survivors. As expected, most reports refer to the more common lymphomas and testicular cancers.

A recently recognized effect of chemotherapy used for the treatment of germ cell tumors is the risk of secondary malignancies. The epipodophyllotoxins teniposide and etoposide are associated with the development of acute myelogenous leukemia (AML) with certain morphologic and cytogenetic features (138–142). This treatment complication appears to be dose- (138,139) and schedule-dependent (141). Of 348 male germ cell tumor patients receiving 3 to 4 courses of BEP as first-line therapy at Indiana University, 2 developed etoposide-related leukemia. None of the 67 patients who received only 3 courses developed AML (138). Similarly, in the study reported by Pedersen-Bjergaard et al., 5 out of 212 patients developed acute leukemia or myelodysplastic syndrome after etoposide therapy (139). However, all patients who developed AML received more than 2000 mg/m² of etoposide. None of the 130 patients who received less than this dose developed AML. Morphologically, these leukemias are monocytic or myelo-monocytic (M4 or M5). Characteristic chromosomal translocations (mostly involving the 11q23 region) are frequently, but not always, present. Leukemia after etoposide treatment occurs within 2 to 3 years compared to alkylating agent-induced AML, which has a longer latency period. Late occurrence of chronic myelogenous leukemia after treatment of testicular cancer was reported (143). In the GOG protocol testing the efficacy of BEP in women with ovarian germ cell tumors, 1 case of AML was recorded among 91 patients treated (86). An additional case of lymphoma was diagnosed during follow-up in this series, yet a correlation between chemotherapy and lymphoproliferative disorders has not been reported to date. Taking these issues into account, most clinicians consider BEP as the chemotherapy regimen of choice. The incidence of second neoplasms is quite low, particularly in patients receiving low cumulative etoposide doses. The continued use of etoposide over vinblastine is based on its superior efficacy demonstrated in testis cancer (82). Furthermore, vinblastine-induced abdominal pain and ileus are troublesome for some patients, particularly for those who underwent abdominal surgery, such as women with ovarian germ cell tumors. The risk/benefit ratio continues to favor etoposide over vinblastine.

There also continues to be considerable focus on the long-term effects of chemotherapy on gonadal function. Studies of patients with a variety of cancers suggest that, although ovarian

dysfunction or failure is a risk of chemotherapy, the majority of survivors can anticipate normal menstrual and reproductive function (144–146). Factors such as old age at initiation of therapy, greater cumulative drug dose (147), and longer duration of therapy (146) have an adverse effect on future gonadal function. Successful pregnancies after treatment with combination chemotherapy have been well documented in other types of malignancies, including Hodgkin's disease, nonHodgkin's lymphomas, and leukemia. There are similar reports in patients with malignant OGCTs (133,148–151).

In a review of the UTMDACC series (148), 27 (68%) of 40 patients who had retained a normal contralateral ovary and uterus maintained regular menses consistently after completion of chemotherapy and 33 (83%) were having regular menses at the time of follow-up. Of 16 patients who had attempted to become pregnant, 12 were successful. One patient underwent an elective first-trimester abortion and the other 11 patients bore 22 healthy infants over time, none of which had a major birth defect. In a series from Milan, among 169 patients with ovarian germ cell tumors, 138 underwent fertility-sparing surgery, and of these, 81 underwent adjuvant chemotherapy (133). After treatment, all but one woman recovered menstrual function and 55 conceptions were recorded. Forty normal full-term babies were delivered. There were 4 babies with congenital malformations, 1 in a patient who did not receive chemotherapy and 3 in women who had received chemotherapy (the difference was not statistically significant).

The GOG recently completed an analysis evaluating the quality of life and psychosocial characteristics of survivors of ovarian germ cell tumors compared to matched controls. In this analysis, the survivors appeared to be well adjusted, were able to develop strong relationships, and were free of significant depression (152). The impact on fertility was modest or none in patients undergoing fertility-sparing surgeries (134). OGCT survivors appeared to be free of any major physical illnesses at a median follow-up of 10 years, as compared to matched controls. The only differences were higher rates of reported hypertension (17% vs. 8%, $p = 0.02$), hypercholesterolemia (9.8% vs. 4.4%, $p = 0.09$), and hearing loss (5.3% vs. 1.5%, $p = 0.09$) compared with controls (153). Among chronic functional problems, numbness, tinnitus, nausea elicited by reminders of chemotherapy (vs. general nausea triggers for controls), and Raynaud's symptoms were reported more frequently by survivors. Interestingly, late effects of treatment are more pronounced among children receiving treatment for germ cell tumors (154). Specifically, neurotoxicity, growth abnormalities, pulmonary toxicity, and gastrointestinal toxicity have been reported in a higher proportion than in adult patients. Despite persistence of a few sequelae of treatment, in general, OGCT survivors enjoy a healthy life comparable to that of controls, justifying administration of curative treatment in full and timely dosing.

SUMMARY

Virtually all patients with early-stage, completely resected OGCTs survive after careful surgical staging and 3 courses of adjuvant BEP. Furthermore, up to 80% of patients with incompletely resected or advanced tumors are expected to be long-term survivors. Acute toxicity of treatment is relatively modest. An important, but fortunately unusual late complication of treatment is etoposide-induced leukemia. However, patients receiving the usually administered cumulative dose of etoposide are at low risk for developing AML. Otherwise, late consequences of chemotherapy are limited. Efforts should concentrate on fertility preservation for patients who desire subsequent pregnancies.

The majority of dysgerminoma patients have stage I disease at diagnosis. These patients usually can be treated with unilateral salpingo-oophorectomy and careful postoperative observation without adjuvant treatment. Chemotherapy is offered at the time of recurrence. In patients with more advanced but resected disease, the risk of recurrence is significant enough to warrant up-front adjuvant treatment, which for most patients is chemotherapy because of its near universal effectiveness and limited impact on fertility. In patients with incompletely resected tumor or for patients who recur after previous radiation, chemotherapy similar to that given for tumors other than dysgerminoma is appropriate.

Surgery continues to have a pivotal role in the management of all patients with OGCTs. Initial careful surgical staging is important for selection of appropriate subsequent therapy. Second-look laparotomy is not necessary in patients who have

no residual tumor after their initial surgical procedure and who receive adjuvant chemotherapy. This procedure also does not seem warranted in patients with advanced tumors without elements of teratoma. The judicious use of surgery followed by chemotherapy will cure the majority of patients with ovarian germ cell tumors at the expense of minimal and predictable immediate and late toxicities. In most circumstances fertility can be preserved.

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REFERENCES

1. Tavassoli FA, Devilee P, eds. *World Health Organization Classification of Tumors: Pathology and genetics of tumours of the breast and female genital organs*. Lyon, France: IARC Press; 2003.
2. Kurman RJ, Norris HJ. Malignant germ cell tumors of the ovary. *Hum Pathol*. 1977;8(5):551–564.
3. Sever M, Jones TD, Roth LM, et al. Expression of CD117 (c-kit) receptor in dysgerminoma of the ovary: diagnostic and therapeutic implications. *Mod Pathol*. 2005;18(11):1411–1416.
4. Cheng L, Thomas A, Roth LM, et al. OCT4: a novel biomarker for dysgerminoma of the ovary. *Am J Surg Pathol*. 2004;28(10):1341–1346.
5. Hoei-Hansen CE, Kraggerud SM, Abeler VM, et al. Ovarian dysgerminomas are characterised by frequent KIT mutations and abundant expression of pluripotency markers. *Mol Cancer*. 2007;6:12.
6. Cheng L, Roth LM, Zhang S, et al. KIT gene mutation and amplification in dysgerminoma of the ovary. *Cancer*. 2011;117(10):2096–2103.
7. Kurman RJ, Norris HJ. Endodermal sinus tumor of the ovary: a clinical and pathologic analysis of 71 cases. *Cancer*. 1976;38(6):2404–2419.
8. Roth LM. Variants of yolk sac tumor. *Pathol Case Rev*. 2004;10:186–192.
9. Damjanov I, Amenta PS, Zarghami F. Transformation of an AFP-positive yolk sac carcinoma into an AFP-negative neoplasm. Evidence for in vivo cloning of the human parietal yolk sac carcinoma. *Cancer*. 1984;53:1902–1907.
10. Ramalingam P, Malpica A, Silva EG, et al. The use of cytokeratin 7 and EMA in differentiating ovarian yolk sac tumors from endometrioid and clear cell carcinomas. *Am J Surg Pathol*. 2004;28(11):1499–1505.
11. Kurman RJ, Norris HJ. Embryonal carcinoma of the ovary: a clinicopathologic entity distinct from endodermal sinus tumor resembling embryonal carcinoma of the adult testis. *Cancer*. 1976;38:2420–2433.
12. Beck JS, Fulmer HF, Lee ST. Solid malignant ovarian teratoma with “embryoid bodies” and trophoblastic differentiation. *J Pathol*. 1969;99(1):67–73.
13. Vance RP, Geisinger KR. Pure nongestational choriocarcinoma of the ovary. Report of a case. *Cancer*. 1985;56(9):2321–2325.
14. Kurman RJ, Norris HJ. Malignant mixed germ cell tumors of the ovary. A clinical and pathologic analysis of 30 cases. *Obstet Gynecol*. 1976;48(5):579–589.
15. Gershenson DM, Del Junco G, Copeland LJ, et al. Mixed germ cell tumors of the ovary. *Obstet Gynecol*. 1984;64(2):200–206.
16. Lorigan PC, Grierson AJ, Goepel JR, et al. Gestational choriocarcinoma of the ovary diagnosed by analysis of tumour DNA. *Cancer Lett*. 1996;104(1):27–30.
17. Riopel MA, Spellerberg A, Griffin CA, et al. Genetic analysis of ovarian germ cell tumors by comparative genomic hybridization. *Cancer Res*. 1998;58(14):3105–3110.
18. Kraggerud SM, Szymanska J, Abeler VM, et al. DNA copy number changes in malignant ovarian germ cell tumors. *Cancer Res*. 2000;60(11):3025–3030.
19. Yanai-Inbar I, Scully RE. Relation of ovarian dermoid cysts and immature teratomas: an analysis of 350 cases of immature teratoma and 10 cases of dermoid cyst with microscopic foci of immature tissue. *Int J Gynecol Pathol*. 1987;6(3):203–212.
20. Norris HJ, Zirkin HJ, Benson WL. Immature (malignant) teratoma of the ovary: a clinical and pathologic study of 58 cases. *Cancer*. 1976;37(5):2359–2372.
21. O'Connor DM, Norris HJ. The influence of grade on the outcome of stage I ovarian immature (malignant) teratomas and the reproducibility of grading. *Int J Gynecol Pathol*. 1994;13(4):283–289.
22. Ferguson AW, Katabuchi H, Ronnett BM, et al. Glial implants in gliomatosis peritonei arise from normal tissue, not from the associated teratoma. *Am J Pathol*. 2001;159(1):51–55.
23. Dickersin GR, Kline IW, Scully RE. Small cell carcinoma of the ovary with hypercalcemia: a report of eleven cases. *Cancer*. 1982;49(1):188–197.
24. Ulbright TM, Roth LM, Stehman FB, et al. Poorly differentiated (small cell) carcinoma of the ovary in young women: evidence supporting a germ cell origin. *Hum Pathol*. 1987;18(2):175–184.
25. Crowder S, Tuller E. Small cell carcinoma of the female genital tract. *Semin Oncol*. 2007;34(1):57–63.
26. Seidman JD. Small cell carcinoma of the ovary of the hypercalcemic type: p53 protein accumulation and clinicopathologic features. *Gynecol Oncol*. 1995;59(2):283–287.
27. Scully RE. Small cell carcinoma of hypercalcemic type. *Int J Gynecol Pathol*. 1993;12(2):148–152.
28. Surti U, Hoffner L, Chakravarti A, et al. Genetics and biology of human ovarian teratomas. I. Cytogenetic analysis and mechanism of origin. *Am J Hum Genet*. 1990;47(4):635–643.
29. Deka R, Chakravarti A, Surti U, et al. Genetics and biology of human ovarian teratomas. II. Molecular analysis of origin of nondisjunction and gene-centromere mapping of chromosome I markers. *Am J Hum Genet*. 1990;47(4):644–655.
30. Baker BA, Frickey L, Yu IT, et al. DNA content of ovarian immature teratomas and malignant germ cell tumors. *Gynecol Oncol*. 1998;71(1):14–18.
31. Murty VV, Dmitrovsky E, Bosl GJ, et al. Nonrandom chromosome abnormalities in testicular and ovarian germ cell tumor cell lines. *Cancer Genet Cytogenet*. 1990;50(1):67–73.
32. Speleman F, De Potter C, Dal Cin P, et al. i(12p) in a malignant ovarian tumor. *Cancer Genet Cytogenet*. 1990;45(1):49–53.
33. Shen DH, Khoo US, Zhang Y, et al. Cytogenetic study of malignant ovarian germ cell tumors by chromosome in situ hybridization. *Int J Gynecol Cancer*. 1998;8:222–232.
34. Hart WR, Burkons DM. Germ cell neoplasms occurring in gonadoblastomas. *Cancer*. 1979;43(2):669–678.
35. Gershenson DM, Copeland LJ, Kavanagh JJ, et al. Treatment of malignant nondysgerminomatous germ cell tumors of the ovary with vincristine, dactinomycin, and cyclophosphamide. *Cancer*. 1985;56(12):2756–2761.
36. Poynter JN, Amatruda JF, Ross JA. Trends in incidence and survival of pediatric and adolescent patients with germ cell tumors in the United States, 1975 to 2006. *Cancer*. 2010;116(20):4882–4891.
37. Poynter JN, Radzom AH, Spector LG, et al. Family history of cancer and malignant germ cell tumors in children: a report from the Children's Oncology Group. *Cancer Causes Control*. 2010;21(2):181–189.
38. Asadourian LA, Taylor HB. Dysgerminoma. An analysis of 105 cases. *Obstet Gynecol*. 1969;33(3):370–379.
39. De Backer A, Madern GC, Oosterhuis JW, et al. Ovarian germ cell tumors in children: a clinical study of 66 patients. *Pediatr Blood Cancer*. 2006;46(4):459–464.
40. Gordon A, Lipton D, Woodruff JD. Dysgerminoma: a review of 158 cases from the Emil Novak Ovarian Tumor Registry. *Obstet Gynecol*. 1981;58(4):497–504.
41. Christman JE, Teng NN, Lebovic GS, et al. Delivery of a normal infant following cisplatin, vinblastine, and bleomycin (PVB) chemotherapy for malignant teratoma of the ovary during pregnancy. *Gynecol Oncol*. 1990;37(2):292–295.
42. Farahmand SM, Marchetti DL, Asirvatham JE, et al. Ovarian endodermal sinus tumor associated with pregnancy: review of the literature. *Gynecol Oncol*. 1991;41:156–160.

43. Horbelt D, Delmore J, Meisel R, et al. Mixed germ cell malignancy of the ovary concurrent with pregnancy. *Obstet Gynecol.* 1994;84(4 Pt 2):662–664.
44. Rajendran S, Hollingworth J, Scudamore I. Endometrial sinus tumour of the ovary in pregnancy. *Eur J Gynaecol Oncol.* 1999;20(4):272–274.
45. Bakri YN, Ezzat A, Akhtar, et al. Malignant germ cell tumors of the ovary. Pregnancy considerations. *Eur J Obstet Gynecol Reprod Biol.* 2000;90(1):87–91.
46. Sekiya S, Seki K, Nagai Y. Rise of serum CA 125 in patients with pure ovarian yolk sac tumors. *Int J Gynaecol Obstet.* 1997;58(3):323–324.
47. Mangili G, Sigismondi C, Gadducci A, et al. Outcome and risk factors for recurrence in malignant ovarian germ cell tumors: a MITO-9 retrospective study. *Int J Gynecol Cancer.* 2011;21(8):1414–1421.
48. Ayhan A, Bildirici I, Gunalp S, et al. Pure dysgerminoma of the ovary: a review of 45 well staged cases. *Eur J Gynaecol Oncol.* 2000;21(1):98–101.
49. De Palo G, Lattuada A, Kenda R, et al. Germ cell tumors of the ovary: the experience of the National Cancer Institute of Milan. I. Dysgerminoma. *Int J Radiat Oncol Biol Phys.* 1987;13(6):853–860.
50. Bjorkholm E, Lundell M, Gyftodimos A, et al. Dysgerminoma. The Radiumhemmet series 1927–1984. *Cancer.* 1990;65(1):38–44.
51. Santoni R, Cionini L, D'Elia F, et al. Dysgerminoma of the ovary: a report on 29 patients. *Clin Radiol.* 1987;38(2):203–206.
52. Berg FD, Kurzl R, Hinrichsen MJ, et al. Familial 46,XY pure gonadal dysgenesis and gonadoblastoma/dysgerminoma: case report. *Gynecol Oncol.* 1989;32(2):261–267.
53. Fisher RA, Salm R, Spencer RW. Bilateral gonadoblastoma/dysgerminoma in a 46 XY individual: case report with hormonal studies. *J Clin Pathol.* 1982;35(4):420–424.
54. Kingsbury AC, Frost F, Cookson WO. Dysgerminoma, gonadoblastoma, and testicular germ cell neoplasia in phenotypically female and male siblings with 46 XY genotype. *Cancer.* 1987;59(2):288–291.
55. Schwartz PE. Surgery of germ cell tumours of the ovary. *Forum (Genova).* 2000;10(4):355–365.
56. Peccatori F, Bonazzi C, Chiari S, et al. Surgical management of malignant ovarian germ-cell tumors: 10 years' experience of 129 patients. *Obstet Gynecol.* 1995;86(3):367–372.
57. Gershenson DM. Fertility-sparing surgery for malignancies in women. *J Natl Cancer Inst Monogr.* 2005;(34):43–47.
58. Saunders DM, Ferrier AJ, Ryan J. Fertility preservation in female oncology patients. *Int J Gynecol Cancer.* 1996;6:161–167.
59. Slayton RE, Hreshchyshyn MM, Silverberg SC, et al. Treatment of malignant ovarian germ cell tumors: response to vincristine, dactinomycin, and cyclophosphamide (preliminary report). *Cancer.* 1978;42(2):390–398.
60. Williams SD, Blessing JA, Moore DH, et al. Cisplatin, vinblastine, and bleomycin in advanced and recurrent ovarian germ-cell tumors. A trial of the Gynecologic Oncology Group. *Ann Intern Med.* 1989;111(1):22–27.
61. Scarabelli C, Gallo A, Carbone A. Secondary cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. *Gynecol Oncol.* 2001;83(3):504–512.
62. Parazzini F, Raspagliesi F, Guarnerio P, et al. Role of secondary surgery in relapsed ovarian cancer. *Crit Rev Oncol Hematol.* 2001;37(2):121–125.
63. Williams SD, Blessing JA, DiSaia PJ, et al. Second-look laparotomy in ovarian germ cell tumors: the gynecologic oncology group experience. *Gynecol Oncol.* 1994;52(3):287–291.
64. Andre F, Fizazi K, Culine S, et al. The growing teratoma syndrome: results of therapy and long-term follow-up of 33 patients. *Eur J Cancer.* 2000;36(11):1389–1394.
65. Chen RJ, Huang PT, Lin MC, et al. Advanced stage squamous cell carcinoma arising from mature cystic teratoma of the ovary. *Acta Obstet Gynecol Scand.* 2001;80(1):84–86.
66. Ronnett BM, Seidman JD. Mucinous tumors arising in ovarian mature cystic teratomas: relationship to the clinical syndrome of pseudomyxoma peritonei. *Am J Surg Pathol.* 2003;27(5):650–657.
67. Vartanian RK, McRae B, Hessler RB. Sebaceous carcinoma arising in a mature cystic teratoma of the ovary. *Int J Gynecol Pathol.* 2002;21(4):418–421.
68. Shen DH, Khoo US, Xue WC, et al. Ovarian mature cystic teratoma with malignant transformation. An interphase cytogenetic study. *Int J Gynecol Pathol.* 1998;17(4):351–357.
69. Geisler JP, Goulet R, Foster RS, et al. Growing teratoma syndrome after chemotherapy for germ cell tumors of the ovary. *Obstet Gynecol.* 1994;84 (4 Pt 2):719–721.
70. Itani Y, Kawa M, Toyoda S, et al. Growing teratoma syndrome after chemotherapy for a mixed germ cell tumor of the ovary. *J Obstet Gynaecol Res.* 2002;28(3):166–171.
71. Kattan J, Droz JP, Culine S, et al. The growing teratoma syndrome: a woman with nonseminomatous germ cell tumor of the ovary. *Gynecol Oncol.* 1993;49(3):395–399.
72. Gershenson DM, Copeland LJ, del Junco G, et al. Second-look laparotomy in the management of malignant germ cell tumors of the ovary. *Obstet Gynecol.* 1986;67(6):789–793.
73. Albers P, Bender H, Yilmaz H, et al. Positron emission tomography in the clinical staging of patients with Stage I and II testicular germ cell tumors. *Urology.* 1999;53(4):808–811.
74. Hain SE, O'Doherty MJ, Timothy AR, et al. Fluorodeoxyglucose positron emission tomography in the evaluation of germ cell tumours at relapse. *Br J Cancer.* 2000;83(7):863–869.
75. Kollmannsberger C, Oechsle K, Dohmen BM, et al. Prospective comparison of [18F]fluorodeoxyglucose positron emission tomography with conventional assessment by computed tomography scans and serum tumor markers for the evaluation of residual masses in patients with nonseminomatous germ cell carcinoma. *Cancer.* 2002;94(9):2353–2362.
76. Sanchez D, Zudaire JJ, Fernandez JM, et al. 18F-fluoro-2-deoxyglucose-positron emission tomography in the evaluation of nonseminomatous germ cell tumours at relapse. *BJU Int.* 2002;89(9):912–916.
77. Sugawara Y, Zasadny KR, Grossman HB, et al. Germ cell tumor: differentiation of viable tumor, mature teratoma, and necrotic tissue with FDG PET and kinetic modeling. *Radiology.* 1999;211(1):249–256.
78. De Santis M, Becherer A, Bokemeyer C, et al. FDG-PET as prognostic indicator for seminoma residuals: an update from the SEMPET study. Proceedings of ASCO; 2003.
79. Murphy JJ, Tawfeeq M, Chang B, et al. Early experience with PET/CT scan in the evaluation of pediatric abdominal neoplasms. *J Pediatr Surg.* 2008;43(12):2186–2192.
80. Basu S, Rubello D. PET imaging in the management of tumors of testis and ovary: current thinking and future directions. *Minerva Endocrinol.* 2008;33(3):229–256.
81. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med.* 1977;87(3):293–298.
82. Williams SD, Birch R, Einhorn LH, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med.* 1987;316(23):1435–1440.
83. Slayton RE, Park RC, Silverberg SG, et al. Vincristine, dactinomycin, and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary. A Gynecologic Oncology Group Study (a final report). *Cancer.* 1985;56(2):243–248.
84. Gershenson DM, Kavanagh JJ, Copeland LJ, et al. Treatment of malignant nondysgerminomatous germ cell tumors of the ovary with vinblastine, bleomycin, and cisplatin. *Cancer.* 1986;57(9):1731–1737.
85. Gershenson DM, Morris M, Cangir A, et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin. *J Clin Oncol.* 1990;8(4):715–720.
86. Williams S, Blessing JA, Liao SY, et al. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. *J Clin Oncol.* 1994;12(4):701–706.
87. Culine S, Lhomme C, Kattan J, et al. Cisplatin-based chemotherapy in the management of germ cell tumors of the ovary: The Institut Gustave Roussy Experience. *Gynecol Oncol.* 1997;64(1):160–165.
88. Segelov E, Campbell J, Ng M, et al. Cisplatin-based chemotherapy for ovarian germ cell malignancies: the Australian experience. *J Clin Oncol.* 1994;12(2):378–384.
89. Dimopoulos MA, Papadopolou M, Andreopoulou E, et al. Favorable outcome of ovarian germ cell malignancies treated with cisplatin or carboplatin-based chemotherapy: a Hellenic Cooperative Oncology Group study. *Gynecol Oncol.* 1998;70(1):70–74.
90. Einhorn LH. Curing metastatic testicular cancer. *Proc Natl Acad Sci USA.* 2002;99(7):4592–4595.
91. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. *J Clin Oncol.* 1989;7(3):387–391.
92. Einhorn LH. Salvage therapy for germ cell tumors. *Semin Oncol.* 1994;21(4 Suppl. 7):47–51.
93. Bokemeyer C, Kollmannsberger C, Meisner C, et al. First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: a multivariate and matched-pair analysis. *J Clin Oncol.* 1999;17(11):3450–3456.
94. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol.* 2007;25(3):247–256.
95. Daugaard G, Skoneczna I, Aass N, et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSCG, and Grupo Germinal (EORTC 30974). *Ann Oncol.* 2011;22:1054–1061.
96. Murugesu N, Schmid P, Dancy G, et al. Malignant ovarian germ cell tumors: identification of novel prognostic markers and long-term outcome after multimodality treatment. *J Clin Oncol.* 2006;24(30):4862–4866.

97. Messing MJ, Gershenson DM, Morris M, et al. Primary treatment failure in patients with malignant ovarian germ cell neoplasms. *Int J Gynecol Cancer*. 1992;2(6):295–300.
98. Broun ER, Nichols CR, Turns M, et al. Early salvage therapy for germ cell cancer using high dose chemotherapy with autologous bone marrow support. *Cancer*. 1994;73(6):1716–1720.
99. Broun ER, Nichols CR, Gize G, et al. Tandem high dose chemotherapy with autologous bone marrow transplantation for initial relapse of testicular germ cell cancer. *Cancer*. 1997;79(8):1605–1610.
100. Lotz JP, Andre T, Donsimoni R, et al. High dose chemotherapy with ifosfamide, carboplatin, and etoposide combined with autologous bone marrow transplantation for the treatment of poor-prognosis germ cell tumors and metastatic trophoblastic disease in adults. *Cancer*. 1995;75(3):874–885.
101. Einhorn LH, Williams SD, Chamness A, et al. High dose chemotherapy and stem cell rescue for metastatic germ cell tumors. *N Engl J Med*. 2007;357(4):340–348.
102. Loehrer PJ Sr, Gonin R, Nichols CR, et al. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. *J Clin Oncol*. 1998;16(7):2500–2504.
103. Hinton S, Catalano P, Einhorn LH, et al. Phase II study of paclitaxel plus gemcitabine in refractory germ cell tumors (E9897): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2002;20(7):1859–1863.
104. Nichols CR, Roth BJ, Loehrer PJ, et al. Salvage chemotherapy for recurrent germ cell cancer. *Semin Oncol*. 1994;21(5 Suppl. 12):102–108.
105. Einhorn LH, Brame MJ, Juliar B, et al. Phase II study of paclitaxel plus gemcitabine salvage chemotherapy for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. *J Clin Oncol*. 2007;25(5):513–516.
106. Kollmannsberger C, Beyer J, Liersch R, et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: a study of the German Testicular Cancer Study Group. *J Clin Oncol*. 2004;22(1):108–114.
107. Mann JR, Raafat F, Robinson K, et al. The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. *J Clin Oncol*. 2000;18:3809–3818.
108. McKeage MJ, Evans BD, Atkinson C, et al. Carbon monoxide diffusing capacity is a poor predictor of clinically significant bleomycin lung. New Zealand Clinical Oncology Group. *J Clin Oncol*. 1990;8(5):779–783.
109. Loehrer PJ Sr, Johnson D, Elson P, et al. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. *J Clin Oncol*. 1995;13(2):470–476.
110. de Wit R, Stoter G, Kaye SB, et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. *J Clin Oncol*. 1997;15:1837–1843.
111. Bajorin DE, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. *J Clin Oncol*. 1993;11(4):598–606.
112. Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol*. 1997;15:1844–1852.
113. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol*. 1994;12(11):2471–2508.
114. Cushing B, Giller R, Ablin A, et al. Surgical resection alone is effective treatment for ovarian immature teratoma in children and adolescents: a report of the pediatric oncology group and the children's cancer group. *Am J Obstet Gynecol*. 1999;181(2):353–358.
115. Marina NM, Cushing B, Giller R, et al. Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: a Pediatric Oncology Group/Children's Cancer Group Intergroup Study. *J Clin Oncol*. 1999;17(7):2137–2143.
116. Dark GG, Bower M, Newlands ES, et al. Surveillance policy for stage I ovarian germ cell tumors. *J Clin Oncol*. 1997;15(2):620–624.
117. Bonazzi C, Peccatori F, Colombo N, et al. Pure ovarian immature teratoma, a unique and curable disease: 10 years' experience of 32 prospectively treated patients. *Obstet Gynecol*. 1994;84(4):598–604.
118. Buskirk SJ, Schray MF, Podratz KC, et al. Ovarian dysgerminoma: a retrospective analysis of results of treatment, sites of treatment failure, and radiosensitivity. *Mayo Clin Proc*. 1987;62(12):1149–1157.
119. LaPolla JP, Benda J, Vigliotti AP, et al. Dysgerminoma of the ovary. *Obstet Gynecol*. 1987;69(6):859–864.
120. Mitchell MF, Gershenson DM, Soeters RP, et al. The long-term effects of radiation therapy on patients with ovarian dysgerminoma. *Cancer*. 1991;67(4):1084–1090.
121. Krepart G, Smith JP, Rutledge F, et al. The treatment for dysgerminoma of the ovary. *Cancer*. 1978;41(3):986–990.
122. Thomas GM, Dembo AJ, Hacker NF, et al. Current therapy for dysgerminoma of the ovary. *Obstet Gynecol*. 1987;70(2):268–275.
123. Patterson DM, Murugasu N, Holden L, et al. A review of the close surveillance policy for stage I female germ cell tumors of the ovary and other sites. *Int J Gynecol Cancer*. 2008;18(1):43–50.
124. Lawson AP, Adler GF. Radiotherapy in the treatment of ovarian dysgerminomas. *Int J Radiat Oncol Biol Phys*. 1988;14(3):431–434.
125. Freed JH, Cassir JF, Pierce VK, et al. Dysgerminoma of the ovary. *Cancer*. 1979;43(3):798–805.
126. Marks RD, Underwood PB, Othersen HB, et al. Dysgerminoma—100% control with combined therapy in six consecutive patients with advanced disease. *Int J Radiat Oncol Biol Phys*. 1978;4(5):453–456.
127. Boice JD Jr, Engholm G, Kleiner RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res*. 1988;116(1):3–55.
128. Culine S, Lhomme C, Kattan J, et al. Cisplatin-based chemotherapy in dysgerminoma of the ovary: thirteen-year experience at the Institut Gustave Roussy. *Gynecol Oncol*. 1995;58(3):344–348.
129. Williams SD, Blessing JA, Hatch KD, et al. Chemotherapy of advanced dysgerminoma: trials of the Gynecologic Oncology Group. *J Clin Oncol*. 1991;9(11):1950–1955.
130. Williams SD, Kauderer J, Burnett AF, et al. Adjuvant therapy of completely resected dysgerminoma with carboplatin and etoposide: a trial of the Gynecologic Oncology Group. *Gynecol Oncol*. 2004;95(3):496–499.
131. Perrin LC, Low J, Nicklin JL, et al. Fertility and ovarian function after conservative surgery for germ cell tumors of the ovary. *Aust N Z J Obstet Gynaecol*. 1999;39(2):243–245.
132. Kanazawa K, Suzuki T, Sakumoto K. Treatment of malignant ovarian germ cell tumors with preservation of fertility: reproductive performance after persistent remission. *Am J Clin Oncol*. 2000;23(3):244–248.
133. Zanetta G, Bonazzi C, Cantu M, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. *J Clin Oncol*. 2001;19(4):1015–1020.
134. Gershenson DM, Miller AM, Champion VL, et al. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007;25(19):2792–2797.
135. Muram D, Gale CL, Thompson E. Functional ovarian cysts in patients cured of ovarian neoplasms. *Obstet Gynecol*. 1990;75(4):680–683.
136. Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. *Endocrinol Metab Clin North Am*. 1998;27(4):927–943.
137. Casey AC, Bhodauria S, Shapter A, et al. Dysgerminoma: the role of conservative surgery. *Gynecol Oncol*. 1996;63(3):352–357.
138. Nichols CR, Breeden ES, Loehrer PJ, et al. Secondary leukemia associated with a conventional dose of etoposide: review of serial germ cell tumor protocols. *J Natl Cancer Inst*. 1993;85(1):36–40.
139. Pedersen-Bjergaard J, Daugaard G, Hansen SW, et al. Increased risk of myelodysplasia and leukaemia after etoposide, cisplatin, and bleomycin for germ-cell tumours. *Lancet*. 1991;338(8763):359–363.
140. Pui CH. Epipodophyllotoxin-related acute myeloid leukaemia. *Lancet*. 1991;338(8780):1468.
141. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N Engl J Med*. 1991;325(24):1682–1687.
142. Ratain MJ, Kaminer LS, Bitran JD, et al. Acute nonlymphocytic leukemia following etoposide and cisplatin combination chemotherapy for advanced non-small-cell carcinoma of the lung. *Blood*. 1987;70(5):1412–1417.
143. Pedersen-Bjergaard J, Brondum-Nielsen K, Karle H, et al. Chemotherapy-related late occurring Philadelphia chromosome in AML, ALL and CML. Similar events related to treatment with DNA topoisomerase II inhibitors? *Leukemia*. 1997;11(9):1571–1574.
144. Horning SJ, Hoppe RT, Kaplan HS, et al. Female reproductive potential after treatment for Hodgkin's disease. *N Engl J Med*. 1981;304(23):1377–1382.
145. Byrne J, Mulvihill JJ, Myers MH, et al. Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. *N Engl J Med*. 1987;317(21):1315–1321.
146. Siris ES, Leventhal BG, Vaitukaitis JL. Effects of childhood leukemia and chemotherapy on

- puberty and reproductive function in girls. *N Engl J Med*. 1976;294(21):1143–1146.
147. Nicosia SV, Matus-Ridley M, Meadows AT. Gonadal effects of cancer therapy in girls. *Cancer*. 1985;55(10):2364–2372.
 148. Gershenson DM. Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumors. *J Clin Oncol*. 1988;6(2):270–275.
 149. Brewer M, Gershenson DM, Herzog CE, et al. Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. *J Clin Oncol*. 1999;17(9):2670–2675.
 150. Pektasides D, Rustin GJ, Newlands ES, et al. Fertility after chemotherapy for ovarian germ cell tumours. *Br J Obstet Gynaecol*. 1987;94(5):477–479.
 151. Rustin GJ, Pektasides D, Bagshawe KD, et al. Fertility after chemotherapy for male and female germ cell tumours. *Int J Androl*. 1987;10(1):389–392.
 152. Champion V, Williams SD, Miller A, et al. Quality of life in long-term survivors of ovarian germ cell tumors: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 2007;105(3):687–694.
 153. Matei D, Miller AM, Monahan P, et al. Chronic physical effects and health care utilization in long-term ovarian germ cell tumor survivors: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009;27(25):4142–4149.
 154. Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. 1999;21(2):115–122.
 155. Zaghloul MS, Khattab TY. Dysgerminoma of the ovary: good prognosis even in advanced stages. *Int J Radiat Oncol Biol Phys*. 1992;24(1):161–165.

Ovarian Sex Cord–Stromal Tumors

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The intraovarian matrix that supports the germ cells and is covered by the surface epithelium consists of cells originating from the sex cords and mesenchyme of the embryonic gonad. Granulosa cells and Sertoli cells, generally considered to be homologous, are derived from the sex cord cells, whereas the pluripotential mesenchymal cells are the precursors of the theca cells, Leydig cells, and fibroblasts. Neoplastic transformation of these cellular constituents, either singly or in various combinations collectively, results in neoplasms that are termed sex cord-stromal tumors (SCSTs). The classification of the SCSTs provides the template from which this chapter endeavors to stratify and define these tumor entities according to their morphologic characteristics (Table 26.1).

The SCSTs are estimated to account for approximately 7% of all malignant ovarian neoplasms (1). Although SCSTs account for a decreasing proportion of all ovarian malignancies with advancing age, the annual age-related incidence continues to increase through the seventh decade of life (2). Overall, the majority of these tumors are benign or of low malignant potential and are associated with a favorable long-term prognosis. In addition, a significant proportion of SCSTs are diagnosed in patients younger than age 40 years and have the potential to produce a variety of steroid hormones. Hence, adequate knowledge of the natural history of each of these tumors is imperative to diagnose and individualize appropriately definitive surgical and adjuvant therapy.

SCSTs account for nearly 90% of all functioning ovarian neoplasms (3). With the exception of fibromas, the clinical presentation of patients with SCSTs is frequently governed by the clinical manifestations resulting from the endocrinologic abnormalities. Excessive estrogen production, whether from increased tumor synthesis or peripheral conversion of androgens, influences end-organ responses, which are usually age-dependent and can range from isosexual precocious puberty to menometrorrhagia to postmenopausal bleeding. In addition, the associated risks for endometrial cancer and possibly breast cancer must be recognized (4–6). Conversely, the rapid onset of signs ranging from early defeminization to frank virilization heralds a hyperandrogenic state. Elevated circulating levels of testosterone and/or androstenedione provide strong evidence for the presence of an SCST. Although granulosa cell, theca cell, and Sertoli cell tumors are generally considered to be estrogenic, and Sertoli-Leydig cell and steroid cell tumors are predominantly androgenic, the functional endocrinologic capacities of these tumors are impossible to predict based on their morphologic features. It should also be noted that miscellaneous ovarian tumors, both primary and metastatic, that are not in the SCST family may be androgenic or estrogenic if their stroma is stimulated to undergo luteinization.

GRANULOSA CELL TUMORS

Although granulosa cell tumors (GCTs) of the ovary were initially described by Rokitansky in 1859 (7), the etiopathogenesis of these neoplasms remains ill defined. At least in part, this is a reflection of the low incidence of GCTs, and hence the limited number of cases managed at any single institution. Although molecular aberrations crucial to the pathogenesis of GCTs have been elucidated recently, to our knowledge there are no recognized risk factors for their development (4,8). Reproductive factors, including the use of fertility-promoting agents and oral contraceptives, do not correlate consistently with the development of disease. Unkila-Kallio et al. (9) studied a possible link between fertility-promoting agents and GCTs using the nationwide Finnish Cancer Registry. They analyzed the occurrence of GCTs in Finland during the time period 1965 to 1994 against sales statistics for ovulation inducers. The incidence of GCTs declined by nearly 40% from 1965–1969 to 1985–1994 despite a 13-fold increase in the use of clomiphene citrate and a 200-fold increase in human menopausal gonadotropin use; oral contraceptive use increased fivefold. No hereditary predisposition for any of the SCSTs has been identified (10). Of note, a recent case report described the occurrence of adult GCTs in 2 first-degree relatives (11).

GCTs comprise 5% of all ovarian malignancies, but account for approximately 70% of malignant SCSTs (4–6, 12–19). The annual incidence of GCTs in the United States and other developed countries varies from 0.4 to 1.7 cases per 100,000 women (5,6,8,18,20,21). Quirk and Natarajan reported histology-specific age-adjusted ovarian cancer incidence rates that were standardized to the recently adopted year 2000 U.S. standard population (22). They utilized data gathered from the Surveillance, Epidemiology, and End Results (SEER) Program for the years 1992–1999. Out of a total of 23,484 microscopically confirmed cases of primary ovarian cancer, 293 (1.2%) were of sex cord–stromal origin. Although GCTs have been diagnosed from infancy through the tenth decade of life, the peak incidence for these tumors occurs during the perimenopausal decade. The average age at the time of diagnosis in over 750 cases was 52 years (4–6,13,15–18). Considering that GCTs occurring after the third decade of life appear to be histologically distinct in most instances from those occurring in children and younger adults, the clinical and pathologic characteristics for the juvenile and adult GCTs will be addressed separately.

Table 26.1 **Classification of Sex Cord–Stromal Tumors**

Granulosa-Stromal Cell Tumors
Granulosa cell tumor
Adult type
Juvenile type
Tumors in the thecoma-fibroma group
Thecoma
Fibroma-fibrosarcoma
Sclerosing stromal tumor
Sertoli-Stromal Cell Tumors
Sertoli cell tumor
Leydig cell tumor
Sertoli–Leydig cell tumor
Well differentiated
Of intermediate differentiation
Poorly differentiated
With heterologous elements
Retiform
Mixed
Sex Cord Tumor with Annular Tubules
Unclassified
Gynandroblastoma
Steroid cell tumors
Stromal luteoma
Leydig cell tumor
Hilus cell tumor
Leydig cell tumor, nonhilus type
Steroid cell tumor not otherwise specified

Granulosa Cell Tumors: Adult Type

Adult-type granulosa cell tumors (AGCTs), as histologically described below, account for 95% of all GCTs. The majority of patients will present with one or a combination of the following clinical symptoms: abnormal vaginal bleeding, abdominal distention, and abdominal pain (5,6,15–18,23). The latter symptoms are most frequently attributable to the gross size of the tumor at the time of diagnosis, with the majority exceeding 10 cm in diameter and many exceeding 15 cm (5,16,18). In one series, 12% had ascites at diagnosis (23). In many series, menometrorrhagia, oligomenorrhea, or amenorrhea in premenopausal women or bleeding in postmenopausal women is the most common reason for seeking medical assistance. These and other clinical manifestations such as breast tenderness, uterine myohypertrophy, and endometrial hyperplasia are consistent with the presence of an estrogen-secreting tumor.

The endocrine function of AGCTs, specifically the production of estrogens, has been repeatedly demonstrated by assessment of the end organ, the endometrium, and measurements of peripheral levels of estrogen before and after surgery. In a detailed retrospective analysis of endometrial specimens from patients (n = 69) with GCTs, Gusberg and Kardon (24) observed histologic features consistent with unopposed estrogen, including atypical adenomatous hyperplasia in 42% of the evaluated cohort, adenocarcinoma *in situ* (4) in 5%, and invasive adenocarcinoma in

22%. Similarly, Evans et al. (4) noted endometrial hyperplasia in 55% and adenocarcinoma in 13% of their GCT study population. Other investigators have corroborated the high prevalence of glandular hyperplasia and have reported adenocarcinoma frequencies ranging from 3% to 27% (5,6,13,15–18,25,26). Selective ovarian venous catheterizations during surgery have documented hormonal production, including the secretion of large quantities of estrogen from the ovary harboring the GCT. The return of serum estrogen to physiologic levels after definitive treatment has been witnessed repeatedly. Occasionally, patients with GCTs present with endometrial changes (decidual reaction of the stroma or secretory characteristics of the glands) consistent with tumor production of progesterone (27). Rarely, virilizing changes such as oligomenorrhea, hirsutism, and other masculinizing signs may accompany GCTs (28–30).

Pathology

AGCTs have an average diameter of approximately 12 cm, but a subset, 10%–15% of the cases, are small and not appreciated on pelvic examination (31). Most characteristically, they are predominantly cystic, with numerous locules filled with fluid or clotted blood and separated by solid tissue (Fig. 26.1), or they are solid, with large areas of hemorrhage. The solid tissue may be gray-white or yellow and soft or firm. A rare tumor is cystic, usually thin walled, but occasionally thick walled, and multilocular or unilocular (29).

Microscopic examination reveals an almost exclusive population of granulosa cells or, more often, an additional component of theca cells, fibroblasts, or both. The granulosa cells grow in a wide variety of patterns. The better-differentiated tumors usually have microfollicular, macrofollicular, insular, or trabecular patterns. The microfollicular pattern is characterized by numerous small cavities (Call-Exner bodies) (Fig. 26.2) that may contain eosinophilic fluid, one or a few degenerating nuclei, hyalinized basement-membrane material, or, rarely, basophilic fluid. The microfollicles are typically separated by well-differentiated granulosa cells that contain scanty cytoplasm and pale, angular or oval, often grooved nuclei arranged haphazardly in relation to one another and to the follicles. The uncommon macrofollicular pattern is characterized by cysts lined by well-differentiated granulosa cells beneath which theca cells are present. The

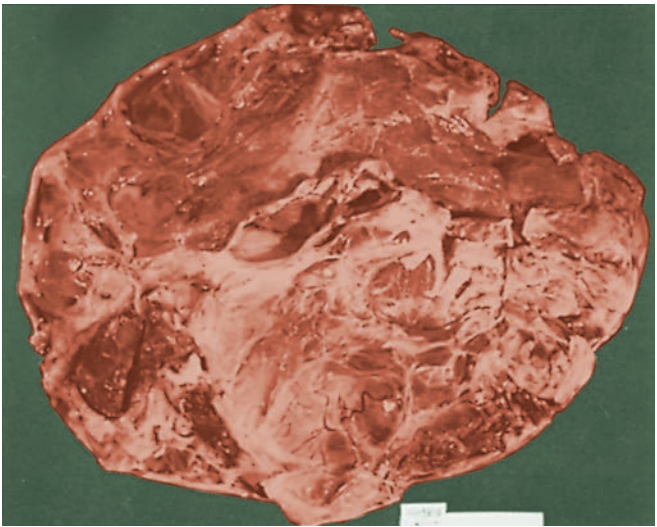


FIGURE 26.1. Granulosa cell tumor: The sectioned surface is composed predominantly of multiple cysts filled with blood.
Source: Reprinted with permission from Case Records of the Massachusetts General Hospital. Case 89–1961. *N Engl J Med.* 1961;265:1210–1214.

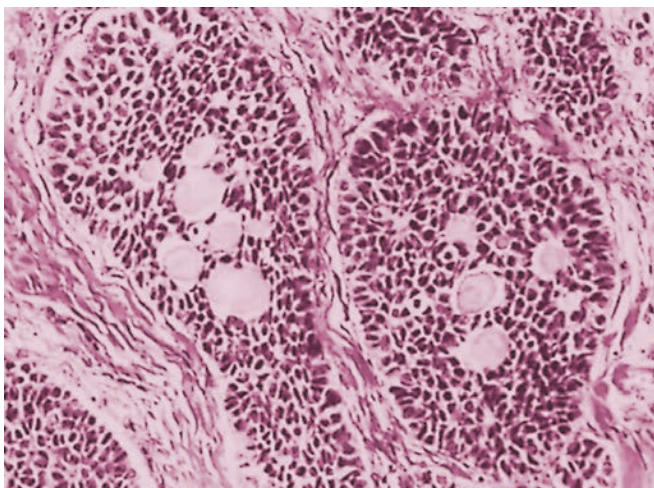


FIGURE 26.2. Granulosa cell tumor; adult type, microfollicular pattern. Several nests of granulosa cells with small oval and angular nuclei enclose multiple Call-Exner bodies.

trabecular and insular forms of GCTs are characterized by bands and islands of granulosa cells separated by fibromatous or thecomatous stroma. The less well-differentiated forms of the adult granulosa cell tumor typically have a water silk (moiré silk), gyriform, or diffuse (sarcomatoid) pattern alone or in combination. The first 2 patterns are manifested by parallel undulating or zigzag rows of granulosa cells, generally in single file, whereas the diffuse form is characterized by a monotonous, patternless cellular growth. In some adult granulosa cell tumors, the neoplastic cells have moderate to abundant quantities of dense or vacuolated cytoplasm; the term *luteinized granulosa cell tumor* is appropriate when such cells predominate (27). The cells in GCTs usually have round to oval, pale, and often grooved nuclei (Fig. 26.2), but rarely the cells are spindle shaped, resembling a cellular fibroma or low-grade fibrosarcoma; mitotic figures may be numerous, but are rarely atypical. There is usually only mild nuclear atypia, but approximately 2% of tumors contain mononucleate and multinucleate cells with large, bizarre, hyperchromatic nuclei, the presence of which does not appear to worsen the prognosis (32).

Natural History

Adult granulosa cell tumors are low-grade malignancies with a propensity to remain localized and demonstrate indolent growth. Ninety percent are stage I at diagnosis (26). The 10-year survival rate for stage I disease ranges from 86% to 96%; for more advanced disease at diagnosis, 26% to 49% (26). Bilaterality occurs in less than 10% (23). Tumor rupture occurred in 22% of a series of 97 cases (23). A unique feature of GCTs is recurrences at extended time intervals from primary therapy, suggesting the presence of persistent occult disease with a very indolent growth rate. For patients who recur, the median time to recurrence is 6 years and median survival after recurrence is 5.6 years (4,13). Numerous reports exist of recurrences occurring more than a decade following primary treatment (33,34).

Prognostic Factors

The staging system for GCTs is the same as that used for epithelial ovarian cancer (International Federation of Gynecology and Obstetrics [FIGO]). Whereas surgical stage has been recognized as the most important prognostic factor for GCTs, the impact of tumor size, rupture, histologic subtype, nuclear atypia, and mitotic activity on outcome is less clear and larger,

well-characterized series are necessary to clarify existing discrepancies (8,35,36). As noted above, GCTs are large and therefore prone to rupture. Rupture appears to adversely impact survival in stage I patients, justifying stratification as stage IC (13). However, the prognostic importance of positive cytology and surface involvement is less defined in stage I GCTs (8). In a series of 176 GCTs, only residual tumor after surgery (a surrogate for stage) and tumor size >13.5 cm were associated with recurrence on multivariate analysis (37). In other reports, tumor size lost independent predictability when stratified by stage (5,14,18,20,37). Increasing degrees of nuclear atypia and increasing mitotic frequency per 10 high-power fields (HPFs) have been correlated inversely with prognosis. Specimens from patients with more advanced disease tend to demonstrate higher grade of atypia and/or more mitotic figures (5,13,14,18). Despite its somewhat subjective assessment, nuclear grade has been reported to be a reliable prognostic indicator in stage I cases (13,18). The significance of histologic subtypes and ploidy status has been debated, and they appear to be of minimal value. Several investigative groups (4,5,12–14,18) have failed to confirm Kottmeier's (38) report of the prognostic importance of histologic patterns alone in GCTs. Similarly, the results of investigations utilizing flow cytometric analysis of DNA content have been inconsistent. Klemi et al. (39) reported a significant survival advantage for patients with tumors demonstrating normal ploidy and/or an S-phase fraction of less than 6%. However, other investigators have suggested that nondiploid GCTs are infrequently encountered (40,41). Chadha et al. (40) reported that 3 of 5 aneuploid tumors from a total population of 43 pathologically diagnosed GCTs were vimentin negative but positive for cytokeratin and epithelial membrane antigen, and therefore cautioned that such highly aneuploid tumors may represent undifferentiated carcinomas. Indeed, it is clear that some series of GCTs in the literature include undifferentiated carcinomas not otherwise specified, or recently recognized entities such as the large-cell carcinoma of hypercalcemic type. Therefore, series with unusually large numbers of late-stage or poor-prognosis cases should be evaluated cautiously.

Investigators have analyzed several potential molecular markers, including p53 status, telomerase, Ki-67, c-myc, HER2/neu, and VEGF in GCTs (42–47). To date, no molecular marker provides prognostic information for GCTs beyond what is known from stage and histopathologic parameters.

Ala-Fossi et al. stained 30 GCTs for the inhibin subunit. All 24 stage I and II tumors were positive, whereas 4 of 6 stage II–IV tumors were negative. Those that were negative were poorly differentiated and exhibited rapid disease progression. Whether other observers would have accepted these tumors as valid GCTs is a concern. Stage was the sole independent prognostic factor (48).

Serum Markers

Recognizing that the majority of patients presenting with advanced GCTs will recur, the identification of a specific serum tumor marker(s) would facilitate early detection of recurrent disease and monitoring of treatment effectiveness (4,5,16,18). As noted above, serum estrogens are generally produced by GCTs and have been utilized as an indicator of disease status (49). Unfortunately, serum estradiol levels are occasionally normal, and more frequently are only marginally increased, making them less than ideal for monitoring in a significant number of patients. Several proteins derived from granulosa cells, including inhibin, follicle-regulating protein, and müllerian-inhibiting substance, are readily assayable in serum and forwarded as useful diagnostic monitoring markers (50–58). In a prospective evaluation of 27 patients with GCTs, Jobling et al. (52) demonstrated that serum inhibin levels are typically elevated sevenfold above normal follicular phase levels prior to primary

surgical management. Mom et al. showed that inhibin B was the predominant form of inhibin secreted by these tumors, with a sensitivity and specificity of 89% and 100% compared to 67% and 100% for inhibin A. Elevations in inhibin B were present in 85% of recurrences and predated clinical evidence of recurrence by a median of 11 months (59). In recent years, inhibin and calretinin have become useful immunohistochemical markers to assist in the diagnosis of GCTs and, for that matter, other SCSTs (60).

Granulosa Cell Tumors: Juvenile Type

Ovarian neoplasms are relatively rare in childhood and adolescence. When encountered, the majority are of germ cell origin, with only 5% to 7% being SCSTs. The latter, consisting predominantly of the granulosa cell type in this age group, demonstrates a distinct tumor biology from the typical granulosa cell tumor (AGCT) considered above (61). Approximately 90% of the GCTs diagnosed in prepubertal girls and in most women less than 30 years of age will be of the juvenile type (JGCT). In a clinicopathologic analysis of 125 cases of JGCT, 44% occurred prior to age 10 years and only 3% after the third decade of life (62). The majority of prepubertal patients present with clinical evidence of isosexual precocious pseudopuberty, which may include breast enlargement, development of pubic hair, increased vaginal secretions, advanced somatic development, and other secondary sex characteristics (62–66). Serum estradiol levels were reported as being elevated in 17 of 17 cases of JGCTs with pseudopuberty (64). In addition, elevated levels of serum progesterone (6 of 10) and testosterone (6 of 8) were likewise observed, as well as suppressed levels of luteinizing hormone and follicle-stimulating hormone. The occasional patient will harbor an androgen-secreting JGCT accompanied by virilization (62,64,65). Although the signs of either precocious pseudopuberty or virilization are dramatic, the most consistent clinical sign at presentation in patients with JGCTs is increasing abdominal girth. Young et al. (62) indicated that in only 2 of 113 nonpregnant patients with JGCTs was the treating physician unable to palpate a mass on abdominal, pelvic, and/or rectal examination. Abdominal pain, dysuria, and constipation may coexist. Infrequently, a surgical emergency is encountered following spontaneous rupture or torsion of the enlarged ovary. Juvenile granulosa cell tumors may occur in infants, who appear to have a more favorable prognosis than older individuals (67). Hasiakos et al. described a recent case of JGCT associated with pregnancy and reviewed the literature (68).

The frequency of bilaterality for JGCTs is estimated to be 5%, similar to AGCTs (69). When stage was assigned based on surgical and histologic parameters, 88% were stage IA, 2% stage IB, 8% stage IC, and 3% stage II. As noted, extraovarian spread is infrequently encountered at exploration, whereas rupture of the tumor is noted in approximately 10% of cases. Ascites contributes to the abdominal distention in 10% to 36% of cases (62,64).

JGCTs have been reported in association with enchondromatosis alone (Ollier's disease) or concomitantly with hemangiomas (Maffucci's syndrome) (64,70–72). Individuals with these relatively uncommon mesodermal dysplasias generally present prior to puberty and frequently develop secondary neoplasms, most commonly sarcomas, after the second decade of life. Juvenile granulosa cell tumors are the next most frequent tumor associated with these disorders and become evident during the first and second decades of life. These observations appear to imply more than coincidental occurrences and suggest a generalized mesodermal dysplasia, perhaps contributing to the pathogenesis of these neoplastic processes. In addition, congenital bilateral JGCTs of the ovary have been reported in leprechaunism, a disease characterized by insulin resistance resulting from an insulin-receptor defect (73).

Pathology

The appearances of JGCTs are similar to the adult form; a solid and cystic neoplasm, in which the cysts contain hemorrhagic fluid, is common (62,63,66). Uniformly solid and uniformly cystic neoplasms are also encountered; the latter may be multilocular or, in rare instances, unilocular. The solid component is typically yellow-tan or gray and occasionally exhibits extensive necrosis, hemorrhage, or both.

Microscopic examination typically reveals a predominantly solid cellular tumor with focal follicle formation, but occasionally, a uniformly solid or a uniformly follicular pattern is seen. In the solid areas, the neoplastic cells may be arranged diffusely or as multiple nodules of various sizes. The follicles typically vary in size and shape; Call-Exner bodies are rarely encountered, and the follicles rarely reach the large size of those in the macrofollicular AGCT. The follicular lumens in the juvenile tumor contain eosinophilic or basophilic fluid, which stains with mucicarmine in approximately 2 of 3 cases.

The 2 characteristic cytologic features of the neoplastic juvenile granulosa cells that distinguish them from those of AGCT are their generally rounded, hyperchromatic nuclei, which almost always lack grooves, and their almost invariable moderate to abundant eosinophilic or vacuolated (luteinized) cytoplasm (Fig. 26.3). Nuclear atypia in JGCTs varies from minimal to marked; in approximately 13% of the cases, severe degrees are present. The mitotic rate also varies greatly but is generally higher than that seen in AGCTs, often being 5 or more per HPF (62,63).

Natural History

In the initial series by Young et al., 98% of 125 patients with JGCTs were less than 35 years of age, and 78% were 20 years or less (62). Notwithstanding the customary presenting complaint of increased abdominal girth and the clinical documentation of a large mass (64% >10 cm), 90% of the JGCTs analyzed by Young et al. (62) were stage IA or IB. The corresponding survival rate for these patients with an average follow-up of 3.5 years was 97%. Included were 9 stage IA2 patients with rupture of the tumor, all of whom were alive and free of disease. Patients presenting with associated isosexual pseudoprecocious puberty may have a more favorable prognosis. Assessing 80 such cases from 212 reported JGCTs, only 2 cancer-related deaths (2.5%)

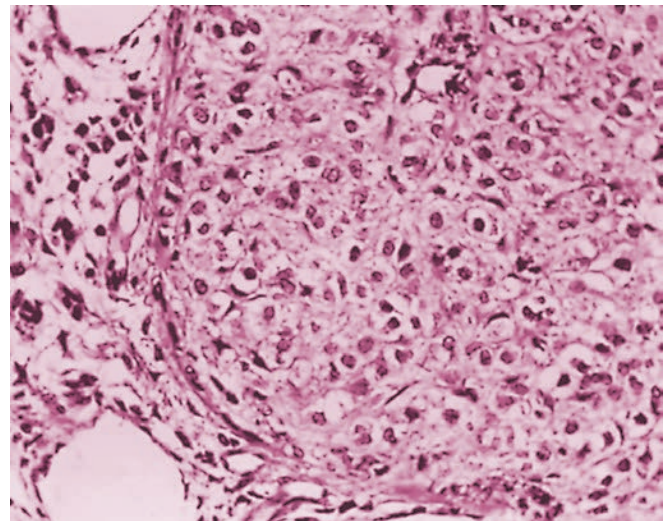


FIGURE 26.3. Granulosa cell tumor; juvenile type. A nodule of tumor is composed of large cells with abundant cytoplasm and slightly pleomorphic, hyperchromatic nuclei.

were observed. Presumably, the clinical manifestations lead to early diagnosis and excellent outcomes (62,64–66).

Although the presentation of early symptoms and localized disease are similar to AGCTs, the natural history of JGCTs differs notably in several respects. Although the adult form frequently includes a latency period with recurrences remote from initial diagnosis, the juvenile counterpart is characteristically aggressive in advanced stages and the time to relapse of limited duration, generally within 3 years of initial diagnosis (62,64,66). Thirteen cases of stage II, III, or IV disease were abstracted from 3 analyses with a combined sample size of 180 patients (62,64,65). Of these 13 cases, only 3 patients (23%) were alive when reported, and notably, the recurrences and deaths occurred within a relatively brief interval.

Prognostic Factors

Young et al. (62) noted surgical stage to represent the most reliable prognostic indicator. Tumor size, mitotic activity, and nuclear atypia were significant predictors only when analyzed without regard to stage. In that series, rupture did not correlate with outcome. Schneider et al. reported on a group of 54 SCSTs in children and adolescents from Germany (45 JGCTs and 9 others) (74). They addressed the outcome of patients with “accidental” stage IC disease, defined as violation of the tumor capsule during surgery, versus “natural” stage IC tumors, with preoperative rupture or malignant ascites. Among 12 patients with accidental stage IC disease, there were no recurrences. In contrast, 5 of the 9 patients with natural stage IC disease recurred ($p = 0.001$). Assessment of DNA content via flow cytometry in JGCTs demonstrated nondiploid patterns in nearly half (75,76). However, Jacoby et al. (75) were unable to correlate DNA ploidy or S-phase fraction (SPF) with either stage of disease or prognosis in patients with localized disease. In the series by Schneider et al., mitotic activity correlated with prognosis (74). There were no relapses in 35 patients whose tumors exhibited low or moderate mitotic activity. Among those with high mitotic activity (>19 mitoses per 10 HPFs), approximately half recurred.

Serum Markers

Although information specific to juvenile granulosa cell tumors is limited, the various tumor markers discussed above for AGCTs would appear to be applicable to JGCTs for monitoring of recurrent disease.

TUMORS IN THE THECOMA-FIBROMA GROUP

Considering that the ovarian stromal cell is the precursor of both fibroblasts and theca cells, pure thecomas and pure fibromas appear to represent extremes in a continuum, with a significant percentage of the tumors having admixtures of lipid-laden, steroid-secreting cells and collagen-producing spindle cells. Nonetheless, the vast majority of tumors in the thecoma-fibroma group are readily subcategorized based on relatively distinct clinical and histologic characteristics. The major subcategories include thecoma, fibroma-fibrosarcoma, and the sclerosing stromal cell tumor (SST).

Thecoma

Theca cell tumors (TCTs), or thecomas (Fig. 26.4), are composed of lipid-laden stromal cells, occasionally demonstrating luteinization, and are almost invariably clinically benign (4,77,78).

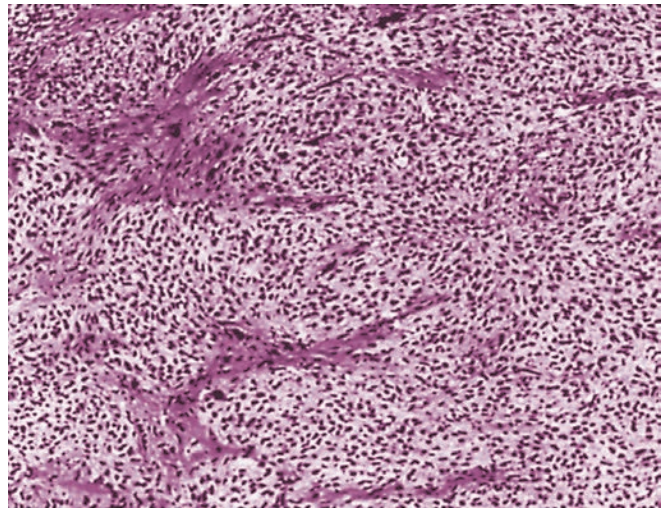


FIGURE 26.4. Thecoma. The tumor is composed of a mass of clear, vacuolated cells with round to oval nuclei intersected by bands of fibromatous tissue.

Source: Reprinted with permission from Morris JM, Scully RE. *Endocrine Pathology of the Ovary*. St. Louis, MO: Mosby, 1958.

Thecomas account for approximately 1% of ovarian neoplasms and occur at a more advanced age than other SCSTs. The majority of patients are in their sixth and seventh decades at the time of diagnosis (4,77). Combining 2 large series totaling over 140 patients, less than 10% presented prior to age 30 years. Notably, the luteinized tumors are an exception to this generalization, with 30% occurring in women before their fourth decade of life (79). Assessing a compendium of nearly 300 cases, bilaterality occurs with a frequency of approximately 2% and extraovarian spread occurs rarely, if at all (4,77,78,80).

The primary presenting signs and symptoms in patients with TCTs are abnormal vaginal bleeding and/or an abdominal/pelvic mass (77,78,80). The former urges initiation of medical intervention in the majority of postmenopausal patients, whereas an increasing abdominal girth or a palpable mass is more frequently the main presenting complaint of premenopausal patients. Lesion size has been reported to vary from less than 1 to 40 cm in diameter (77,78,80). Ascites is occasionally encountered.

Thecomas are considered to be among the most hormonally active of the SCSTs. The abnormal bleeding encountered in 60% of patients is presumably attributable to excess estrogen production (77,78). In the series reported by Evans et al. (4), endometrial hyperplasia was observed in 37% of the evaluable patients, and adenocarcinoma consistent with an unopposed estrogen effect was documented in an additional 27%. All the uterine cancers were well differentiated and minimally invasive, but 2 patients subsequently died of endometrial carcinoma. Other coexisting uterine pathologic findings potentially influenced by elevated circulating estrogen levels included leiomyomata, myohypertrophy, and endometrial polyps. Conversely, Zhang et al. (79) noted that nearly one-half of the evaluated luteinized thecomas were either nonfunctional or androgenic, resulting in a relatively significant frequency of masculinization.

An enigmatic tumor that has been considered to be a variant of luteinized thecoma has been associated with sclerosing peritonitis (81). These tumors are often bilateral and frequently have a brisk mitotic rate, but have not been shown to have metastatic potential. Sclerosing peritonitis has, however, been fatal owing to complications pursuant to it. Schonman et al. present a case of luteinized thecoma associated with sclerosing peritonitis treated with ovarian wedge resection (82). Despite a recurrent bowel obstruction, she was successfully treated with high-dose

steroids. She achieved pregnancy and was free of symptoms 18 months following treatment.

Fibroma-Fibrosarcoma

Fibromas represent the most commonly encountered SCST, accounting for approximately 4% of all ovarian neoplasms. These endocrine-inert tumors are seldom bilateral and vary in size from microscopic to extremely large masses. Although infrequently diagnosed prior to age 30 years, fibromas can occur at any age; the average age of diagnosis is the latter half of the fifth decade of life (83). As their size increases, fibromas tend to become more edematous, leading to the escape of increasing quantities of fluid from the tumor surfaces. Ascites is detected in association with 10%–15% of ovarian fibromas exceeding a diameter of 10 cm (84). Furthermore, 1% of patients develop a hydrothorax in addition to the hydroperitoneum (Meigs' syndrome) (85). Gorlin's syndrome represents an inherited predisposition to the development of ovarian fibromas along with several other abnormalities, the most frequent of which is the appearance of basal-cell nevi at an early age (86).

Although ovarian fibromas are generally benign, approximately 10% will demonstrate increased cellularity and varying degrees of pleomorphism and mitotic activity. Fibromatous tumors characterized histologically by an increased cellular density and brisk mitotic activity are designated cellular fibromas and are considered to be tumors of low malignant potential, particularly if ruptured or associated with adhesions (87). In contrast, fibrosarcomas are highly malignant neoplasms. These tumors are distinguished by their greater cellular density and, most notably, moderate to marked pleomorphism (88).

Sclerosing Stromal Cell Tumors

SSTs were initially described by Chalvardjian and Scully (89) in 1973 as a distinct subgroup within the thecoma-fibroma family of ovarian tumors. Accounting for less than 5% of SCSTs, this relatively rare tumor characteristically differentiates itself histologically and clinically from both thecomas and fibromas (90,91). Histologically, the presence of pseudolobulation of cellular areas separated by edematous connective tissue, increased vascularity, and prominent areas of sclerosis are distinguishing features. Clinically, SSTs commonly become manifest during the second and third decades of life, with 80% being diagnosed prior to age 30 years, which is unique among ovarian stromal tumors (92). The signs and symptoms that most commonly necessitate medical evaluation include menstrual irregularities and/or pelvic pain (93). Despite the relatively large tumor size, which ranges from clinically undetectable to 20 cm or more in greatest diameter, ascites is seldom encountered; this further contrasts SSTs from fibromas (93). In contrast to thecomas, SSTs were originally considered to be inactive endocrinologically (89). However, a limited number of cases have been subsequently reported in which steroidogenic activity has been clinically demonstrable (93–96). To date, all SSTs have been clinically benign, and with one exception (97), all have been unilateral. Although a recent report noted an elevated CA-125 level, which the investigators speculated was perhaps nonspecific (98), no specific tumor marker has been identified for SSTs to date.

Natural History

Ovarian thecomas, fibromas, and SSTs are considered to be benign neoplasms, and any associated morbidity or mortality is attributable to the treatment modalities or the sequelae of concurrent disease (4,77,80,83,99). Examples of the latter are deaths from endometrial carcinoma resulting from the unopposed estrogen produced by the thecomas (4). Although several

cases of "malignant thecomas" have been reported, critical reappraisal of such tumors invariably results in histologic reassignment to sarcomas or diffuse granulosa cell tumors (100). DNA ploidy analyses of thecomas and fibromas demonstrate aneuploid patterns in the majority, most commonly trisomy and/or tetrasomy 12, which offer a clue to their pathogenesis (101,102).

Prognostic Factors

The prognosis for patients diagnosed with cellular fibromas is generally considered to be quite favorable. Recurrences of these tumors of low malignant potential are generally correlated with adherent disease, rupture, or incomplete removal at the time of primary cytoreduction (87). Fibrosarcomas are associated with an extremely poor prognosis, but fortunately they are rare.

SERTOLI STROMAL CELL TUMORS

Neoplasms arising in the ovary exhibiting morphologic characteristics similar to those of the testes during various stages of gonadogenesis were recognized and elegantly described by Meyer (103,104). He reasoned that the origin of these tumors was the male blastema and coined the term *arrhenoblastoma*. Considering the functional nature of these male homologs and the varying degrees of associated defeminization and/or masculinization, the term *androblastoma* was also adopted. However, Morris and Scully (105), in 1958, contended that both designations implied masculinization, which is frequently absent, and furthermore facilitated the inclusion of a variety of unrelated androgen-producing ovarian tumors. Therefore, they recommended the adoption of the morphologic designation Sertoli-Leydig cell tumor (SLCT), which also allowed a consistent nomenclature for the general classification of SCSTs of the ovary. The SLCTs include tumors composed of Sertoli cells only, Leydig cells only, and a combination of Sertoli and Leydig cells.

Sertoli Cell Tumors

Sertoli cell tumors are rare, accounting for less than 5% of all SLCTs (92). The average age at presentation is about 30 years, but this lesion can occur at any age. Evidence of estrogen production has been observed in approximately two-thirds of the reported cases. Consistent with excess estrogen production, isosexual precocious puberty has been witnessed during the first decade of life, menstrual disorders during the reproductive decades, and postmenopausal bleeding in the decades after the climacteric. Reflecting tumor size (average 9 cm), capsular distention, and/or adnexal torsion, and abdominal distention and/or pain are frequent complaints. Pelvic examination generally confirms the presence of the tumor under these circumstances. The frequency with which excessive renin production has been associated with Sertoli cells appears to exceed mere chance (106–108). Evaluation of refractory hypertension and hypokalemia has rarely eventuated in the discovery of a Sertoli cell tumor as the origin of the excess renin. An occasional Sertoli cell tumor has arisen in a patient with the Peutz-Jeghers syndrome (PJS) (109).

Pathology

On gross examination, these rare tumors are typically solid, lobulated, and yellow (92,110). Microscopic examination typically shows hollow or solid tubules lined by cells that usually have relatively bland cytologic features, but rare tumors exhibit moderate to severe nuclear atypia. In most tumors, a tubular pattern predominates, but occasionally a diffuse pattern is conspicuous.

Prognosis

The great majority of these rare tumors have been unilateral stage I lesions. The greater majority of Sertoli cell tumors are well differentiated, and only rare tumors are malignant (92). Excision of the tumor results in prompt resolution of the hyperestrogenic state. (Leydig cell tumors are discussed in the section on steroid cell tumors below.)

Sertoli-Leydig Cell Tumors

SLCTs are extremely uncommon, accounting for less than 0.2% of all ovarian tumors. As implied by their designation, the tumors contain both Sertoli and Leydig cell elements. Many of the clinical characteristics are related to the degree of histologic differentiation and the presence of a retiform pattern and/or heterologous elements (described below). The average patient age at diagnosis is approximately 25 years, with the majority (70%–75%) of the tumors becoming clinically manifest during the second and third decades of life. Less than 10% occur either prior to menarche or after the climacterium. Patients harboring well-differentiated tumors present at an average age of 35 years, or 10 years later than patients with intermediate or poorly differentiated lesions. Conversely, tumors with retiform patterns are generally detected 10 years earlier than the intermediate and poorly differentiated tumors (111–113). Based on the compiled data from 3 reported series totaling over 300 patients, the frequency of extraovarian spread of disease at the time of diagnosis is approximately 2% to 3%. In addition, the likelihood of encountering bilateral tumors is even less frequent (111–113).

The most frequent complaints at the time of presentation of these generally healthy adolescents and young adults are menstrual disorders, virilization, and nonspecific symptoms resulting from an abdominal mass. Nearly one-half of the patients experience sufficient abdominal pain or discomfort or note abdominal distention or palpate a mass on self-examination to prompt professional assessment. Whereas capsular distention and/or intralesional hemorrhage or necrosis of the tumor and/or adjacent visceral compression by the tumor account for the associated chronic or intermittent pain, acute abdominal pain necessitating emergency intervention invariably reflects vascular compromise from torsion. While lesion size varies according to histologic differentiation (approximately 5 cm for well-differentiated tumors to >15 cm for poorly differentiated tumors), abdominal, vaginal, and/or rectal examination readily identifies an adnexal mass in approximately 95% of symptomatic patients. The most common premonitory symptoms, namely, menstrual disorders and subtle androgenic manifestations, predate by several months, and less often, by years, the recognition of the overt clinical signs or symptoms. Irregular bleeding, oligomenorrhea, and postmenopausal bleeding, retrospectively, have been attributed to either excess androgens or estrogens. The etiology of the latter is presumably the peripheral conversion of androgens to estrogens or, rarely, from an estrogen-secreting SLCT. Frank virilization occurs in 35% of the patients with SLCTs, and another 10% to 15% have some clinical manifestations consistent with androgen excess. The most frequent androgenic symptom complex encountered includes amenorrhea, voice deepening, and hirsutism. In addition, breast atrophy, clitorimegaly, loss of female contour, and temporal hair recession, for example, are signs of masculinization witnessed in patients with SLCTs (111–113). The prevalence of androgenic manifestations appears to be independent of the degree of histologic differentiation, but is observed less frequently in heterologous SLCTs and only occasionally in patients harboring retiform lesions (112,114–117). Although the preoperative diagnosis of SLCT in the absence of androgenic excess may be impossible, this neoplastic entity should constitute the primary preoperative diagnosis in patients with androgenic manifestations presenting

during the second through the fourth decades of life with a unilaterally palpable adnexal mass.

Uncommonly, estrogen manifestations are witnessed in the context of presumed end-organ estrogenic responses, including postmenopausal bleeding and endometrial polyp formation, hyperplasia, and adenocarcinoma. Cautious interpretation of such observations is required, realizing that peripheral conversion of androgens to estrogens may be as plausible as a primary estrogen-secreting SLCT. As expected from the clinical findings, most patients demonstrating signs of defeminization or virilization have elevated plasma testosterone levels (111–113). Whereas plasma androstenedione may occasionally be elevated, the urinary 17-ketosteroids, including dehydroepiandrosterone, are usually normal, with the occasional patient presenting with a slightly elevated level. An elevated testosterone/androstenedione ratio generally suggests the presence of an androgen-secreting ovarian tumor, most likely an SLCT. Recognizing that certain gonadotropin-releasing hormone (GnRH) agonists modulate androgen production by downregulating gonadotropin levels and through a direct effect on the ovary, Pascale et al. (118) demonstrated successful suppression of testosterone and androstenedione in five virilized women with the administration of GnRH agonists. Their data suggest that androgen-secreting tumors of the ovary appear to be less autonomous than such tumors originating in the adrenal gland. Surgical excision of the SLCTs results in a precipitous drop in androgen levels and, over time, partial to complete resolution of the clinical manifestations associated with androgen excess is observed.

The coexistence of other diseases with SLCTs has been chronicled. The frequency with which thyroid disease is observed in these patients appears to exceed mere chance. Furthermore, several cases of other mesenchymal tumors have occurred in patients with SLCTs, including sarcoma botryoides of the cervix as well as Ollier's disease (112,119). The latter is a rare disease, but it is associated with other SCSTs, specifically JGCTs, as noted above. Finally, a tendency toward familial occurrence appears to exist (112).

Pathology

Gross Features

Sertoli-Leydig cell tumors vary in size from small to huge masses, but most are between 5 and 15 cm in diameter. The majority are solid, often yellow, and lobulated (Fig. 26.5), but many are solid and cystic. Pure cystic tumors are exceptionally rare, in contrast to the situation with GCTs. Poorly differentiated tumors tend to be larger than those more differentiated, and contain areas of hemorrhage and necrosis more frequently (112). Tumors with heterologous or retiform components are more often cystic than other tumors in this category (114,115,117,120). The heterologous tumors occasionally simulate mucinous cystic tumors on gross examination, and retiform tumors may contain large edematous intracystic papillae, resembling serous papillary tumors, or may be soft and spongy with varying degrees of cystification (117).

Microscopic Features

Well-differentiated SLCTs are characterized by a predominantly tubular pattern (121). On low-power examination, a nodular architecture is often conspicuous, with fibrous bands intersecting lobules composed of small, round, hollow, or, less often, solid tubules lined by well-differentiated cells and separated by variable numbers of Leydig cells. Rarely the tubules appear pseudoendometrioid (122).

Sertoli-Leydig cell tumors of intermediate and poor differentiation form a continuum characterized by a variety of patterns and combinations of cell types (111–113). Some tumors exhibit intermediate differentiation in some areas and poor differentiation in others, and less commonly, tumors of intermediate

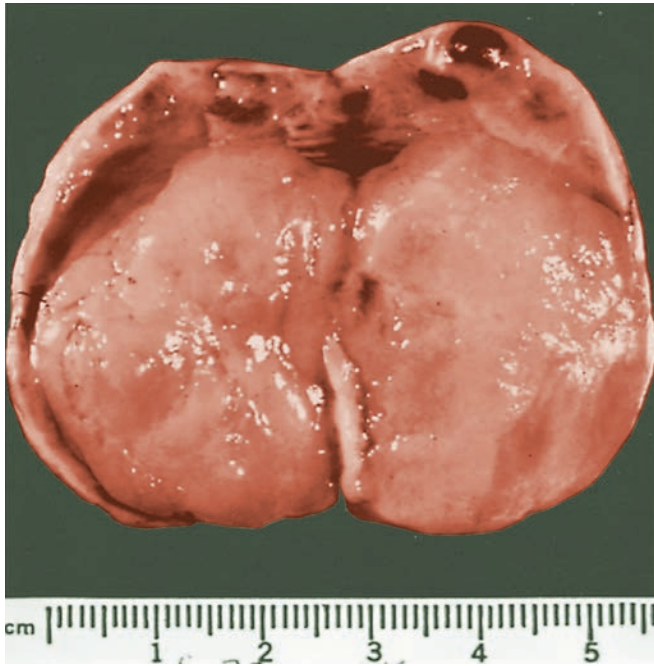


FIGURE 26.5. Sertoli-Leydig cell tumor. The sectioned surface of the tumor is focally lobulated and was yellow in the fresh state.

differentiation contain well-differentiated foci. Both the Sertoli cells and the Leydig cells may exhibit varying degrees of immaturity. In tumors of intermediate differentiation, immature Sertoli cells have small, round, oval, or angular nuclei and generally scanty cytoplasm and are arranged typically in ill-defined masses, often creating a lobulated appearance on low power; solid and hollow tubules, nests, broad columns of Sertoli cells, and, most characteristically, thin cords resembling the sex cords of the embryonic testis are often present (Fig. 26.6). These structures are separated by stroma, which ranges from fibromatous to densely cellular to edematous, and typically contains clusters of well-differentiated Leydig cells (Fig. 26.6). Cysts containing eosinophilic secretion may be present and create a thyroid-like appearance, and follicle-like spaces are encountered rarely. The Sertoli cell and Leydig cell elements, singly or in combination, may contain varying and sometimes large amounts of lipid in the form of small or large droplets. When a significant amount of the stromal component is made up of immature cellular mesenchymal tissue with high mitotic activity resembling a nonspecific sarcoma, the tumor is poorly differentiated.

Fifteen percent of SLCTs have a substantial retiform component, and are so designated because they are composed of a network of elongated tubules and cysts, both of which may contain papillae, resembling the rete testis (32). This pattern is usually accompanied by other patterns of SLCTs, but sometimes an entire tumor has a retiform pattern.

Heterologous elements occur in approximately 20% of Sertoli cell tumors (118,123). In a series of these tumors, 18% contain glands and cysts lined by moderately to well-differentiated intestinal-type epithelium (118). Mesenchymal heterologous elements, encountered in 5% of Sertoli cell tumors, include islands of cartilage arising on a sarcomatous background, areas of embryonal rhabdomyosarcoma, or both (123).

Natural History

SLCTs display characteristics that differ markedly from their epithelial counterparts, notably in regard to their malignant potential. Despite an average size of approximately 16 cm, only

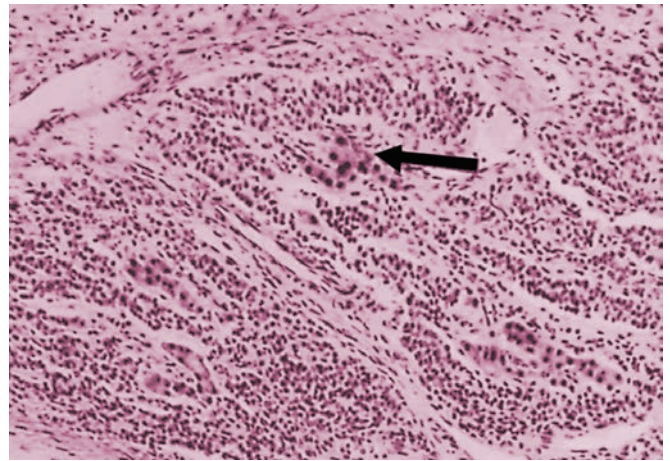


FIGURE 26.6. Sertoli-Leydig cell tumor; intermediate differentiation. Nests of large Leydig cells (arrow) lie among bands of immature Sertoli cells.

Source: Reprinted with permission from Morris JM, Scully RE. *Endocrine Pathology of the Ovary*. St. Louis, MO: Mosby; 1958.

2% to 3% of SLCTs have demonstrable extraovarian spread at the time of detection. Furthermore, Young et al. (62) identified only 29 clinically malignant cases in their series of 220 SLCTs having variable observation intervals, and they noted an 18% malignancy rate among 164 patients with adequate follow-up. At least in part, the more favorable prognosis reflects the abrupt onset of androgenic manifestations and the early detection of nonspecific symptoms, which promote prompt medical assessment. Nevertheless, the natural history of the malignant variant includes early recurrences, with approximately two-thirds becoming evident within 1 year of treatment and only 6%–7% recurring after 5 years. The abdominal cavity (including the pelvis) and the retroperitoneal nodes are the most frequent sites for recurrences. In addition, the contralateral ovary, lungs, liver, and bone are other reported sites of recurrent metastatic disease. The collective salvage rates in patients with clinically malignant disease are low, with extrapolated estimates being less than 20%.

Prognostic Factors

Stage is the most important predictor of outcome in SLCTs. Fortunately, 97% of SLCTs are reportedly stage I at diagnosis, and less than 20% of these localized tumors become clinically malignant. The most cogent phenotypic prognostic determinant for stage I SLCTs is the degree of histologic differentiation (111–113). Approximately one-half of the reported SLCTs are of intermediate differentiation, 10% are well differentiated, 20% are heterologous, and the remainder are poorly differentiated. No extraovarian spread or subsequent recurrences were encountered by Young and Scully (121) among 23 well-differentiated SLCTs. However, approximately 10% of intermediate and 60% of poorly differentiated tumors, as well as 20% of heterologous tumors, demonstrated clinically malignant behavior (112). The heterologous tumors contain either endodermal elements such as gastrointestinal epithelium and carcinoids or mesenchymal elements including skeletal muscles and/or cartilage. The endodermal elements are typically associated with intermediately differentiated homologous elements and represent 75% of the heterologous SLCTs. Their corresponding prognosis parallels that of the intermediately differentiated homologous tumors. In contrast, heterologous tumors containing mesenchymal elements account for 5% of all SLCTs and invariably coexist with a poorly differentiated homologous component. The clinically aggressive malignant behavior of poorly differentiated heterologous tumors is witnessed in the extremely low survival (112).

Retiform patterns, tumor size, mitotic activity, and tumor rupture appear to increase in frequency as the degree of tumor differentiation decreases (111–113). Approximately 10% of neoplasms express histologic patterns resembling the rete testis. They are more commonly observed in younger patients (average age, 15 years) and are generally larger, possibly secondary to the less frequent association of androgenic manifestations and hence a later clinical presentation (114–117). Sertoli-Leydig cell tumors harboring a retiform pattern are associated with a 20% malignancy rate, significantly higher than the 12% non-retiform SLCT rate. Young and Scully (117) noted that 14 of 25 retiform cases were of intermediate differentiation, with 1 demonstrating poorly differentiated homologous histology and 10 exhibiting heterologous elements (3 intermediate and 7 poorly differentiated). Arguably, the less favorable prognosis reflects the frequency of associated heterologous and/or poorly differentiated homologous lesions. This concept is supported by the findings that the majority of the metastatic lesions do not contain retiform patterns (117). However, the adverse characteristics of the retiform component are witnessed when examining tumors of intermediate differentiation. Although only 4 of over 100 reported intermediately differentiated SLCTs were clinically malignant, 3 of the 4 contained retiform patterns (112).

Tumor size, mitotic activity, and tumor rupture have been reported to influence prognosis (111,112). The size, mitotic index, and rupture frequency appear to increase as histologic dedifferentiation increases. Notwithstanding these associations, substratification of intermediate and poorly differentiated lesions according to these parameters identifies significant prognostic differences.

The frequency of androgen excess has been addressed above, with 50% or more of patients diagnosed with SLCTs either directly or indirectly displaying clinical manifestations of hyperandrogenism. Serum testosterone levels are invariably elevated when virilization is present, and selective venous catheterization has documented the ovary as the site of origin (124,125). In addition, immunostaining was positive for testosterone in eight SLCTs analyzed, including a limited number of tumors from patients without clinical signs or symptoms of androgen excess (2,126). The Leydig cells, as anticipated, were shown to be the cell of origin for the synthesis of testosterone. Following cytoreductive surgery, the serum testosterone levels are rapidly cleared from the circulation and have been reported on occasion to increase again as a function of the burden of recurrent metastatic disease.

Other unique secretory products, namely, inhibin and alpha fetoprotein (AFP), have been reported in a limited number of SLCTs and are proteins generally equated with GCTs and germ cell tumors, respectively (115,117,125–127). In addition to GCTs, the Sertoli and Leydig cells have been shown to produce inhibin in testicular tissues, and presumably these same cell types are the site of origin in the SLCTs. Motoyama et al. (127) summarized the literature and reported the 14th case of an elevated serum AFP accompanying SLCTs. A clinically malignant course was appreciated in 43% of the described population, which had a mean age of 16 years. In addition, the majority (57%) was described as having a retiform component, a frequency substantially higher than the 10% usually seen in larger SLCT samples. Perhaps preferential AFP sampling accounts for a portion of this seemingly unusually high frequency in that, histologically, the retiform pattern may be confused with an endodermal sinus tumor, particularly in the absence of clinical androgenic manifestations. The Sertoli and Leydig cells appear to be the cells of origin for AFP within the tumor. Employing immunostaining, Gagnon et al. (126) confirmed that Leydig cells appear to be the predominant site for AFP synthesis, but Sertoli cells are also capable of producing this oncoprotein. Testing 4 retiform and 4 nonretiform SLCTs, they demonstrated a 50% positivity rate in both histologic subtypes. The precise frequency of both inhibin

and AFP positivity and their correlation with disease activity await larger confirmatory assessments.

OVARIAN SEX-CORD TUMOR WITH ANNULAR TUBULES

In 1970, Scully (69) described a limited series of unique ovarian tumors characterized by either simple or complex ring-shaped tubules and proposed the morphologic designation ovarian sex cord tumor with annular tubules (SCTATs). The distinctive cellular elements of these neoplasms were judged to be histologically representative of an intermediate between Sertoli cell and GCTs. Shen et al. (128) reported that SCTATs accounted for 6% of the sex-cord tumors treated at their institution. An association with PJS was likewise recognized, and in a subsequent report of 74 cases of SCTAT, Young et al. (129) noted that approximately 1 in 3 SCTATs occurred in patients with PJS. Ovarian sex cord tumors with annular tubules occurring in association with PJS are typically small (many microscopic), multifocal, calcified, and bilateral. The average age of presentation is the early to mid-portion of the fourth decade of life (129,130). The non-PJS tumors are considerably larger, seldom multifocal or calcified, and invariably unilateral. The average age of these patients is the mid to latter portion of the third decade of life.

Abnormal vaginal bleeding is the most common presenting complaint, including menstrual irregularities during the reproductive era and postmenopausal bleeding during the mature years. Menometrorrhagia followed by prolonged episodes of amenorrhea is commonly experienced in the non-PJS patients. Abdominal pain or discomfort is less frequently encountered, but generally accompanies grossly involved adnexa or other incidental pelvic pathology. In addition, the signs and symptoms accompanying intussusception secondary to colonic polyp formation may be manifested in PJS-associated patients. The majority of PJS-associated SCTATs are not detectable via clinical examination and are appreciated unexpectedly during surgical or pathologic assessment. In contrast, the majority of non-PJS SCTATs are palpable on abdominal and/or vaginal examination. Although these tumors are seldom encountered during the first decade of life, isosexual precocity is invariably witnessed when SCTATs are diagnosed in affected children (129–132).

Considering the rarity of both PJS, an autosomal dominant disorder, and SCTAT, the frequency of concurrency of these two processes suggests a potential linkage in their pathogenesis. Approximately 36% of SCTATs are observed in patients with PJS. In addition, 15% of PJS-associated SCTATs also develop adenoma malignum of the cervix (AMC), a neoplasm that defies early diagnosis and is associated with a relatively high mortality rate (129,133–135). A recent report of 34 patients with PJS demonstrated a significantly elevated risk (relative risk = 20.3) of breast and gynecologic malignancies in women (136); 1 patient had a Sertoli-Leydig tumor and 3 had sex cord tumors with annular tubules. The PJS gene was mapped to chromosome 19p13.3 (137) and was later identified as a novel serine threonine kinase, STK11 (138). Because of the wide variety of malignancies occurring in individuals with PJS, STK11 is believed to function as a general tumor-suppressor gene.

Contingent on the patient's age, precocious puberty, menstrual irregularities, or postmenopausal bleeding are clinical manifestations of SCTATs, indirectly attesting to their endocrine activity (129–133,135,139,140). These signs of hyperestrogenism and the corresponding effects on the endometrium were readily recognized in the initial description of these unique tumors (61). Numerous reports have confirmed the presence of endometrial hyperplasia and/or polyp formation, particularly in PJS-associated SCTATs. Although similar signs in endometrial

histology can be observed in non-PJS SCTATs, clinical histories of menorrhagia followed by episodes of amenorrhea are more frequently obtained (128–131,139,140). Endometrial sampling in a limited population of such patients has demonstrated a spectrum from atrophic glandular to secretory or decidualized endometrium suggestive of significant levels of progesterone production (128,130,140). Assessment of circulating steroid levels has confirmed the presence of excessive estrogen in essentially all SCTAT cases (128,139–141). However, normal progesterone levels have been observed in PJS-associated tumors, but elevated quantities of progesterone have been documented in non-PJS patients (128,139–141). Shen et al. (128) demonstrated elevated estrogen and progesterone levels (and normal testosterone levels) in 2 SCTAT patients without PJS having documented glandular atrophy and decidual stromal changes. Utilizing selective ovarian venous sampling, Crain (140) demonstrated a significant progesterone gradient between peripheral and ovarian venous serum in a non-PJS patient with pseudodecidual changes of the endometrium. Complete resolution of the manifestations attributed to these hormonal imbalances has been routinely witnessed with surgical extirpation of the ovarian neoplasm.

Pathology

Grossly, the PJS-associated tumors are solid and yellow. The non-PJS-associated neoplasms may be similar, but in some cases, they are solid and cystic or mostly cystic. This tumor is characterized microscopically by the presence of simple and complex annular tubules (Fig. 26.7). The simple tubules have the shape of a ring, with the nuclei oriented around the periphery and around a central hyalinized body composed of basement membrane material; an intervening anuclear cytoplasmic zone forms the major component of the ring. The more numerous complex tubules are rounded structures made up of intercommunicating rings revolving around multiple hyaline bodies. In patients with PJS, the tumors are typically multifocal and exhibit calcification.

Prognostic Factors

Notwithstanding their histologic similarities, the differences in the natural history and hence long-term prognosis for SCTATs associated with PJS and SCTATs independent of PJS are readily apparent. Those detected in women with PJS are benign.

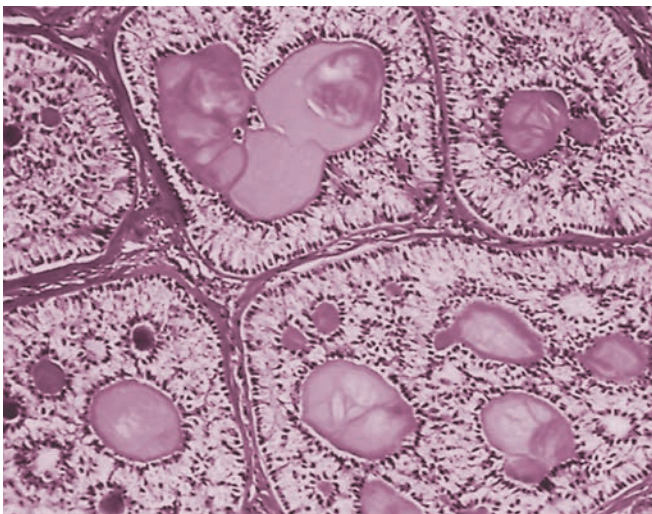


FIGURE 26.7. Sex-cord tumor with annular tubules. Numerous rounded tubules encircle multiple hyaline bodies.

Important in the management of this entity, however, is the recognition that approximately 15% of these patients will harbor an AMC. In addition, there are almost always exceptions to the rule. Barker et al. reported a 54-year-old woman with SCTAT and PJS who demonstrated aggressive malignant behavior and had multiple recurrences (142). The authors also reviewed the literature, identifying 2 previous such patients. As a result of delayed declaration of symptoms, the diagnosis of AMC is frequently made following examination of the hysterectomy specimen. As evident in the recent review by Srivatsa et al. (135), the prognosis for PJS patients with SCTAT and AMC is ominous, reflecting high AMC recurrence rates and refractoriness to treatment.

Based on the compiled data from 4 reported series totaling 63 patients with SCTATs without clinically apparent PJS, the clinical malignancy rate approximated 20% (128–131). Primary extraovarian extension and/or the recurrence frequency has been correlated with the original tumor size and mitotic activity. The tumor characteristically has a relatively long doubling time, a propensity for lymphatic dissemination, and an aptness to remain lateralized. As the primary ovarian lesion is invariably unilateral, the lymphatic metastases are invariably ipsilateral, extending within the confines from the paraortic region to the supraclavicular area. The nature of the retroperitoneal metastases generally facilitates surgical resection and repeat cytoreduction. The tumor's indolent growth pattern, coupled with the relative ease of resection, affords patients extended palliation.

Because SCTATs possess characteristics of both granulosa cells and Sertoli cells, tumor markers elicited by either or both cell types might find utility in the diagnosis and surveillance of these tumors as well. The observed increased serum estrogen levels and the corresponding clinical manifestations recognized with SCTATs suggest utility in monitoring hormone levels. Unfortunately, serum estradiol lacks adequate sensitivity, particularly when the residual tumor volume is limited. However, recent reports demonstrate the potential value and sensitivity of two unique secretory proteins as tumor markers for SCTATs. Gustafson et al. (141) illustrated the applicability of monitoring serum inhibin and müllerian-inhibiting substance (MIS) in the management of a patient with advanced, recurrent SCTAT. More recently, Puls et al. (143) likewise reported an excellent correlation between serum inhibin and MIS levels and the clinical status of a patient with SCTAT during chemotherapy administration. The ultimate utility of these tumor markers awaits accrual of sufficient numbers of patients with SCTATs to address adequately sensitivity and specificity issues.

SEX CORD-STROMAL TUMORS, UNCLASSIFIED

This ill-defined group of tumors, which accounts for less than 10% of those in the sex cord-stromal category, comprises those in which a predominant pattern of testicular or ovarian differentiation is not clearly recognizable. Talerman et al. (144) have recently segregated from within this category a group of tumors for which they have proposed the designation “diffuse nonlobular androblastoma.” The 6 ovarian tumors they reported were mostly estrogenic and had a predominant diffuse proliferation of cells resembling theca cells, granulosa cells, or both, but 5 of the six cases also contained steroid-type cells and tubules typical of Sertoli cell neoplasia.

SCSTs may be particularly difficult to subclassify when they occur in pregnant patients because of alterations in their usual clinical and pathologic features (145). Their nature is rarely suggested clinically because during pregnancy, estrogenic

manifestations are not recognizable, and androgenic manifestations are rare. In one study, 17% of 36 SCSTs that were removed during pregnancy were placed in the unclassified group, and many of those that were classified in the granulosa cell or Sertoli-Leydig cell category had large areas with an indifferent appearance (145).

Gynandroblastoma

Gynandroblastoma is an extremely rare SCST if strict morphologic criteria are followed to establish the diagnosis. Microscopically, these tumors must demonstrate readily identifiable (at least 10%) granulosa cells and tubules of Sertoli cells. Not surprisingly, the corresponding stromal cells, namely, theca and/or Leydig cells, may also be present in varying degrees. Martin-Jimenez et al. (146) recently reviewed the world literature and were able to identify only 17 authenticated cases of gynandroblastoma. Patients presented at an average age of 29.5 years (range, 16–65 years) with primary symptoms of menstrual disturbances consistent with the predominant functional status of the tumor. Commonly, a hyperandrogenic clinical profile is elicited, but signs and symptoms of excessive estrogens or no endocrine manifestations can be encountered. Amenorrhea, hirsutism, and clitorimegaly are frequently noted in association with elevated testosterone levels. Conversely, the common end-organ responses to hyperestrogenism include menometrorrhagia, postmenopausal bleeding, and endometrial hyperplasia. Although the unilateral masses are typically small, 75% are palpable prior to surgical exploration and are characterized by well-differentiated ovarian and testicular constituent elements. Regardless of the associated hormonal activity, gynandroblastomas are considered to be tumors of low malignant potential. To date, only a single case was reported to have been clinically malignant and resulted in death of the patient (147). A gynandroblastoma in pregnancy has also been reported (148).

Steroid Cell Tumors

Steroid cell tumors (SCTs) constitute only 0.1% of all ovarian neoplasms. The predominant components of these tumors are steroid hormone-secreting cells including lutein cells, Leydig cells, and adrenocortical cells. Until recently, the term *lipid cell tumors* was applied to these neoplasms, but Hayes and Scully (149) noted that 25% of such designated tumors did not contain appreciable intracellular fat. Hence, the functional designation steroid cell tumors was suggested and stratified into 3 subclasses: stromal luteoma, Leydig cell tumor, and steroid cell tumors not otherwise specified. The first 2 categories are essentially invariably benign, but some in the third group are malignant.

Stromal Luteoma

In 1964, Scully et al. (150) described the stromal luteoma as a distinctive type of steroid cell tumor. These relatively small (<3 cm) tumors are localized within the parenchyma of the ovary and account for approximately 25% of SCTs. They are thought to arise from luteinized stromal cells or their precursors. Histologically, the adjacent ovarian matrix as well as the contralateral ovary demonstrate stromal hyperthecosis in the vast majority of cases. The distinction between nodular hyperthecosis and stromal luteomas has been arbitrarily based on size, with lesions <5 mm being referred to as nodular hyperthecosis. In contrast to stromal hyperthecosis, stromal luteomas are rarely bilateral.

The average age at which stromal luteomas are diagnosed is the latter half of the sixth decade of life, with 80% occurring after the climacterium (149). Considering that the predominant

functional profile is estrogenic, the result of either direct tumor secretion or peripheral conversion of androgens, it is not surprising that abnormal vaginal bleeding is the primary complaint. In a series of 25 cases reported by Hayes and Scully (149), information regarding the histologic architecture of the endometrium was known for 17 cases, which included 14 cases of hyperplasia and a single case of a well-differentiated adenocarcinoma of the endometrium. Conversely, 12% of the patients presented with clinical manifestations of hyperandrogenism. In their analysis, 20% of the tumors were functionally quiescent and were detected incidentally during histologic assessment of surgical specimens processed for a variety of other indications.

Prognostic Factors

Considering the small size and lack of atypical histology, the posttreatment course is benign. To date, we are unaware of a single adverse outcome. Any untoward sequelae related to the stromal luteoma would presumably reflect secondary events from prolonged excessive hormone secretions such as an endometrial carcinoma.

Leydig Cell Tumors

Leydig cell tumors account for only 15% to 20% of SCTs. Histologically, the cellular elements are indistinguishable from lutein cells or adrenocortical cells except for the presence of crystals of Reinke, a requirement based on either light or electron microscopy for definitive diagnosis. Roth and Sternberg (151) subdivided these tumors according to location and possibly the cell of origin, namely, Leydig cell tumors of hilar type versus nonhilar type. Whereas the latter presumably arise from ovarian stromal cells and are extremely rare, the former tumors are located in the hilus of the ovary and encroach on or extend into the ovarian stroma in varying degrees. Other tumors containing features of Leydig cell tumors (such as location in the ovarian hilus or adjacent to nonmyelinated nerve fibers, location within a continuum of hilar cell hyperplasia, fibrinoid vascular changes in the tumor, clustering of cells around vessels) but lacking crystals of Reinke are preferably categorized as steroid cell tumors not otherwise specified (152). By combining 2 reviews (152,153) that summarize the English-language literature prior to and after 1966, 38 Reinke-positive cases affording adequate abstraction were identified. These invariably unilateral tumors are typically small, ranging in size from 0.7 to 15 cm, with a mean of 2.7 cm, and are therefore frequently not detectable via clinical examination or pelvic imaging. Similar to stromal luteomas, the age of diagnosis is 58 years (range, 37 to 86 years), with only a small percentage occurring prior to the climacterium. The initial clinical manifestations are usually consistent with a hyperandrogenic state. Overt signs of virilization are observed in greater than 80% of the patients. These include one or more of the following: hirsutism, acne, deepening of the voice, breast atrophy, clitorimegaly, and male-pattern baldness. In contrast to the frequently dramatic onset and progression of virilization witnessed with SLCTs, ovarian Leydig cell tumors are generally characterized by a more indolent course. Paraskevas and Scully (152) reported an interval of 7 years between recognized onset of signs and symptoms of androgen excess and diagnosis. Analysis of serum androgens demonstrated testosterone to be consistently elevated while urinary 17-ketosteroids were normal or marginally increased. These observations suggest minimal production of androstenedione or dehydroepiandrosterone by these tumors.

Conversely, estrogenic manifestations are occasionally witnessed, such as irregular menses or postmenopausal bleeding (152,153). Pathologic assessment of the uterus may reveal endometrial hyperplasia, polyp formation, and/or carcinoma in the presence or absence of leiomyomata and/or myohypertrophy.

Whether the hyperestrogenic features are a result of tumor secretion of estrogens or peripheral conversion of androgens to estrogens remains to be ascertained.

Prognostic Factors

In a review of the English literature through 1988, 38 Reinke-positive cases were accrued and only a single case of a clinically malignant lesion was identified (152,153). Based on tumor size (15 cm) alone, this sole example might be considered to be an outlier. Hence, similar to stromal luteomas, ovarian Leydig cell tumors are essentially benign neoplasms with the primary postsurgical concerns consisting of regression of the androgen-induced alterations. Generally speaking, significant regression is witnessed, but significant residual sequelae are appreciated in approximately one-half of the patients.

Steroid Cell Tumors Not Otherwise Specified

Neoplasms identified as steroid cell tumors but lacking the specific characteristics of stromal luteomas or Leydig cell tumors are collectively classified as steroid cell tumors not otherwise specified (SCTNOS). These tumors constitute the majority of steroid cell tumors and undoubtedly include both Leydig cell tumors and stromal luteomas that fail to meet specific identification criteria already noted. Although serving as a catchment for an undefined percentage of steroid hormone-secreting tumors, as a group, the SCTNOS have nonetheless unique characteristics. The natural history and biology of these tumors are significantly different when compared to Leydig cell tumors or stromal luteomas.

Although the average age at presentation of patients harboring SCTNOS is 43 years (10 to 15 years earlier than stromal luteomas and/or Leydig cell tumors), these tumors have been diagnosed from early childhood to the ninth decade of life (154). In addition, these generally solid yellow tumors are larger than the other SCTs. The average size at diagnosis approximates 8.5 cm (range, 1.2 to 45.0 cm). Furthermore, a higher frequency of bilaterality (5%) in advanced disease is encountered with these neoplasms. In their review of 63 collated cases, Hayes and Scully (154) reported that 81% of cases had localized disease (stage I), 6% had stage II disease, and 13% had stage III or IV disease. Curiously, they noted the average age (54 years) of patients with advanced disease was 10 years older than the group as a whole. At least in part, these findings reflect the absence of documented advanced malignancies during the first 2 decades of life.

Clinical signs and/or symptoms of androgen excess ranging from heterosexual precocity in prepubertal girls to amenorrhea, hirsutism, and/or virilization during the reproductive and/or postmenopausal ages prompt the majority of patients to seek medical advice (154,155). Not infrequently, the duration of these androgenic changes may have extended over many years (156). Additional concerns at presentation include increasing abdominal girth reflecting tumor size and, rarely, ascites, abdominal pain, cushingoid symptoms, and irregular uterine bleeding. The latter may represent clinical manifestations of estrogen excess (154,157), which has been suggested to occur at a frequency of 6% to 23%. Whether the source of estrogen is *de novo* synthesis by the tumor or from peripheral conversion of androgens remains to be determined. Isosexual precocious pseudopuberty has been detected in young girls harboring SCTNOS (154,158,159). An additional 10% to 15% of patients are asymptomatic, with tumors being detected incidentally during routine pelvic examination or at the time of hysterectomy or other surgical interventions.

The steroid hormone-secreting capacities of SCTNOS are more diverse than those of most SCTs. Whereas approximately 1 in 4 patients does not demonstrate clinical manifestations

of hormonal imbalances, the majority of patients with SCTNOS have evidence of androgen excess (10%–15% estrogen excess), and a lesser percentage have evidence of cortisol excess. These excesses are demonstrable via assessment of end-organ responses and serum/plasma steroid levels. Whereas elevated plasma levels of corticosteroids are typically observed in conjunction with SCTNOS, the number of overt presentations with Cushing's syndrome is limited (158,160–162). However, 17% of the clinically malignant tumors reported by Hayes and Scully (154) were associated with Cushing's syndrome. The serum testosterone and androstenedione levels are invariably elevated, as are urinary 17-ketosteroids; presumably, the latter reflect the level of excess androstenedione production.

Pathology

Gross Features

The tumors are typically solid, well circumscribed, occasionally lobulated (Fig. 26.8), and average 8.4 cm in diameter (154). Approximately 5% are bilateral. They are typically yellow or orange but are occasionally red, dark brown, or black. Necrosis, hemorrhage, and cystic degeneration are occasionally observed.

Microscopic Features

On microscopic examination, the tumor cells are typically arranged diffusely but occasionally grow in nests, irregular clusters, thin cords, and columns. The polygonal to rounded tumor cells have distinct cell borders, central nuclei, and moderate to abundant amounts of cytoplasm that varies from eosinophilic and granular to vacuolated and spongy (Fig. 26.9). In approximately 60% of the cases, nuclear atypia is absent or minimal and mitotic activity is low (less than 2 mitotic figures [MFs] per 10 HPFs). In the remaining cases, grades 1 to 3 nuclear atypia (Fig. 26.3) is present, usually associated with an increase in mitotic activity (up to 15 MFs per 10 HPFs).

Prognosis

In contrast to the benign natural history of both ovarian Leydig cell tumors and stromal luteomas, SCTNOS are associated with a relatively high rate of clinical malignancy. In the largest series in the literature, 43% of patients with follow-up of

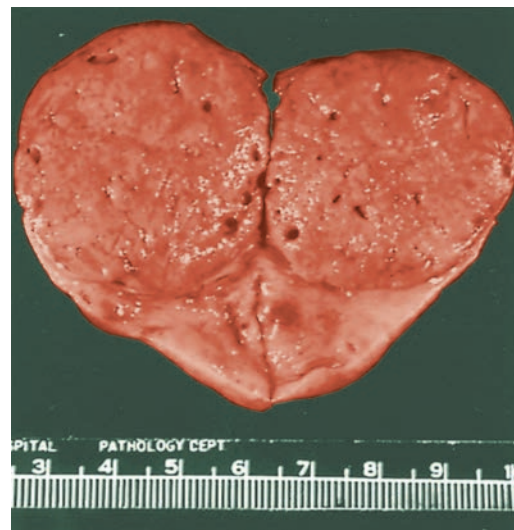


FIGURE 26.8. Steroid cell tumor; unclassified. The sectioned surface of the tumor is lobulated and was yellow-orange in the fresh state. This tumor was from a 9-year-old virilized girl.

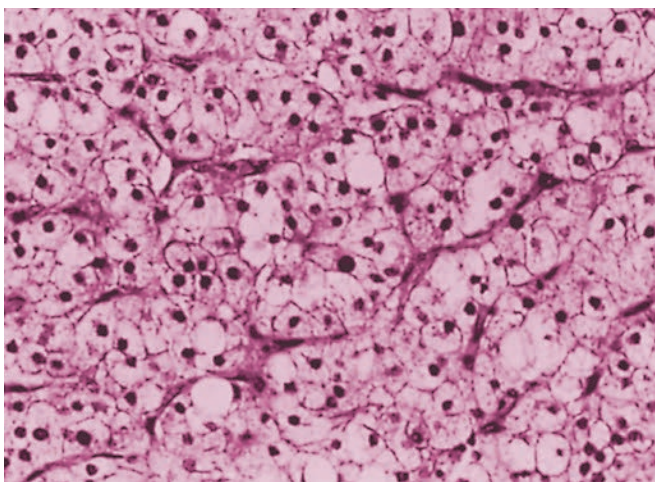


FIGURE 26.9. Steroid cell tumor: The tumor cells are large and rounded and laden with lipid vacuoles.

Source: Reprinted with permission from Hayes MC, Scully RE. Ovarian steroid cell tumors not otherwise specified [lipid cell tumors]: a clinicopathologic analysis of 63 cases. *Am J Surg Pathol.* 1987;11:835–845.

3 or more years demonstrated extraovarian disease either at primary surgery or during subsequent follow-up (163). Unfortunately, to date, salvage therapy has been abysmal. Multiple factors appear to correlate with the frequency of disseminated disease including age, stage, tumor size, mitotic activity, tumor necrosis, hemorrhage, and symptoms of Cushing's syndrome. The average age of patients with clinical malignancies was 16 years older than patients without metastatic disease and having had 3 or more years of observation. No clinically malignant cases have been reported to date in patients less than 20 years of age. All malignant SCTNOS were reported to measure 7 cm or more in greatest diameter (154). In fact, 78% of all tumors 7 cm or larger were malignant, whereas only 21% of all benign tumors exceeded this dimension. The most cogent determinant correlating with malignant potential was mitotic activity, with 92% of malignant tumors displaying 2 or more MFs per 10 HPFs. Similarly, in the presence of necrosis, 86% were malignant; if hemorrhage was present, 77% were malignant. In addition, 3 of 4 patients (17% of all malignant cases) with recognizable Cushing's syndrome harbored clinically malignant disease (154).

Although the majority of recurrences become clinically manifest within 3 years of diagnosis, Hayes and Scully (154) reported that 22% of recurrences occurred after 3 years and that, in fact, all of these cases occurred after 5 years; the longest interval witnessed was 19 years. Therefore, the duration of post-treatment surveillance should be adjusted accordingly. The only currently available utilizable markers for SCTNOS include the steroid hormones that were elevated prior to definitive treatment.

TREATMENT

The definitive management of SCSTs is dependent on 1 or more of the following: surgical stage, histologic subtype, patient's age and desire for fertility preservation, and various prognostic factors. Surgical resection alone is sufficient for SCSTs lacking malignant potential. Postoperative adjunctive therapy should be considered for patients with advanced disease and Sertoli-Leydig cell tumors with poor differentiation or heterologous elements (164).

Operative Management

Surgery remains the cornerstone of treatment for patients with SCSTs. Definitive therapy for SCSTs commences with an abdominal exploration through an adequate vertical midline incision. Following sampling of peritoneal washings for cytologic assessment, inspection and palpation of the viscera are conducted to detect macroscopic disease. Fertility-sparing surgery with unilateral salpingo-oophorectomy appears appropriate for patients with stage IA disease wishing preservation of their reproductive potential. In a review of the 1988 to 2001 SEER database, Zhang et al. identified 376 patients with ovarian SCST (165). The survival for the group of 110 patients with stage I-II disease who underwent conservative surgery without hysterectomy was similar to that of patients who underwent standard surgery. For older patients or those with advanced-stage disease or bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy are usually indicated. Resection of the ovarian tumor constitutes sufficient therapy for the essentially benign neoplasms, including thecomas, fibromas, gynandroblastomas, stromal luteomas, Leydig cell, sclerosing stromal, Sertoli cell, and well-differentiated SLCTs. Furthermore, sex cord tumors with annular tubules associated with PJS are also considered to be benign and can be similarly managed, but it is imperative that the endocervix be evaluated and subsequently monitored for the potential development of an AMC. Conversely, histologic confirmation of GCTs, intermediate or poorly differentiated Sertoli-Leydig cell tumors, SCSTs with annular tubules independent of PJS, and steroid cell tumors not otherwise specified will require definitive surgical staging. This includes multiple peritoneal biopsies, omentectomy, and resection of grossly suspicious pelvic or paraaortic lymph nodes. Careful inspection of the peritoneum is critical as residual disease is strongly correlated with recurrence. However, there appears to be little benefit to performing routine lymphadenectomy in the absence of grossly suspicious lymph nodes. In 3 series totaling 180 patients with GCTs and SLCTs, no lymph node metastases were found among those who underwent pelvic and/or paraaortic lymphadenectomy (166–168). Furthermore, isolated retroperitoneal recurrences are rare. In 34 patients with recurrent GCTs, 2 recurred in the retroperitoneum only; 2 in the pelvis and retroperitoneum; and 1 in the pelvis, abdomen, and retroperitoneum (166). In another series of 87 patients, only 2 of 18 recurrences were isolated to the retroperitoneum (167). Overall, only approximately 10% to 15% of first recurrences involve the retroperitoneum. Following careful surgical staging, in the absence of extraovarian disease conservation of the uterus and contralateral ovary is reasonable in patients wishing preservation of fertility. However, if the uterus is preserved a thorough curettage must be performed in all patients with estrogen-producing tumors whether they are considered to be benign or potentially malignant (4). If maintenance of fertility is not a concern or if extraovarian spread of disease is documented, a hysterectomy and residual salpingo-oophorectomy should be performed. Although no randomized evidence exists pertaining to the efficacy of cytoreduction in SCSTs, based on the benefits observed with their epithelial counterparts, we endorse an aggressive maximum effort at primary surgery if metastatic disease is encountered. In a recent multivariate analysis of 176 patients with GCTs, only residual disease after primary surgery and tumor size were predictive of recurrence (37). The value of secondary tumor reduction continues to be controversial but appears to be meritorious for the more indolent tumor types such as GCTs and SCTATs not associated with PJS. Repeat cytoreduction frequently affords these patients extended palliation. It is therefore mandatory that the surgeon have the technical expertise to facilitate optimal surgical management.

Postoperative Management and Management of Recurrent Disease

Granulosa Cell Tumors (Adult)

The vast majority of women with stage I disease have an excellent prognosis after surgery alone and do not require adjuvant therapy. For those with stage IC disease, consideration can be given to adjuvant therapy on an individualized basis. Most women presenting with stages II–IV disease would be advised to have postoperative therapy depending on their individual characteristics.

Whereas some investigators have reported improved outcomes in patients treated with adjuvant radiation therapy, other investigators have found no clear value to the use of adjuvant radiation therapy (4,6,16,169). Because of the rarity of GCT, it is difficult to conduct prospective trials in these patients. Two retrospective reports provide some data on the use of radiotherapy. Savage et al. reviewed the courses of 62 women treated for adult GCTs at the Royal Marsden Hospital from 1969 to 1995 (170). Thirty-eight (61%) had stage I disease. Eleven of the stage I patients had adjuvant pelvic radiation. The 10-year disease-free survival of these patients was 77% versus 78% for stage I patients treated with surgery alone. Unfortunately, neither complete surgical staging information nor the features that led to the selection of patients for adjuvant radiation was provided. For 8 patients with inoperable disease (or residual disease postoperatively), radiation resulted in complete responses in 4 (50%) that lasted 16 months to 5 years.

Wolf et al. reported on 34 patients with GCTs treated with radiation at the M.D. Anderson Cancer Center, 14 of whom had measurable disease (169). Six of the 14 (43%) had a clinical complete response. Three of the responders were alive without evidence of disease 10 to 21 years after radiation.

The Gynecologic Oncology Group (GOG) has reported the largest series of women with ovarian SCSTs treated with chemotherapy. They used 4 cycles of cisplatin, bleomycin, and etoposide (BEP) (171). Eligible patients had incompletely resected stage II to IV or recurrent disease. Seventy-five patients entered but 18 were ineligible because of incorrect histology or disease status. Of the 57 eligible patients, 41 had recurrent disease and 16 had primary disease. Thirty-nine had gross residual disease following surgery. Forty-eight had GCTs, 7 had SLCTs, one had a malignant thecoma, and 1 had an unclassified SCST. This chemotherapy combination was considered to be active, with 11 of 16 primary-disease patients and 21 of 41 recurrent-disease patients remaining progression free at a median follow-up of 3 years. Recognizing the prolonged natural history of these tumors, longer follow-up of this cohort will be important. The regimen was fairly toxic, with 2 bleomycin-related fatalities among the first 6 patients treated with the initial bleomycin dose of 20 U/m² (maximum 30 U) weekly for 9 weeks. The bleomycin dose was then reduced (20 U/m² every 3 weeks × 4 cycles) with no mention of further toxicity. Grade 4 myelotoxicity occurred in 61% of the patients. The value of bleomycin in the treatment of this tumor type remains in question (172).

Gershenson et al. (173) also reported on the use of BEP in a group of 9 women with poor-prognosis SCSTs of the ovary (7 had metastatic disease). The median progression-free survival was 14 months, with a median survival time of 28 months. These investigators, in the same publication, describe activity with paclitaxel in patients with granulosa cell tumors who have failed platinum-based therapies. In an earlier series, Gershenson et al. (163) found that cisplatin, doxorubicin, and cyclophosphamide were shown to have activity in the treatment of metastatic ovarian stromal tumors, including two

Sertoli-Leydig cell tumors. The overall response rate was 63% in this series.

The management of patients with recurrent disease must be individualized. Given the characteristic indolent growth pattern of GCTs, with long disease-free intervals, surgical resection of disease recurrence is often the initial step in the management of appropriate patients. Pecorelli et al. treated 38 patients with advanced (n = 7) or recurrent (n = 31) GCTs with cisplatin, vinblastine, and bleomycin (PVB) on a prospective trial through the European Organization for Research and Treatment of Cancer (EORTC) (174). Of the 7 women who presented with advanced disease (stages II–IV), 1 was alive and disease-free at 81 months. Five died between 4 and 12 months after the start of PVB, and another was alive with disease at 2 months. Among the 31 women with recurrent disease, 7 were alive without further evidence of disease from 24 to 81 months from the start of PVB. Consistent with the indolent course observed with GCTs in some women, another 11 women were alive with disease at a mean of 45 months from the start of PVB (median, 39 months).

The wisdom of using a germ cell-like regimen for stromal tumors is questionable. Uygun et al. reported on a small series of 11 women with recurrent GCTs (175). Most had cyclophosphamide, Adriamycin (doxorubicin), and cisplatin (CAP) in the adjuvant setting. Four were treated with cyclophosphamide and cisplatin for recurrence and survived 35 to 73 months after recurrence.

Taxanes have also been reported to have activity in SCSTs. A case report documented a dramatic response to paclitaxel in a patient with a GCT 2 years following cessation of platinum-based therapy (176). Subsequently, Brown et al. reported a retrospective review of the M.D. Anderson Cancer Center experience with taxane therapy in 44 patients with newly diagnosed or recurrent SCSTs (177). Eleven patients received paclitaxel and a platinum drug for newly diagnosed SCST; all were alive at the time of the study, with a median follow-up of 52 months. Of 37 patients treated with a taxane for recurrent SCST, 7 had no measurable disease after secondary cytoreductive surgery, and 30 had measurable disease. The response rate in the latter cohort was 42%. In a follow-up study, Brown et al. retrospectively compared the efficacy and side effects of taxanes, with or without platinum, to the combination of BEP (178). The outcomes of the 2 groups were similar, but the side effects associated with the BEP regimen appeared to be greater. The authors concluded that taxane and platinum chemotherapy warrants further investigation in SCSTs. The GOG is currently conducting a phase 2 trial of paclitaxel in women with stromal tumors with measurable disease (GOG protocol 187)—either previously untreated or recurrent. In addition, a GOG randomized phase 2 study of paclitaxel and carboplatin versus BEP in patients with SCSTs is also ongoing.

Considerable rationale exists for the utilization of hormone-based approaches in GCTs. A proportion of these tumors express steroid hormone receptors (179). Responses of GCTs, occasionally long-term, to medroxyprogesterone acetate and to GnRH antagonists have been reported (180–184). Fishman et al. (185) treated 6 patients with recurrent or persistent GCTs with monthly intramuscular injections of leuprolide acetate. Four patients had received prior cisplatin-based chemotherapy. Five patients had evaluable disease: 2 had partial responses and 3 had stable disease. The leuprolide was well tolerated.

Aromatase inhibitors have also been used in GCTs. Three reports have documented remissions in 7 women who received aromatase inhibitors for recurrent GCTs (186–188).

Anti-angiogenesis drugs have also been reported to have activity in sex cord-stromal tumors. Farkkila et al. found that VEGF and VEGF-2 were highly expressed in primary and recurrent GCTs (189). In addition, although tumor VEGF

protein expression was not predictive of tumor recurrence in this series, high levels of circulating VEGF were found in the serum of women with primary GCTs. Tao et al. reported on 8 patients with recurrent GCTs (7 adult and 1 juvenile) who were treated with bevacizumab (190). One patient had a complete response and 2 had a partial response. The GOG has recently completed a phase II study of bevacizumab for recurrent sex cord-stromal tumors, the results of which are pending.

Granulosa Cell Tumors (Juvenile)

Calaminus et al. (191) reported the outcome of 33 patients with JGCTs—24 treated with surgery alone and 9 with surgery and cisplatin-based chemotherapy. There have been 6 relapses, with 60 months median follow-up: 2 of 20 stage IA, 2 of 8 stage IC, and 2 of 5 stage IIC to IIIC. Three patients with stage IIC to IIIC disease treated with adjuvant cisplatin-based therapy remain disease-free at 46 to 66 months after diagnosis. Furthermore, Powell and Otis (192) reported short-term disease control in 2 teenagers with stage III JGCTs following surgery and cisplatin-based chemotherapy.

German investigators published their 15-year experience (1985–2000) with 54 SCSTs in children and adolescents (74). Forty-five were JGCTs. Twelve received adjuvant chemotherapy for stages IC to IIIC disease. BEP and cisplatin, etoposide, and ifosfamide (PEI) were the most commonly used regimens. Six patients remained in remission after adjuvant chemotherapy from 15 to 106 months later. A seventh developed a contralateral JGCT 10 years after her initial primary tumor. Five of the 12 have recurred, 3 of whom died 16 to 28 months from diagnosis.

Powell et al. have reported a patient with long-term disease-free survival following salvage chemotherapy for recurrent JGCT (193). The patient had presented with stage IIIC disease initially treated by resection of all gross disease followed by carboplatin and etoposide for 6 cycles. She recurred 13 months later with limited disease in the liver and a mass at the inferior aspect of the spleen. She underwent gross total resection followed by 6 cycles of bleomycin and paclitaxel. She was disease-free 44 months later, delivering a normal baby at cesarean section.

Sertoli-Leydig Cell Tumors

Therapy for those few individuals presenting with high-stage SLCTs, as well as for individuals with recurrent disease, must be individualized. The effectiveness of radiation therapy is unknown (113). Reports exist of responses to vincristine, actinomycin D, and cyclophosphamide (VAC) and cisplatin, doxorubicin, and cyclophosphamide (163,194). Schneider et al. reported 3 patients with SLCTs who were treated with platinum-based chemotherapy (74). One patient with stage IC disease with intermediate differentiation received 2 cycles of the combination of cisplatin and etoposide and was disease-free at 47 months. Two other patients, both of whom had stage IC poorly differentiated SLCTs, were dead of tumor at 7 and 19 months after receiving either BEP or PEI. Given the functional hormonal nature of many of these neoplasms, consideration could also be given to some form of hormonal manipulation, such as luteinizing hormone-releasing agonists or antagonists (195).

Recently, the Italian cooperative group, Multicentre Italian Trials in Ovarian Cancer (MITO), reported their experience with 21 patients with SLCTs (196). Five patients received adjuvant chemotherapy—platinum-based chemotherapy in 4 (BEP in 2 and paclitaxel/carboplatin in two), and 1 received

the combination of methotrexate, 5-fluorouracil, and cyclophosphamide. Three of the 5 patients subsequently died of disease. Seven patients (1 stage IAG1, 3 stage IAG2, 1 stage ICG2, and 2 stage IIICG3) relapsed, 4 of whom had stage IA disease and did not receive adjuvant chemotherapy. Five of these patients were treated with surgery plus chemotherapy, 1 received chemotherapy alone, and 1 received palliation only. All 6 patients who received chemotherapy were treated with platinum-based regimens—either BEP or paclitaxel/carboplatin. At the time of the report, 2 patients—one with stage IAG1 and one with Stage IAG2—were clinically disease-free, and the other 5 were dead of disease.

Sex Cord Tumor with Annular Tubules

Given the rarity of this tumor, the collective experience with systemic therapy for SCTATs is scant. Their endocrine activities suggest that the tumors may retain responsiveness to perturbation of gonadotropin levels. A recent case report documents a complete response to etoposide, bleomycin, and cisplatin in a patient with recurrent SCTAT (143).

MOLECULAR PATHOGENESIS

Our current knowledge regarding various autocrine and endocrine regulatory mechanisms influencing ovarian function, the overexpression of inhibin in several SCSTs, the alterations in ovarian steroidogenesis, and the changes in circulating gonadotropin levels in SCSTs provide clues regarding the pathogenesis of these tumors. Investigations to date exploring the interactive regulatory mechanisms of inhibin, activin, follistatin, and follicle-stimulating hormone (FSH) have predominantly utilized GCTs. Follicle-stimulating hormone provides a fundamental regulatory role in the differentiation processes of granulosa cells during the early stages of follicle development. Specifically, FSH stimulates cell proliferation (mitosis), increases the availability of cell-surface prolactin and luteinizing hormone receptors, and induces aromatase activity, resulting in increased estradiol production. Other growth-regulatory factors such as insulin-like growth factor and epidermal growth factor modulate these actions, including the enhancement of the mitogenic effects of FSH. In addition, FSH secretion from the anterior pituitary is modulated in part by the serum levels of inhibin, activin, estrogens, and/or androgens.

Inhibin, a heterodimeric glycoprotein hormone composed of an α -subunit and 1 of 2 β -subunits, is secreted by the granulosa cells of the ovary (197). Inhibin A consists of α A and β A; inhibin B consists of α B and β B. Petraglia et al. (198) demonstrated that serum inhibin B was dramatically increased in 8 of 9 patients with GCTs, while inhibin A was slightly increased in all patients. Its major physiologic function is to inhibit the secretion of FSH by the anterior pituitary gland (199). Inhibin is expressed in excessive quantities by GCTs. Although it maintains its regulatory function pertaining to FSH suppression, it appears to be ineffective in controlling estrogen production and cell proliferation within the gonad. Robertson et al. have recently reviewed the various serum-based assays for inhibin (200).

Activin, also a peptide hormone of ovarian granulosa cell origin, is composed of 2 β -subunits that are identical to those of inhibin. In contrast to inhibin, activin stimulates the secretion of FSH, induces the production of estradiol while having a negative impact on progesterone production, and promotes granulosa cell differentiation (199).

Several investigative teams are pursuing studies to elucidate the underlying genetic and biologic changes that give rise to SCSTs, especially GCTs. Lin et al. performed comparative genomic hybridization of a set of 37 adult-type GCTs (36 primaries, 1 recurrence) obtained from 5 hospitals in Taiwan (201). All patients had stage I disease except for 1 stage III patient with limited disease at initial diagnosis. Twenty-two (61%) of the 36 primary tumors had chromosomal imbalances. The non-random changes included loss of 22q in 31% of tumors, gain of chromosome 14 in 25% of tumors, and gain of chromosome 12 in 14% of tumors. Monosomy 22 frequently coexisted with trisomy 14. High-level amplification, as can be seen in many aggressive carcinomas, was not detected in any of these GCTs. Findings were similar to those reported by Mayr et al. (202). As a sole abnormality, trisomy 12 has also been found in fibromas and fibroepitheliomas, in addition to GCTs (203,204). Menczer et al. looked for HER2/neu expression in 12 GCTs and saw no immunohistochemical staining (205). An Austrian group looked at the immunohistochemical expression of the HER family of receptors—HER1 (EGFR), HER2, HER3, and HER4—in 38 adult GCTs and 2 of the juvenile type (206). Thirty-one cases (77.5%) were positive for at least 1 of the receptors (EGFR, HER3, or HER4). None of the 40 cases showed a positive reaction for HER2. Twenty-six of 40 (65%) showed reactivity for EGFR. HER3 and HER4 expression were observed in 18 (45%) and 23 (57.5%) tumors, respectively. Kusamura et al. also looked for HER2 expression in 18 GCTs: all cases were negative (207). They also showed a markedly low likelihood of immunohistochemical staining for p53 and low proliferative indices in these tumors.

Richards et al. used a mouse model to investigate granulosa cell tumorigenesis (208). They showed that formation of GCTs by stable activation of β -catenin (CTNNB1) in granulosa cells is accelerated by concomitant *Kras* activation or *PTEN* loss. It has yet to be confirmed if these are crucial pathways in the development of GCTs in humans. Recently, Shah and colleagues performed whole-transcriptome paired-end RNA sequencing on 4 GCTs (209). They discovered a point mutation missense point mutation, 402C→G (C134W), in *FOXL2*, a member of the forkhead-winged helix family of transcription factors. This gene is known to be involved in ovarian differentiation and is required for the normal development of granulosa cells (210,211). They confirmed the presence of this mutation in 86 of 89 adult GCTs, while it was present in only 1 of 10 juvenile GCTs. Interestingly, review of the 3 mutation negative adult GCTs revealed that 2 were in fact not true GCTs. The use of immunostaining for *FOXL2* rather than molecular screening was subsequently shown to be diagnostically useful with sensitivity and specificity of 80% and 99% for SCSTs (212). These results support a molecular basis for the disparate clinical course observed between juvenile and adult GCTs, provide a means to improve diagnosis in difficult cases, and suggest that *FOXL2* is a key driver of GCT pathogenesis.

The other major recent finding has been that of *DICER1* mutations in ovarian SCSTs (213–215). Schultz et al. reported that, among 296 kindreds including 325 children with pleuropulmonary blastoma (PPB), 3 children had both PPB and SLCT (213). Among family members of PPB patients, they identified 6 ovarian SCSTs. Germline *DICER1* mutations were identified in 4 of 6 patients with SCSTs from PPB kindreds and in 2 of 3 children with ovarian SCSTs and no personal or family history of PPB. In another report, Heravi-Moussavi et al. found somatic *DICER1* mutations in the RNase IIIb domain in 26/43 (60%) SLCTs, including 4 tumors with additional germline *DICER1* mutations (214). Thus far, the finding of neither of these mutations has translated into a therapeutic target.

Chu et al. examined the estrogen receptor isoform gene expression in a small series of GCTs and serous cystadenocarcinomas

of the ovary (4 of each) (216). They saw widespread expression of estrogen receptor (ER)- α in both tumor types but at relatively low levels, similar to or less than what is seen in the endometrium. ER- β expression in the GCTs, however, was several-fold higher than that of ER- α . Fuller and Chu have provided an informative review of various signaling pathways that are important in the regulation of growth, differentiation, and apoptosis of normal granulosa cells, which may contribute to the molecular pathogenesis of GCTs (217). Because of the important role of the insulin-like growth factor (IGF) system in development of the dominant follicle, and its contribution to epithelial ovarian cancer, Alexiadis et al. characterized the expression of several components of the IGF system in a series of nine GCTs (218). Interestingly, pregnancy-associated plasma protein-A expression was highest in the GCTs. PAPP-A is a metalloproteinase synthesized by granulosa cells, the activity of which leads to increased IGF bioavailability. Anttonen et al. studied samples from a cohort of 80 GCT patients from the University of Helsinki and examined several growth regulatory factors known to be important in normal granulosa cell function, including anti-müllerian hormone, inhibin- α , and GATA transcription factors (219). They found a correlation between high GATA-4 expression and higher likelihood of recurrence.

The natural history of SCSTs is uniquely different from that of their epithelial counterparts and provides an intriguing tumor model. The vast majority of these neoplasms are characteristically of low malignant potential. They are typically unilateral and remain localized, retain hormone-secreting functions, and infrequently develop recurrences, many of which are delayed. In contrast, a small percentage of otherwise phenotypically similar tumors demonstrate a more virulent course and are generally refractory to therapy. The SCST subtypes display a bimodal age distribution, notably with JGCTs, SSCTs, SLCTs, and SCTATs occurring predominantly during the first 3 decades of life. Furthermore, the association of these tumors with several uncommon congenital disease entities, such as enchondromatosis, leprechaunism, and PJS, occurs at frequencies that exceed mere chance. Uniquely, several of these functioning neoplasms, including AGCTs, JGCTs, SLCTs, and SCTATs, overexpress growth-regulatory substances including inhibin, müllerian-inhibiting substance, and follicle-regulating protein. Given the limited number of ovarian SCSTs available for study, our current understanding of the mechanism of oncogenesis in these tumors is understandably limited.

SUMMARY

The principal problem related to the study of SCSTs and the development of effective therapy is their rarity. Although this interesting group of tumors has been studied extensively from a histologic standpoint, there are surprisingly few features that distinguish tumors that are more likely to recur or have aggressive behavior, and much of the information is conflicting.

Surgery remains the cornerstone of treatment for patients with SCSTs. Furthermore, for young patients desirous of fertility preservation, fertility-sparing surgery is possible in a large proportion related to the propensity of these tumors to be unilateral and nonmetastatic. Patients who appear to have a worse prognosis and for whom postoperative therapy would appear to be indicated include those with metastatic SCSTs of any histotype and those with stage I poorly differentiated SLCTs. For patients with SCSTs confined to the ovary, postoperative therapy is not recommended. For those with stage IC disease, the issue of postoperative therapy is unresolved.

Standard postoperative treatment consists of platinum-based chemotherapy. The BEP regimen is currently the most popular combination. However, this is a relatively toxic regimen; hence,

the interest in alternative combinations, such as taxane/platinum chemotherapy. However, more study of this latter combination is warranted. An ongoing GOG study should help resolve this issue.

Beyond platinum-based chemotherapy, there is no consensus concerning recommended second-line or salvage therapy.

Hormonal medications clearly have some degree of activity in GCTs. Anti-angiogenesis agents hold promise. In addition, there is probably a limited role for radiation. This gap in our armamentarium underscores the need for novel target-based therapeutics developed through the study of the genes and pathways involved in the pathogenesis of these neoplasms.

REFERENCES

- Koonings PP, Campbell K, Mishell DR Jr, et al. Relative frequency of primary ovarian neoplasms: a 10-year review. *Obstet Gynecol.* 1989;74:921-926.
- Cramer DW, Devesa SS, Welch WR. Trends in the incidence of endometrioid and clear cell cancers of the ovary in the United States. *Am J Epidemiol.* 1981;114:201-208.
- Tavassoli FA. Ovarian tumors with functioning manifestations. *Endocrinol Pathol.* 1994;5:137-148.
- Evans AT, Gaffey TA, Malkasian GD Jr, et al. Clinicopathologic review of 118 granulosa and 82 theca cell tumors. *Obstet Gynecol.* 1980;55:231-238.
- Malmstrom H, Hogberg T, Risberg B, et al. Granulosa cell tumors of the ovary: prognostic factors and outcome. *Gynecol Oncol.* 1994;52:50-55.
- Ohel G, Kaneti H, Schenker JG. Granulosa cell tumors in Israel: a study of 172 cases. *Gynecol Oncol.* 1983;15:278-286.
- Rokitansky CV. Über abnormalities des corpus luteum. *Allg Wien Med Z.* 1859;4:253-254.
- Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. *J Clin Oncol.* 2003;21:1180-1189.
- Unkila-Kallio L, Leminen A, Tiitinen A, et al. Nationwide data on falling incidence of ovarian granulosa cell tumours concomitant with increasing use of ovulation inducers. *Hum Reprod.* 1998;13:2828-2830.
- Werness BA, Ramus SJ, Whittemore AS, et al. Histopathology of familial ovarian tumors in women from families with and without germline *BRCA1* mutations. *Hum Pathol.* 2000;31:1420-1424.
- Stevens TA, Brown J, Zander DS, et al. Adult granulosa cell tumors of the ovary in two first-degree relatives. *Gynecol Oncol.* 2005;98:502-505.
- Bjorkholm E. Granulosa cell tumors: a comparison of survival in patients and matched controls. *Am J Obstet Gynecol.* 1980;138:329-331.
- Bjorkholm E, Silfversward C. Prognostic factors in granulosa-cell tumors. *Gynecol Oncol.* 1981;11:261-274.
- Fox H, Agrawal K, Langley FA. A clinicopathologic study of 92 cases of granulosa cell tumor of the ovary with special reference to the factors influencing prognosis. *Cancer.* 1975;35:231-241.
- Pankratz E, Boyes DA, White GW, et al. Granulosa cell tumors. A clinical review of 61 cases. *Obstet Gynecol.* 1978;52:718-723.
- Piura B, Nemet D, Yanai-Inbar I, et al. Granulosa cell tumor of the ovary: a study of 18 cases. *J Surg Oncol.* 1994;55:71-77.
- Schweppe KW, Beller FK. Clinical data of granulosa cell tumors. *J Cancer Res Clin Oncol.* 1982;104:161-169.
- Stenwig JT, Hazekamp JT, Beecham JB. Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. *Gynecol Oncol.* 1979;7:136-152.
- Young RH, Scully RE. Ovarian sex cord-stromal tumours: recent advances and current status. *Clin Obstet Gynaecol.* 1984;11:93-134.
- Bjorkholm E, Silfversward C. Granulosa- and theca-cell tumors. Incidence and occurrence of second primary tumors. *Acta Radiol Oncol.* 1980;19:161-167.
- Muir CS, Waterhouse JAH, Mack TM, et al. *Cancer Incidence in Five Continents*. IARC Scientific Publication No. 88, Vol V. Lyon, France: International Agency for Research on Cancer; 1987.
- Quirk JT, Natarajan N. Ovarian cancer incidence in the United States, 1992-1999. *Gynecol Oncol.* 2005;97:519-523.
- Cronje HS, Niemand I, Bam RH, et al. Review of the granulosa-theca cell tumors from the Emil Novak ovarian tumor registry. *Am J Obstet Gynecol.* 1999;180:323-327.
- Gusberg SB, Kardon P. Proliferative endometrial response to theca-granulosa cell tumors. *Am J Obstet Gynecol.* 1971;111:633-643.
- Stuart GC, Dawson LM. Update on granulosa cell tumours of the ovary. *Curr Opin Obstet Gynecol.* 2003;15:33-37.
- Chen VW, Ruiz B, Killeen J, et al. Pathology and classification of ovarian tumors. *Cancer.* 2003;97(suppl. 10):2631-2642.
- Young RH, Oliva E, Scully RE. Luteinized adult granulosa cell tumors of the ovary: a report of four cases. *Int J Gynecol Pathol.* 1994;13:302-310.
- Zanagnolo V, Pasinetti B, Sartori E. Clinical review of 63 cases of sex cord stromal tumors. *Eur J Gynaecol Oncol.* 2004;25(4):431-438.
- Nakashima N, Young RH, Scully RE. Androgenic granulosa cell tumors of the ovary. A clinicopathologic analysis of 17 cases and review of the literature. *Arch Pathol Lab Med.* 1984;108:786-791.
- Norris HJ, Taylor HB. Virilization associated with cystic granulosa tumors. *Obstet Gynecol.* 1969;34:629-635.
- Fathalla MF. The occurrence of granulosa and theca tumours in clinically normal ovaries. *J Obstet Gynaecol Br Commonw.* 1967;74:279-282.
- Young RH, Scully RE. Ovarian sex cord-stromal tumors with bizarre nuclei: a clinicopathologic analysis of 17 cases. *Int J Gynecol Pathol.* 1983;1:325-335.
- Spencer HW, Mullings AM, Char G, et al. Granulosa-theca cell tumor of the ovaries. A late metastasizing tumour. *West Indian Med J.* 1999;48: 33-35.
- Dubuc-Lissioir J. Case report: bone metastasis from a granulosa cell tumor of the ovary. *Gynecol Oncol.* 2001;83:400-404.
- Miller BE, Barron BA, Wan JY, et al. Prognostic factors in adult granulosa cell tumor of the ovary. *Cancer.* 1997;79:1951-1955.
- Fujimoto T, Sakuragi N, Okuyama K, et al. Histopathological prognostic factors of adult granulosa cell tumors of the ovary. *Acta Obstet Gynecol Scand.* 2001;80:1069-1074.
- Sun HD, Lin H, Jao MS, et al. A long-term follow-up study of 176 cases with adult-type ovarian granulosa cell tumors. *Gynecol Oncol.* 2012;124:244-249.
- Kottmeier HL. *Carcinoma of the Female Genitalia*. Baltimore, MD: Williams & Wilkins; 1953.
- Klemi PJ, Joensuu H, Salmi T. Prognostic value of flow cytometric DNA content analysis in granulosa cell tumor of the ovary. *Cancer.* 1990;65:1189-1193.
- Chadha S, Cornelisse CJ, Schaberg A. Flow cytometric DNA ploidy analysis of ovarian granulosa cell tumors. *Gynecol Oncol.* 1990;36:240-245.
- Evans MP, Webb MJ, Gaffey TA, et al. DNA ploidy of ovarian granulosa cell tumors. Lack of correlation between DNA index or proliferative index and outcome in 40 patients. *Cancer.* 1995;75:2295-2298.
- Ala-Fossi SL, Maenpaa J, Aine R, et al. Prognostic significance of p53 expression in ovarian granulosa cell tumors. *Gynecol Oncol.* 1997;66:475-479.
- Kappes S, Milde-Langosch K, Kressin P, et al. p53 mutations in ovarian tumors, detected by temperature-gradient gel electrophoresis, direct sequencing and immunohistochemistry. *Int J Cancer.* 1995;64:52-59.
- King LA, Okagaki T, Gallup DG, et al. Mitotic count, nuclear atypia, and immunohistochemical determination of Ki-67, c-myc, p21-ras, c-erbB2, and p53 expression in granulosa cell tumors of the ovary: mitotic count and Ki-67 are indicators of poor prognosis. *Gynecol Oncol.* 1996;61:227-232.
- Liu FS, Ho ES, Lai CR, et al. Overexpression of p53 is not a feature of ovarian granulosa cell tumors. *Gynecol Oncol.* 1996;61:50-53.
- Dowdy SC, O'Kane DJ, Keeney GL, et al. Telomerase activity in sex cord-stromal tumors of the ovary. *Gynecol Oncol.* 2001;82:257-260.
- Färkkilä A, Anttonen M, Pociuviene J, et al. Vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 are highly expressed in ovarian granulosa cell tumors. *Eur J Endocrinol.* 2011;164:115-122.
- Ala-Fossi SL, Aine R, Punnonen R, et al. Is potential to produce inhibins related to prognosis in ovarian granulosa cell tumors? *Eur J Gynaecol Oncol.* 2000;21:187-189.
- Kaye SB, Davies E. Cyclophosphamide, Adriamycin, and cis-platinum for the treatment of advanced granulosa cell tumor, using serum estradiol as a tumor marker. *Gynecol Oncol.* 1986;24:261-264.
- Bogges JF, Soules MR, Goff BA, et al. Serum inhibin and disease status in women with ovarian granulosa cell tumors. *Gynecol Oncol.* 1997;64:64-69.
- Gustafson ML, Lee MM, Asmundson L, et al. Müllerian inhibiting substance in the diagnosis and management of intersex and gonadal abnormalities. *J Pediatr Surg.* 1993;28:439-444.
- Jobling T, Marners P, Healy DL, et al. A prospective study of inhibin in granulosa cell tumors of the ovary. *Gynecol Oncol.* 1994;55:285-289.

53. Lane AH, Lee MM, Fuller AF Jr, et al. Diagnostic utility of müllerian inhibiting substance determination in patients with primary and recurrent granulosa cell tumors. *Gynecol Oncol.* 1999;73:51–55.
54. Lappohn RE, Burger HG, Bouma J, et al. Inhibin as a marker for granulosa cell tumor. *Acta Obstet Gynecol Scand Suppl.* 1992;155:61–65.
55. Lappohn RE, Burger HG, Bouma J, et al. Inhibin as a marker for granulosa cell tumors. *N Engl J Med.* 1989;321:790–793.
56. Rey RA, L'homme C, Marcellac I, et al. Antimüllerian hormone as a serum marker of granulosa cell tumors of the ovary: comparative study with serum alpha-inhibin and estradiol. *Am J Obstet Gynecol.* 1996;174:958–965.
57. Rodgers KE, Marks JF, Ellefson DD, et al. Follicle regulatory protein: a novel marker for granulosa cell cancer patients. *Gynecol Oncol.* 1990;37:381–387.
58. Sluijmer AV, Heineman MJ, Evers JL, et al. Peripheral vein, ovarian vein and ovarian tissue levels of inhibin in a postmenopausal patient with a granulosa cell tumour. *Acta Endocrinol (Copenh).* 1993;129:311–324.
59. Mom CH, Engelen MJA, Willemse PHB, et al. Granulosa cell tumors of the ovary: The clinical value of serum inhibin A and B levels in a large single center cohort. *Gynecol Oncol.* 2007;105:365–372.
60. McCluggage WG, Young R. Immunohistochemistry as a diagnostic aid in the evaluation of ovarian tumors. *Semin Diagn Pathol.* 2005;22(1):3–32.
61. Scully RE. Stromal luteoma of the ovary: a distinctive type of lipoid-cell tumor. *Cancer.* 1964;17:769–778.
62. Young RH, Dickersin GR, Scully RE. Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. *Am J Surg Pathol.* 1984;8:575–596.
63. Lack EE, Perez-Atayde AR, Murthy AS, et al. Granulosa theca cell tumors in premenarchal girls: a clinical and pathologic study of ten cases. *Cancer.* 1981;48:1846–1854.
64. Plantaz D, Flamant F, Vassal G, et al. Granulosa cell tumors of the ovary in children and adolescents. Multicenter retrospective study in 40 patients aged 7 months to 22 years. *Arch Fr Pediatr.* 1992;49:793–798.
65. Vassal G, Flamant F, Caillaud JM, et al. Juvenile granulosa cell tumor of the ovary in children: a clinical study of 15 cases. *J Clin Oncol.* 1988;6:990–995.
66. Zaloudek C, Norris HJ. Granulosa tumors of the ovary in children: a clinical and pathologic study of 32 cases. *Am J Surg Pathol.* 1982;6:513–522.
67. Bouffet E, Basset T, Chetail N, et al. Juvenile granulosa cell tumor of the ovary in infants: a clinicopathologic study of three cases and review of the literature. *J Pediatr Surg.* 1997;32:762–765.
68. Hasiakos D, Papakonstantinou K, Goula K, et al. Juvenile granulosa cell tumor associated with pregnancy: report of a case and review of the literature. *Gynecol Oncol.* 2006;100:426–429.
69. Scully RE. Sex cord tumor with annular tubules: a distinctive ovarian tumor of the Peutz-Jeghers syndrome. *Cancer.* 1970;25:1107–1121.
70. Asirvatham R, Rooney RJ, Watts HG. Ollier's disease with secondary chondrosarcoma associated with ovarian tumour. A case report. *Int Orthop.* 1991;15:393–395.
71. Tamimi HK, Bolen JW. Enchondromatosis (Ollier's disease) and ovarian juvenile granulosa cell tumor. *Cancer.* 1984;53:1605–1608.
72. Tanaka Y, Sasaki Y, Nishihira H, et al. Ovarian juvenile granulosa cell tumor associated with Maffucci's syndrome. *Am J Clin Pathol.* 1992;97:523–527.
73. Brisigotti M, Fabbretti G, Pesce F, et al. Congenital bilateral juvenile granulosa cell tumor of the ovary in leprechaunism: a case report. *Pediatr Pathol.* 1993;13:549–558.
74. Schneider DT, Calaminus G, Wessalowski R, et al. Ovarian sex cord-stromal tumors in children and adolescents. *J Clin Oncol.* 2003;21:2357–2363.
75. Jacoby AF, Young RH, Colvin RB, et al. DNA content in juvenile granulosa cell tumors of the ovary: a study of early- and advanced-stage disease. *Gynecol Oncol.* 1992;46:97–103.
76. Swanson SA, Norris HJ, Kelsten ML, et al. DNA content of juvenile granulosa tumors determined by flow cytometry. *Int J Gynecol Pathol.* 1990;9:101–109.
77. Bjorkholm E, Silfversward C. Theca-cell tumors. Clinical features and prognosis. *Acta Radiol Oncol.* 1980;19:241–244.
78. Norris HJ, Taylor HB. Prognosis of granulosa theca tumors of the ovary. *Cancer.* 1968;21:255–260.
79. Zhang J, Young RH, Arseneau J, et al. Ovarian stromal tumors containing lutein or Leydig cells (luteinized thecomas and stromal Leydig cell tumors)—a clinicopathological analysis of fifty cases. *Int J Gynecol Pathol.* 1982;1:270–285.
80. Barrenetxea G, Schneider J, Centeno MM, et al. Pure theca cell tumors. A clinicopathologic study of 29 cases. *Eur J Gynaecol Oncol.* 1990;11:429–432.
81. Clement PB, Young RH, Hanna W, et al. Sclerosing peritonitis associated with luteinized thecomas of the ovary. *Am J Surg Pathol.* 1994;18:1–13.
82. Schonman R, Klein Z, Edelstein E, et al. Luteinized thecoma associated with sclerosing peritonitis—conservative surgical approach followed by corticosteroid and GnRH agonist treatment—a case report. *Gynecol Oncol.* 2008;111:540–543.
83. Dockerty MB, Mason JC. Ovarian fibromas: clinical and pathologic study of 283 cases. *Am J Obstet Gynecol.* 1944;47:741–752.
84. Samanth KK, Black WC. Benign ovarian stromal tumors associated with free peritoneal fluid. *Am J Obstet Gynecol.* 1970;107:538–545.
85. Meigs JV. Fibroma of the ovary with ascites and hydrothorax: Meigs' syndrome. *Am J Obstet Gynecol.* 1954;67:962–987.
86. Raggio M, Kaplan AL, Harberg JF. Recurrent ovarian fibromas with basal cell nevus syndrome (Gorlin syndrome). *Obstet Gynecol.* 1983;61(suppl. 3):955–965.
87. Prat J, Scully RE. Cellular fibromas of the ovary: a comparative clinicopathologic analysis of seventeen cases. *Cancer.* 1981;47:2663–2670.
88. Irving JA, Alkushi A, Young RH, et al. Cellular fibromas of the ovary: a study of 75 cases including 40 mitotically active tumors emphasizing their distinction from fibrosarcoma. *Am J Surg Pathol.* 2006;30:929–938.
89. Chahvardjian A, Scully RE. Sclerosing stromal tumors of the ovary. *Cancer.* 1973;31:664–670.
90. Gee DC, Russell P. Sclerosing stromal tumours of the ovary. *Histopathology.* 1979;3:367–376.
91. Lam RM, Geitmann P. Sclerosing stromal tumor of the ovary. A light, electron microscopic and enzyme histochemical study. *Int J Gynecol Pathol.* 1988;7:280–290.
92. Young RH, Scully RE. Ovarian Sertoli cell tumors: a report of 10 cases. *Int J Gynecol Pathol.* 1984;2:349–363.
93. Suit PF, Hart WR. Sclerosing stromal tumor of the ovary. An ultrastructural study and review of the literature to evaluate hormonal function. *Cleve Clin J Med.* 1988;55:189–194.
94. Cashell AW, Cohen ML. Masculinizing sclerosing stromal tumor of the ovary during pregnancy. *Gynecol Oncol.* 1991;43:281–285.
95. Ismail SM, Walker SM. Bilateral virilizing sclerosing stromal tumours of the ovary in a pregnant woman with Gorlin's syndrome: implications for pathogenesis of ovarian stromal neoplasms. *Histopathology.* 1990;17: 159–163.
96. Katsube Y, Iwaki Y, Silverberg SG, et al. Sclerosing stromal tumor of the ovary associated with endometrial adenocarcinoma: a case report. *Gynecol Oncol.* 1988;29:392–398.
97. Healy DL, Burger HG, Marners P, et al. Elevated serum inhibin concentrations in postmenopausal women with ovarian tumors. *N Engl J Med.* 1993;329:1539–1542.
98. Van Winter JT, Podratz KC, Gaffey TA. Sclerosing stromal tumor of the ovary in a 13-year-old girl. *Adolesc Pediatr Gynecol.* 1993;6:164–165.
99. Mancuso A, Grosso M, D'Anna R, et al. Anatomical-clinical considerations on the ovarian fibroma. *Clin Exp Obstet Gynecol.* 1995;22:115–119.
100. Waxman M, Vuletin JC, Urcuyo R, et al. Ovarian low-grade stromal sarcoma with thecomatous features: a critical reappraisal of the so-called "malignant thecoma." *Cancer.* 1979;44:2206–2217.
101. Micci F, Haugom L, Abeler VM. Consistent numerical chromosome aberrations in thecofibromas of the ovary. *Virchows Arch.* 2008;452:269–276.
102. Lage JM, Weinberg DS, Huettner PC, et al. Flow cytometric analysis of nuclear DNA content in ovarian tumors. Association of ploidy with tumor type, histologic grade, and clinical stage. *Cancer.* 1992;69:2668–2675.
103. Meyer R. Pathology of some special ovarian tumors and their relation to sex characteristics. *Am J Obstet Gynecol.* 1931;22:697–713.
104. Novak E. Life and works of Robert Meyer. *Am J Obstet Gynecol.* 1947;53:50–64.
105. Morris M, Scully RE. *Endocrine Pathology of the Ovary.* St. Louis: Mosby; 1958;82–96.
106. Aiba M, Hirayama A, Sukurada M, et al. Spironolactone body-like structure in rennin-producing Sertoli-cell tumors of the ovary. *Surg Pathol.* 1990;3:143–149.
107. Ehrlich EN, Dominguez OV, Samuels LT, et al. Aldosteronism and precocious puberty due to an ovarian androblastoma (Sertoli cell tumor). *J Clin Endocrinol Metab.* 1963;23:358–367.
108. Korzets A, Nouriel H, Steiner Z, et al. Resistant hypertension associated with a rennin-producing ovarian Sertoli cell tumor. *Am J Clin Pathol.* 1986;85:242–247.
109. Ferry JA, Young RH, Engel G, et al. Oxyphilic Sertoli cell tumor of the ovary: a report of three cases, two in patients with the Peutz-Jeghers syndrome. *Int J Gynecol Pathol.* 1994;13:259–266.
110. Tavassoli FA, Norris HJ. Sertoli tumors of the ovary. A clinicopathologic study of 28 cases with ultrastructural observations. *Cancer.* 1980;46:2281–2297.
111. Roth LM, Anderson MC, Govan AD, et al. Sertoli-Leydig cell tumors: a clinicopathologic study of 34 cases. *Cancer.* 1981;48:187–197.
112. Young RH, Scully RE. Ovarian Sertoli-Leydig cell tumors with a retiform pattern: a problem in histopathologic diagnosis. A report of 25 cases. *Am J Surg Pathol.* 1983;7:755–771.
113. Zaloudek C, Norris HJ. Sertoli-Leydig tumors of the ovary. A clinicopathologic study of 64

- intermediate and poorly differentiated neoplasms. *Am J Surg Pathol*. 1984;8:405–418.
114. Roth LM, Slayton RE, Brady LW, et al. Retiform differentiation in ovarian Sertoli-Leydig cell tumors. A clinicopathologic study of six cases from a Gynecologic Oncology Group study. *Cancer*. 1985;55:1093–1098.
 115. Talerman A. Ovarian Sertoli-Leydig cell tumor (androblastoma) with retiform pattern. A clinicopathologic study. *Cancer*. 1987;60:3056–3964.
 116. Young RH. Sertoli-Leydig cell tumors of the ovary: review with emphasis on historical aspects and unusual variants. *Int J Gynecol Pathol*. 1993;12:141–147.
 117. Young RH, Scully RE. Ovarian Sertoli-Leydig cell tumors. A clinicopathological analysis of 207 cases. *Am J Surg Pathol*. 1985;9:543–569.
 118. Pascale MM, Pugeat M, Roberts M, et al. Androgen suppressive effect of GnRH agonist in ovarian hyperthecosis and virilizing tumours. *Clin Endocrinol(Oxf)*. 1994;41:571–576.
 119. Weyl-Ben Arush M, Oslander L. Ollier's disease associated with ovarian Sertoli-Leydig cell tumor and breast adenoma. *Am J Pediatr Hematol Oncol*. 1991;13:49–51.
 120. Young RH, Prat J, Scully RE. Ovarian Sertoli-Leydig cell tumors with heterologous elements. I. Gastrointestinal epithelium and carcinoid: a clinicopathologic analysis of thirty-six cases. *Cancer*. 1982;50:2448–2456.
 121. Young RH, Scully RE. Well-differentiated ovarian Sertoli-Leydig cell tumors: a clinicopathological analysis of 23 cases. *Int J Gynecol Pathol*. 1984;3:277–290.
 122. McCluggage WG, Young RH. Ovarian Sertoli-Leydig cell tumors with pseudoendometrioid tubules (pseudoendometrioid Sertoli-Leydig cell tumors). *Am J Surg Pathol*. 2007;31:592–597.
 123. Prat J, Young RH, Scully RE. Ovarian Sertoli-Leydig cell tumors with heterologous elements. II. Cartilage and skeletal muscle: a clinicopathologic analysis of twelve cases. *Cancer*. 1982;50:2465–2475.
 124. Cohen I, Shapira M, Cuperman S, et al. Direct *in-vivo* detection of atypical hormonal expression of a Sertoli-Leydig cell tumour following stimulation with human chorionic gonadotrophin. *Clin Endocrinol(Oxf)*. 1993;39:491–495.
 125. Ohashi M, Hasegawa Y, Haji M, et al. Production of immunoreactive inhibin by a virilizing ovarian tumour (Sertoli-Leydig tumour). *Clin Endocrinol(Oxf)*. 1990;33:613–618.
 126. Gagnon S, Tetu B, Silva EG, et al. Frequency of alpha-fetoprotein production by Sertoli-Leydig cell tumors of the ovary: an immunohistochemical study of eight cases. *Mod Pathol*. 1989;2:63–67.
 127. Motoyama I, Watanabe H, Gotoh A, et al. Ovarian Sertoli-Leydig cell tumor with elevated serum alpha-fetoprotein. *Cancer*. 1989;63:2047–2053.
 128. Shen K, Wu PC, Lang JH, et al. Ovarian sex cord tumor with annular tubules: a report of six cases. *Gynecol Oncol*. 1993;48:180–184.
 129. Young RH, Welch WR, Dickersin GR, et al. Ovarian sex cord tumor with annular tubules: review of 74 cases including 27 with Peutz-Jeghers syndrome and four with adenoma malignum of the cervix. *Cancer*. 1982;50:1384–1402.
 130. Hart WR, Kumar N, Crissman JD. Ovarian neoplasms resembling sex cord tumors with annular tubules. *Cancer*. 1980;45:2352–2363.
 131. Ahn GH, Chi JG, Lee SK. Ovarian sex cord tumor with annular tubules. *Cancer*. 1986;57:1066–1073.
 132. Solh HM, Azoury RS, Najjar SS. Peutz-Jeghers syndrome associated with precocious puberty. *J Pediatr*. 1983;103:593–595.
 133. Nomura K, Furusato M, Nikaido T, et al. Ovarian sex cord tumor with annular tubules. Report of a case. *Acta Pathol Jpn*. 1991;41:701–706.
 134. Podczaski E, Kaminski PF, Pees RC, et al. Peutz-Jeghers syndrome with ovarian sex cord tumor with annular tubules and cervical adenoma malignum. *Gynecol Oncol*. 1991;42:74–78.
 135. Srivatsa PJ, Keeney GL, Podratz KC. Disseminated cervical adenoma malignum and bilateral ovarian sex cord tumors with annular tubules associated with Peutz-Jeghers syndrome. *Gynecol Oncol*. 1994;53:256–264.
 136. Boardman LA, Thibodeau SN, Schaid DJ, et al. Increased risk for cancer in patients with the Peutz-Jeghers syndrome. *Ann Intern Med*. 1998;128:896–899.
 137. Hemminki A, Tomlinson I, Markie D, et al. Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis. *Nat Genet*. 1997;15:87–90.
 138. Jenne DE, Reimann H, Nezu J, et al. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet*. 1998;18:38–43.
 139. Benagiano G, Bigotti G, Buzzi M, et al. Endocrine and morphological study of a case of ovarian sex-cord tumor with annular tubules in a woman with Peutz-Jeghers syndrome. *Int J Gynaecol Obstet*. 1988;26:441–452.
 140. Crain JL. Ovarian sex cord tumor with annular tubules: steroid profile. *Obstet Gynecol*. 1986;68(suppl. 3):75S–79S.
 141. Gustafson ML, Lee MM, Scully RE, et al. Müllerian inhibiting substance as a marker for ovarian sex-cord tumor. *N Engl J Med*. 1992;326:466–471.
 142. Barker D, Sharma R, McIndoe A, et al. An unusual case of sex cord tumor with annular tubules with malignant transformation in a patient with Peutz-Jeghers syndrome. *Int J Gynecol Pathol*. 2009;29:27–32.
 143. Puls LE, Hamous J, Morrow MS, et al. Recurrent ovarian sex cord tumor with annular tubules: tumor marker and chemotherapy experience. *Gynecol Oncol*. 1994;54:396–401.
 144. Talerman A, Hughesdon PE, Anderson MC. Diffuse nonlobular ovarian androblastoma usually associated with feminization. *Int J Gynecol Pathol*. 1982;1:155–171.
 145. Young RH, Dudley AG, Scully RE. Granulosa cell, Sertoli-Leydig cell, and unclassified sex cord-stromal tumors associated with pregnancy: a clinicopathological analysis of thirty-six cases. *Gynecol Oncol*. 1984;18:181–205.
 146. Martin-Jimenez A, Condor-Munro E, Valls-Porcel M, et al. Gynandroblastoma of the ovary. Review of the literature. *J Gynecol Obstet Biol Reprod*. 1994;23:391–394.
 147. Novak ER. Gynandroblastoma of the ovary: review of 8 cases from the Ovarian Tumor Registry. *Obstet Gynecol*. 1967;30:709–715.
 148. Kalir T, Friedman F Jr. Gynandroblastoma in pregnancy: case report and review of literature. *Mt Sinai J Med*. 1998;65:292–295.
 149. Hayes MC, Scully RE. Stromal luteoma of the ovary: a clinicopathological analysis of 25 cases. *Int J Gynecol Pathol*. 1987;6:313–321.
 150. Scully RE, Young RH, Clement PB. *Tumors of the Ovary, Maldeveloped Gonads, Fallopian Tube, and Broad Ligament*. Washington, DC: Armed Forces Institute of Pathology; 1998.
 151. Roth LM, Sternberg WH. Ovarian stromal tumors containing Leydig cells. II. Pure Leydig cell tumor, non-hilar type. *Cancer*. 1973;32:952–960.
 152. Paraskevas M, Scully RE. Hilus cell tumor of the ovary. A clinicopathological analysis of 12 Reinke crystal-positive and nine crystal-negative cases. *Int J Gynecol Pathol*. 1989;8:299–310.
 153. Dunnihoo DR, Grieme DL, Woolf RB. Hilar-cell tumors of the ovary. Report of 2 new cases and a review of the world literature. *Obstet Gynecol*. 1966;27:703–713.
 154. Hayes MC, Scully RE. Ovarian steroid cell tumors (not otherwise specified). A clinicopathological analysis of 63 cases. *Am J Surg Pathol*. 1987;11:835–845.
 155. Harris AC, Wakely PE Jr, Kaplowitz PB, et al. Steroid cell tumor of the ovary in a child. *Arch Pathol Lab Med*. 1991;115:150–154.
 156. Davidson BJ, Waisman J, Judd HL. Long-standing virilism in a woman with hyperplasia and neoplasia of ovarian lipidic cells. *Obstet Gynecol*. 1981;58:753–759.
 157. Taylor HB, Norris HJ. Lipid cell tumors of the ovary. *Cancer*. 1967;20:1953–1962.
 158. Adeyemi SD, Grange AO, Giwa-Osagie OF, et al. Adrenal rest tumour of the ovary associated with isosexual precocious pseudopuberty and cushingoid features. *Eur J Pediatr*. 1986;145:236–238.
 159. Dengg K, Fink FM, Heitger A, et al. Precocious puberty due to a lipid-cell tumour of the ovary. *Eur J Pediatr*. 1993;152:12–14.
 160. Clement PB, Young RH, Scully RE. Clinical syndromes associated with tumors of the female genital tract. *Semin Diagn Pathol*. 1991;8:204–233.
 161. Donovan JT, Otis CN, Powell JL, et al. Cushing's syndrome secondary to malignant lipid cell tumor of the ovary. *Gynecol Oncol*. 1993;50:249–253.
 162. Young RH, Scully RE. Ovarian steroid cell tumors associated with Cushing's syndrome: a report of three cases. *Int J Gynecol Pathol*. 1987;6:40–48.
 163. Gershenson DM, Copeland LJ, Kavanagh JJ, et al. Treatment of metastatic stromal tumors of the ovary with cisplatin, doxorubicin, and cyclophosphamide. *Obstet Gynecol*. 1987;70:765–769.
 164. Gershenson DM. Chemotherapy of ovarian germ cell tumors and sex cord stromal tumors. *Semin Surg Oncol*. 1994;10:290–298.
 165. Zhang M, Cheung MK, Shin JY, et al. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary—an analysis of 376 women. *Gynecol Oncol*. 2007;104:396–400.
 166. Abu-Rustum N, Restivo A, Ivy J, et al. Retroperitoneal nodal metastasis in primary and recurrent granulosa cell tumors of the ovary. *Gynecol Oncol*. 2006;103:31–34.
 167. Thrall MM, Paley P, Pizer E, et al. Patterns of spread and recurrence of sex cord-stromal tumors of the ovary. *Gynecol Oncol*. 2011;122:242–245.
 168. Park JY, Jin KL, Kim DY, et al. Surgical staging and adjuvant chemotherapy in the management of patients with adult granulosa cell tumors of the ovary. *Gynecol Oncol*. 2012;125:80–86.
 169. Wolf JK, Mullen J, Eifel PJ, et al. Radiation treatment of advanced or recurrent granulosa cell tumor of the ovary. *Gynecol Oncol*. 1999;73:35–41.
 170. Savage P, Constenla D, Fisher C, et al. Granulosa cell tumours of the ovary: demographics, survival and the management of advanced disease. *Clin Oncol*. 1998;10:242–245.
 171. Homesley HD, Bundy BN, Hurdteau JA, et al. Bleomycin, etoposide, and cisplatin combination therapy of ovarian granulosa cell tumors and other stromal malignancies: a Gynecologic

- Oncology Group study. *Gynecol Oncol*. 1999;72:131-137.
172. Colombo N, Parma G, Franchi D. An active chemotherapy regimen for advanced ovarian sex cord-stromal tumors. *Gynecol Oncol*. 1999;72:129-130.
 173. Gershenson DM, Morris M, Burke TW, et al. Treatment of poor-prognosis sex cord-stromal tumors of the ovary with the combination of bleomycin, etoposide, and cisplatin. *Obstet Gynecol*. 1996;87:527-531.
 174. Pecorelli S, Wagenaar HC, Vergote IB, et al. Cisplatin (P), vinblastine (V) and bleomycin (B) combination chemotherapy in recurrent or advanced granulosa (-theca) cell tumours of the ovary. An EORTC Gynaecological Cancer Cooperative Group Study. *Eur J Cancer*. 1999;35:1331-1337.
 175. Uygun K, Aydinler A, Saip P, et al. Clinical parameters and treatment results in recurrent granulosa cell tumor of the ovary. *Gynecol Oncol*. 2003;88:400-403.
 176. Tresukosol D, Kudelka AP, Edwards CL, et al. Recurrent ovarian granulosa cell tumor: a case report of a dramatic response to Taxol. *Int J Gynecol Cancer*. 1995;5:156-159.
 177. Brown J, Shvartsman HS, Deavers MT, et al. The activity of taxanes in the treatment of sex cord-stromal ovarian tumors. *J Clin Oncol*. 2004;22:3517-3523.
 178. Brown J, Shvartsman HS, Deavers MT, et al. The activity of taxanes compared with bleomycin, etoposide, and cisplatin in the treatment of sex cord-stromal ovarian tumors. *Gynecol Oncol*. 2005;97:489-496.
 179. Chadha S, Rao BR, Slotman BJ, et al. An immunohistochemical evaluation of androgen and progesterone receptors in ovarian tumors. *Hum Pathol*. 1993;24:90-95.
 180. Fishman A, Kudelka A, Edwards C, et al. GnRH agonist (Depot-Lupron) in the treatment of refractory or persistent ovarian granulosa cell tumor (GCT). *Proc Am Soc Clin Oncol*. 1994;13:236(abst).
 181. Isaacs R, Forgeson G, Allan S. Progestogens for granulosa cell tumours of the ovary [Letter]. *Br J Cancer*. 1992;65:140.
 182. Malik ST, Slevin ML. Medroxyprogesterone acetate (MPA) in advanced granulosa cell tumours of the ovary—a new therapeutic approach? *Br J Cancer*. 1991;63:410-411.
 183. Martikainen H, Penttinen J, Huhtaniemi I, et al. Gonadotropin-releasing hormone agonist analog therapy effective in ovarian granulosa cell malignancy. *Gynecol Oncol*. 1989;35:406-408.
 184. Hardy RD, Bell JG, Nicely CJ, et al. Hormonal treatment of a recurrent granulosa cell tumor of the ovary: case report and review of the literature. *Gynecol Oncol*. 2005;96:865-869.
 185. Fishman A, Kudelka AP, Tresukosol D, et al. Leuprolide acetate for treating refractory or persistent ovarian granulosa cell tumor. *J Reprod Med*. 1996;41:393-396.
 186. Freeman SA, Modesitt SC. Anastrozole therapy in recurrent ovarian adult granulosa cell tumors: a report of 2 cases. *Gynecol Oncol*. 2006;103:755-758.
 187. Korach J, Perri T, Beiner M, et al. Promising effect of aromatase inhibitors on recurrent granulosa cell tumors. *Int J Gynecol Cancer*. 2009;19:830-833.
 188. AlHilli MM, Long HJ, Podratz KC, et al. Aromatase inhibitors in the treatment of recurrent ovarian granulosa cell tumors: Brief report and review of the literature. *J Gynecol Obstet Res*. 2012;38(1):340-344.
 189. Farkkila A, Anttonen M, Pociuviene J, et al. Vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 are highly expressed in ovarian granulosa cell tumors. *Eur J Endocrinol*. 2011;164(1):115-122.
 190. Tao X, Sood AK, Deavers MT, et al. Anti-angiogenesis therapy with bevacizumab for patients with ovarian granulosa cell tumors. *Gynecol Oncol*. 2009;114(3):431-436.
 191. Calaminus G, Wessalowski R, Harms D, et al. Juvenile granulosa cell tumors of the ovary in children and adolescents: results from 33 patients registered in a prospective cooperative study. *Gynecol Oncol*. 1997;65:447-452.
 192. Powell JL, Otis CN. Management of advanced juvenile granulosa cell tumor of the ovary. *Gynecol Oncol*. 1997;64:282-284.
 193. Powell JL, Connor GP, Henderson GS. Management of recurrent juvenile granulosa cell tumor of the ovary. *Gynecol Oncol*. 2001;81:113-116.
 194. Schwartz PE, Smith JP. Treatment of ovarian stromal tumors. *Am J Obstet Gynecol*. 1976;125:402-411.
 195. Emons G, Schally AV. The use of luteinizing hormone releasing hormone agonists and antagonists in gynaecological cancers. *Hum Reprod*. 1994;9:1364-1379.
 196. Sigismondi C, Gadducci A, Lorusso D, et al. Ovarian Sertoli-Leydig cell tumors. A retrospective MITO study. *Gynecol Oncol*. 2012;673-676.
 197. Burger HG. Inhibin. *Reprod Med Rev*. 1992;1:1-20.
 198. Petraglia F, Luisi S, Pautier P, et al. Inhibin B is the major form of inhibin/activin family secreted by granulosa cell tumors. *J Clin Endocrinol Metab*. 1998;83:1029-1032.
 199. Ying SY. Inhibins, activins, and follistatins: gonadal proteins modulating the secretion of follicle-stimulating hormone. *Endocr Rev*. 1988;9:267-293.
 200. Robertson DM, Stephenson T, Pruyers E, et al. Characterization of inhibin forms and their measurement by an inhibin alpha-subunit ELISA in serum from postmenopausal women with ovarian cancer. *J Clin Endocrinol Metab*. 2002;87:816-824.
 201. Lin YS, Eng HL, Jan YJ, et al. Molecular cytogenetics of ovarian granulosa cell tumors by comparative genomic hybridization. *Gynecol Oncol*. 2005;97:68-73.
 202. Mayr D, Kaltz-Wittmer C, Arbogast S, et al. Characteristic pattern of genetic aberrations in ovarian granulosa cell tumors. *Mod Pathol*. 2002;15:951-957.
 203. Fletcher JA, Gibas Z, Donovan K, et al. Ovarian granulosa stromal cell tumors are characterized by trisomy 12. *Am J Pathol*. 1991;138:515-520.
 204. Halperin D, Visscher DW, Wallis T, et al. Evaluation of chromosome 12 copy number in ovarian granulosa cell tumors using interphase cytogenetics. *Int J Gynecol Pathol*. 1995;14:319-323.
 205. Menczer J, Schreiber L, Czernobilsky B, et al. Is Her-2/neu expressed in nonepithelial ovarian malignancies? *Am J Obstet Gynecol*. 2007;196:79e1-79e4.
 206. Leibl S, Bodo K, Gogg-Kammerer M, et al. Ovarian granulosa cell tumors frequently express EGFR (Her-1), Her-3, and Her-4: an immunohistochemical study. *Gynecol Oncol*. 2006;101:18-23.
 207. Kusamura S, Derchain S, Alvarenga M, et al. Expression of p53, c-erbB-2, Ki-67, and CD34 in granulosa cell tumor of the ovary. *Int J Gynecol Cancer*. 2003;13:450-457.
 208. Richards JS, Fan H-Y, Liu Z, et al. Either *Kras* activation or *Pten* loss similarly enhance the dominant-stable CTNNB1-induced genetic program to promote granulosa cell tumor development in the ovary and testis. *Oncogene*. 2012;31:1504-1520.
 209. Shah SP, Köbel M, Senz J, et al. Mutation of *FOXL2* in granulosa-cell tumors of the ovary. *N Engl J Med*. 2009;360:2719-2729.
 210. Cocquet J, Pailhoux E, Jaubert F, et al. Evolution expression of *FOXL2*. *J Med Genet*. 2002;39:916-922.
 211. Schmidt D, Ovitt CE, Anlag K, et al. The murine winged-helix transcription factor *FOXL2* is required for granulosa cell differentiation and ovary maintenance. *Development*. 2004;131:933-942.
 212. Al-Aha O, Huwalt HF, Chow C, et al. *FOXL2* is a sensitive and specific marker for sex cord-stromal tumors of the ovary. *Am J Surg Pathol*. 2011;3(4):484-494.
 213. Schultz KA, Pacheco MC, Yang J, et al. Ovarian sex cord-stromal tumors, pleuropulmonary blastoma and *DICER1* mutations: a report from the International Pleuropulmonary Blastoma Registry. *Gynecol Oncol*. 2011;122:246-250.
 214. Heravi-Moussavi A, Anglesio MS, Cheng SW, et al. Recurrent somatic *DICER1* mutations in nonepithelial ovarian cancers. *N Eng J Med*. 2012;366:234-242.
 215. Rio Frio T, Bahubeshi A, Kanellopoulou A, et al. *DICER1* mutations in familial multinodular goiter with and without ovarian Sertoli-Leydig cell tumors. *JAMA*. 2011;305(1):68-77.
 216. Chu S, Marners P, Burger HG, et al. Estrogen receptor isoform gene expression in ovarian stromal and epithelial tumors. *J Clin Endocrinol Metab*. 2000;85(3):1200-1205.
 217. Fuller PJ, Chu S. Signalling pathways in the molecular pathogenesis of ovarian granulosa cell tumours. *Trends Endocrinol Metab*. 2004;15(3):122-128.
 218. Alexiadis M, Marners P, Chu S, et al. Insulin-like growth factor, insulin-like growth factor-binding protein-4, and pregnancy-associated plasma protein-A gene expression in human granulosa cell tumors. *Int J Gynecol Cancer*. 2006;16:1973-1979.
 219. Anttonen M, Unkila-Kallio L, Leminen A, et al. High GATA-4 expression associates with aggressive behavior, whereas low anti-müllerian hormone expression associates with growth potential of ovarian granulosa cell tumors. *J Clin Endocrinol Metab*. 2005;90(12):6529-6535.

Gestational Trophoblastic Disease: Molar Pregnancy and Gestational Trophoblastic Neoplasia

JULIAN C. SCHINK ■ JOHN R. LURAIN

Gestational trophoblastic disease (GTD) describes a continuum of interrelated lesions that arise from abnormal proliferation of placental trophoblasts, ranging from benign hydatidiform mole to invasive mole, malignant choriocarcinoma (CCA), and placental site trophoblastic tumor (PSTT) (Table 27.1). Hydatidiform moles, both complete and partial, are benign lesions that resolve following uterine evacuation in the vast majority of cases. Persistent GTD refers to disease that does not resolve after molar evacuation or that becomes malignant and requires active management. Invasive moles, CCA, and PSTT, as well as a variant of PSTT called epithelioid trophoblastic tumor (ETT), are collectively referred to as gestational trophoblastic neoplasia (GTN), with varying degrees of malignant potential. GTN most commonly arises after a molar pregnancy, though it can develop after any pregnancy. Historically, GTD was associated with high rates of morbidity and mortality. Hydatidiform mole was associated with serious complications, and the mortality rate for invasive mole approached 15%. The mortality rate for CCA was near 100% if metastatic disease was present and 60% for nonmetastatic disease even if hysterectomy was performed. Earlier detection with ultrasonography, the use of human chorionic gonadotropin (hCG) as a disease-specific biomarker, advances in uterine evacuation, and the introduction of chemotherapy into the management of GTN (1) have significantly decreased the risk of death associated with GTD and have allowed many women to preserve their fertility after treatment. This chapter will describe the epidemiology and pathology of molar pregnancy and GTN and will discuss the changes in diagnosis and management that have transformed GTN from one of the most deadly to one of the most curable solid tumors in women, with cure rates higher than 90%, even in the presence of metastasis (2,3).

EPIDEMIOLOGY

Epidemiologic data for GTD are unreliable, primarily due to inconsistent case definitions, no centralized databases, and the rarity of certain forms of the disease. Similarly, defining the risk factors that contribute to the development of GTD has been challenging, with an inability to adequately identify at-risk populations and a lack of control groups (4). Based on available data, hydatidiform mole develops in women during their reproductive years (5), with an incidence that varies widely across different geographical regions. In North America, Australia, New Zealand, and Europe, the incidence of molar pregnancy has been reported as 0.6 to 1.1 per 1,000 pregnancies, but it is 2- to 3-fold higher in Southeast Asia and Japan (2.0 per 1,000 pregnancies) (6–8). In Taiwan, hydatidiform mole occurs in 1 in

125 pregnancies, whereas the incidence in the United States is approximately 1 in 1,500 pregnancies. In a study from Ireland, the incidence of complete and partial mole was reported as 1 in 1,945 and 1 in 695 pregnancies, respectively (9).

Despite this geographical variation, the risk of hydatidiform mole has not been linked to any specific ethnic or racial differences, cultural factors, or differences in reporting of hospital-based and population-based data (10–12). However, several studies have reported a link between molar pregnancy and socioeconomic and dietary factors, specifically, that the risk of complete molar pregnancy increases with decreased consumption of vitamin A (carotene) and animal fat (13,14). Regions with a higher incidence of vitamin A deficiency also have a higher incidence of molar pregnancy. A history of infertility is also associated with increased risk of complete and partial mole (15), and a history of spontaneous abortion increases the risk of both complete and partial moles 2- to 3-fold compared with women without a history of miscarriage (15–17).

The two strongest risk factors for complete hydatidiform mole are maternal age and prior molar pregnancy (17). Both very young women and women over the age of 40 have a higher risk of complete molar pregnancy, with older women having a 5- to 10-fold higher risk (18,19). In women over the age of 50, 1 in every 3 pregnancies is molar (4). These observations suggest that the ova of older women are predisposed to the abnormal fertilization events that lead to hydatidiform mole. The risk of a second complete molar pregnancy is 1%, approximately 10- to 20-fold higher than the risk of molar pregnancy in the general population (20,21), and the risk of a third mole is 15% to 20% (22,23), regardless of a change in partner (24).

Familial repetitive hydatidiform mole (17) has been linked to a missense mutation in the *NLRP7* locus (25,26) on chromosome 19 (27); in one report, this mutation was present in 60% of patients who had two molar pregnancies (28). The mutated gene is involved in maternal imprinting (29) and is seen in familial clusters of complete moles of biparental origin rather than androgenetic origin (26,30).

There is less information regarding the epidemiology of partial molar pregnancy, though it is clear that it differs from that of complete molar pregnancy (18,19). Partial mole does not appear to be linked to vitamin A deficiency (31) or advanced maternal age (17), but is associated with a history of irregular menstruation and use of high estrogen-containing oral contraceptives (31).

Locally invasive GTN develops in approximately 15% of patients after molar evacuation. CCA occurs in 1 in 50,000 pregnancies (including term, miscarriage, abortion, or ectopic) (32). CCA is 1,000 times more likely to develop after a complete molar pregnancy than after other pregnancy events, with half of all CCA cases arising from molar pregnancies. The risk of

Table 27.1 National Institutes of Health
Clinical Classification of Gestational
Trophoblastic Disease

I. Benign GTD

A. Complete hydatiform mole

B. Partial hydatidiform mole

II. Malignant GTD

A. Nonmetastatic (invasive mole or CCA)

B. Metastatic

1. CCA

2. PSTT

3. ETT

GTD, gestational trophoblastic disease; CCA, choriocarcinoma; PSTT, placental site trophoblastic tumor; ETT, epithelioid trophoblastic tumor.

CCA increases in women with advanced maternal age and prior hydatidiform mole, and is higher in women of Asian, American Indian, and African American descent (12). Menarche after age 12, light menstrual flow, and long-term use of oral contraceptives are also associated with a higher risk of CCA (33), though the association between postmolar GTN and oral contraceptive use is not entirely clear (34,35). Women with type A blood also have an increased risk of CCA (7,36).

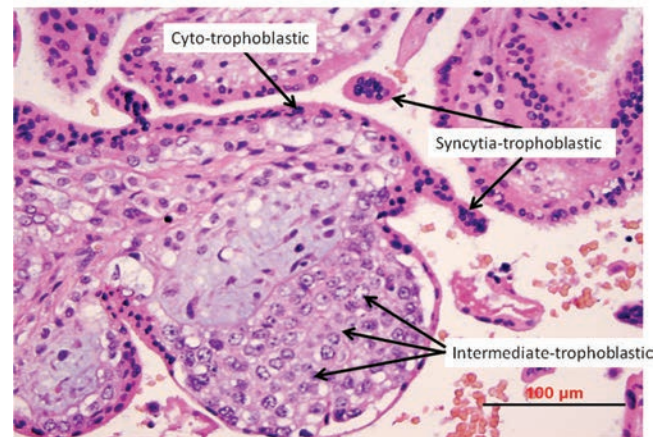
PSTT and ETT are extremely rare forms of malignant GTD, and there are insufficient data to characterize the epidemiology or risk factors. Approximately 95% of PSTT and ETT lesions develop after a term pregnancy or nonmolar abortion (37), often several months or even years later.

PATHOLOGY AND CHROMOSOMAL FEATURES**Trophoblastic Differentiation and GTD**

Molar pregnancies and GTN originate from the placental trophoblast, which is derived from the outermost layer of the blastocyst, called the trophoctoderm (38). The trophoblast is composed of cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast. Syncytiotrophoblast invades the endometrial stroma upon implantation of the blastocyst and secretes hCG and other proteins to regulate the implantation site microenvironment. Cytotrophoblast fuses with syncytiotrophoblast to form the chorionic villi that cover the chorionic sac. Nonvillous cytotrophoblast differentiates into intermediate trophoblast, categorized as either implantation site or chorion type. Implantation site intermediate trophoblast loses the ability to proliferate but invades the maternal decidua and myometrium in a highly controlled manner, migrating to the maternal spiral arteries to facilitate oxygen and waste transfer between the fetus and the mother (Fig. 27.1).

Invasion of healthy trophoblast into the maternal endometrium is a normal, tightly regulated event in pregnancy that is required for the vascular connection between the fetus and the mother. When regulatory mechanisms are impaired, invasive and vascular tumors arise. For example, recent work has described an inhibitory effect of TGF- β and a proteoglycan, decorin, on nonvillous trophoblast cell growth, migration, and invasion, and this negative regulation is lost in trophoblast lesions (39,40).

Most GTD lesions (except partial mole) derive from the fetus and not from the mother, and therefore contain only paternal

Normal chorionic villi**FIGURE 27.1.** Normal trophoblast differentiation. Cytotrophoblast, syncytiotrophoblast and intermediate trophoblast are labeled in this photomicrograph.**Table 27.2** Immunohistochemical Markers for
Differential Diagnosis of GTD

Marker	Application
Ki-67, PCNA, p53	Spontaneous abortion (negative)
	GTD (positive)
	CCA (diffusely positive in 50% cells)
p63	PSTT (>10% labeling index)
	PSTT (negative)
	ETT (positive)
HLA-G	Nonvillous IT (positive)
	PSTT (implantation site IT positive)
	ETT (chorionic-type IT positive)
β hCG	CCA (syncytiotrophoblast positive)
Inhibin α	CCA (trophoblast and IT positive)
	PSTT (diffusely positive)
	ETT (diffusely positive)
hPL	CCA (IT positive)
	PSTT (diffusely positive)
Mel-CAM	PSTT (diffusely positive)
Cytokeratin	CCA (all cells positive)
	PSTT (diffusely positive)
	ETT (diffusely positive)
p57kip2	Complete mole (negative)
	Partial mole (positive)
Cyclin E	ETT (relatively greater staining than placental site nodule)

PCNA, proliferating cell nuclear antigen; GTD, gestational trophoblastic disease; CCA, choriocarcinoma; PSTT, placental site trophoblastic tumor; ETT, epithelioid trophoblastic tumor; IT, intermediate trophoblast.

genetic material (38). A large body of work on the immunobiology of GTD has suggested that a maternal immunologic response is activated by paternal antigens in the trophoblastic cells of GTD lesions, thereby promoting their regression and sensitizing them to chemotherapy; conversely, women with persistent GTD or aggressive disease may have greater histocompatibility such that the paternal antigens do not elicit a strong immune response from the mother (41).

All three types of trophoblast can proliferate to produce GTD lesions (42), and each type expresses different antigens that have been useful in the immunohistochemical analysis and differential diagnosis of trophoblastic lesions (43); they may also provide insight into the pathogenic mechanisms underlying GTN (Table 27.2). Expression of Ki67, proliferating cell nuclear antigen, and p53 are significantly higher in GTD compared with normal tissues and can differentiate between GTD and spontaneous abortion (44). p63 isoforms are differentially expressed in cytotrophoblast and intermediate trophoblast (45) and may be useful in differentiating between PSTT (p63 negative) and ETT (p63 positive). HLA-G is also expressed in intermediate trophoblasts but not in villous cytotrophoblasts or syncytiotrophoblasts, and may be useful in the diagnosis of various GTD lesions (46). Several growth factors and oncogenes are abnormally expressed in molar tissues and CCA (15,47,48). Both complete mole and CCA overexpress c-myc, c-erb2, and bcl-2. Epidermal growth factor receptor (EGFR) was found to be more highly expressed in CCA and complete moles compared with normal placenta and partial moles, suggesting that EGF family members may be involved in GTN pathogenesis (49). In addition, there is increased expression of matrix metalloproteinase (MMP-1 and MMP-2) and decreased expression of tissue inhibitor of metalloproteinase (TIMP)-1 in CCA compared with either hydatidiform

mole or normal placenta, implicating the dysregulation of extracellular matrix (ECM) in the invasion and metastasis of CCA (50). Characterizing the molecular pathogenesis of GTD is an active area of research that may reveal new diagnostic and prognostic markers, as well as lead to targeted therapies.

Hydatidiform Mole

Molar pregnancies arise from the proliferation of villous cytotrophoblast and syncytiotrophoblast, which produces lesions on the maternal decidua (51,52). A comparison of the characteristics and cytogenetics of complete and partial moles is provided in Table 27.3. Complete hydatidiform moles show early uniform enlargement of villi with hyperplastic and atypical trophoblast and do not contain a fetus/embryo or villous capillaries (Fig. 27.2). Most complete moles (approximately 90%) are 46,XX and arise from the fertilization of an “empty” anucleated egg—missing the pronucleus and maternal chromosomes—by a single sperm followed by duplication of paternal haploid chromosomes (Fig. 27.3) (53,54). The other 10% of complete moles are either 46,XY or 46,XX and are produced by dispermic fertilization of an anucleated egg. Some complete moles can also arise from the loss of maternal chromosomes during the first cleavage. Regardless of monospermic or dispermic fertilization, complete moles contain only paternal chromosomes (androgenetic), though maternal DNA is present in the mitochondria of the egg (55). The presence of excess paternal material leads to trophoblastic hyperplasia, with no formation of a fetus due to the absence of maternal chromosomal DNA. Loss of maternally imprinted genes and extra paternally imprinted genes may also inhibit embryo formation (56).

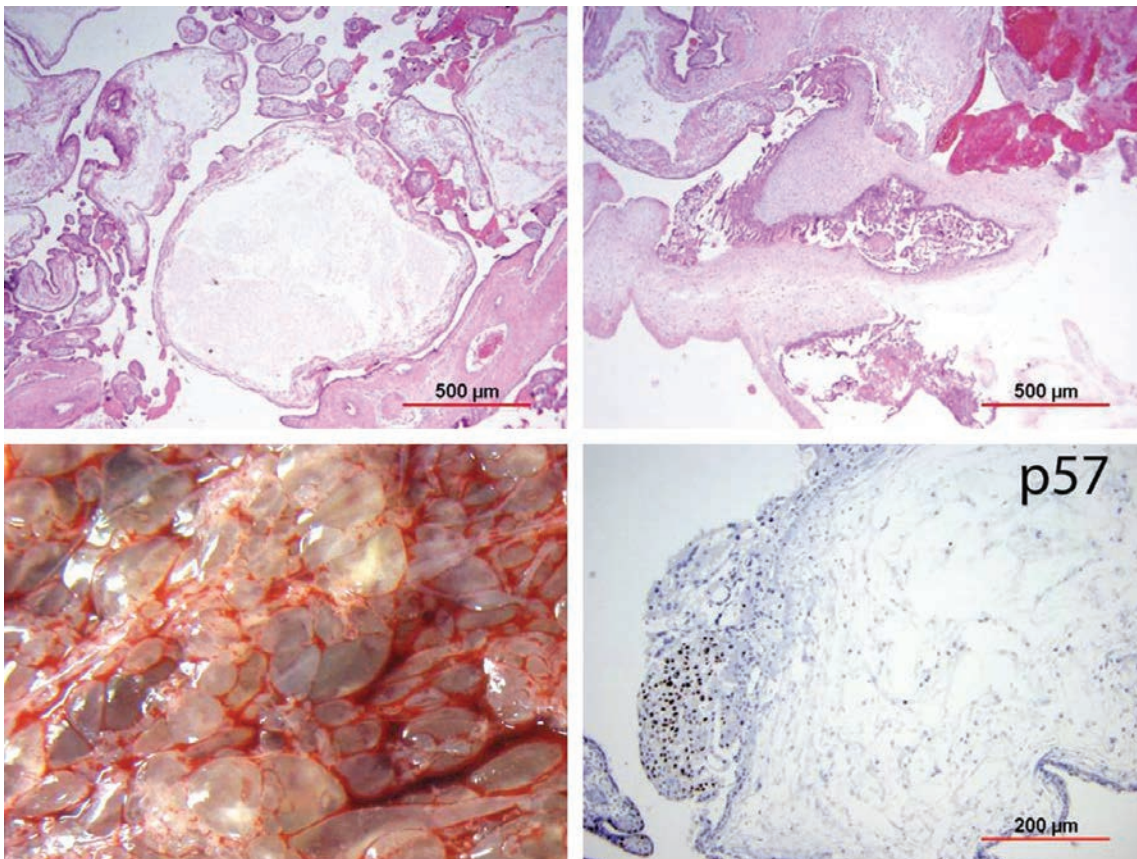


FIGURE 27.2. Complete hydatidiform mole. Upper left: large round chorionic villi with cistern formation; Upper right: large irregular contour with extensive trophoblastic proliferation; Lower left: gross morphology of large cystic chorionic villi; Lower right: chorionic villous stromal cells stain negative for p57.

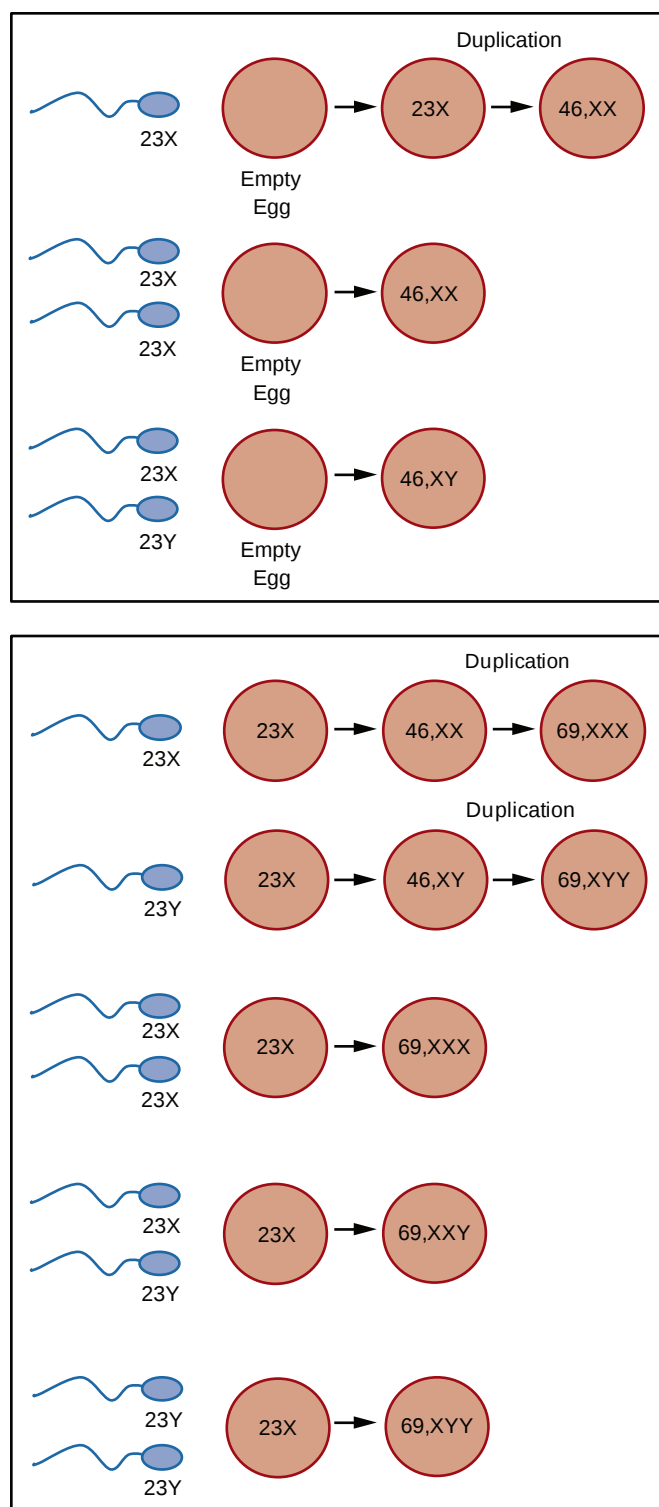


FIGURE 27.3. Karyotypes of complete and partial hydatidiform mole. (A) Complete moles arise from the fertilization of an empty egg with a single sperm that then undergoes duplication (46,XX) or the fertilization of an empty egg with two sperm (46,XX or 46,XY). Complete moles therefore contain only paternal genetic material. (B) Partial moles are triploid (69,XXY; 69,XXX; or 69,YYY) and arise from either dispermic fertilization of a normal egg or duplication of chromosomes in a single sperm after fertilization of a normal egg.

In contrast, partial hydatidiform moles contain fetal/embryonic tissue, and the chorionic villi show varying degrees of focal enlargement and edema, predominantly syncytiotrophoblast hyperplasia, scalloping of the villous outline, prominent stromal inclusions, and functional villous circulation (Fig. 27.4) (57). Like incomplete moles, the trophoblast is hyperplastic but shows only mild atypia. In later stages of partial molar pregnancy, the fetus shows congenital abnormalities, such as syndactyly of the fingers and toes (57). The majority of partial moles are triploid, most often 69,XXY, with two sets of paternal chromosomes as a consequence of either dispermic fertilization of a normal egg or duplication of chromosomes in a single sperm after fertilization of a normal egg (Fig. 27.3) (51,56,58).

Invasive Mole

Invasive mole is a condition in which hydatidiform mole, with hydropic villi and proliferating trophoblast, has invaded the myometrium through the tissue or veins (Fig. 27.5). Molar villi may be observed on the uterine serosa, and extrauterine tubal and ovarian moles can occur (59). Invasive moles are less hydropic, and trophoblastic proliferation is easily seen (Table 27.3) (57).

Choriocarcinoma

Approximately 2% of women with complete moles may develop CCA, characterized by a mixture of cytotrophoblast and syncytiotrophoblast hyperplasia, hemorrhage, and necrosis, and the absence of chorionic villi (Fig. 27.6) (57). Direct invasion of the myometrium and vasculature is also present, which permits metastasis to the lungs, brain, liver, pelvis and vagina, kidney, intestines, and spleen. Immunohistochemical markers can confirm a histologic diagnosis of CCA, with tumors staining strongly for hCG and inhibin α in the trophoblast, human placental lactogen (hPL) and inhibin α in intermediate trophoblast, and cytokeratin in all trophoblast cells (Tables 27.2 and 27.3) (60). Ki-67 is diffusely expressed in approximately half of the cells (61).

Placental Site Trophoblastic Tumor

PSTT lesions are usually diploid and monomorphic, developing from placental implantation site intermediate trophoblast after a normal or aborted uterine pregnancy (62). PSTT lesions contain primarily mononuclear intermediate trophoblast without chorionic villi that infiltrates the uterine wall in sheets or cords between myometrial fibers (Fig. 27.7). Compared with CCA, there is less hemorrhage, necrosis, and vascular invasion, but there is a higher risk of lymphatic metastasis. hCG production is focal, leading to relatively lower serum levels (Table 27.3). These tumors may be diagnosed immunohistochemically, and contain diffuse cytokeratin and human placental lactogen (63), as well as inhibin α (60) and Mel-CAM (Table 27.2) (61). The Ki-67 labeling index is also usually elevated (>10%) in a neoplastic lesion of nonvillous trophoblast (61).

Epithelioid Trophoblastic Tumor

Epithelioid trophoblastic tumor (ETT) is a rare malignant tumor that arises from neoplastic transformation of chorion-type intermediate trophoblast (62). These lesions appear as nodules of mononuclear intermediate trophoblast, surrounded by hyalinized extracellular matrix within extensive necrotic tissue and with preserved blood vessel structure (Fig. 27.8 and Table 27.3). Intratumor hemorrhage and metastases are rarely observed.

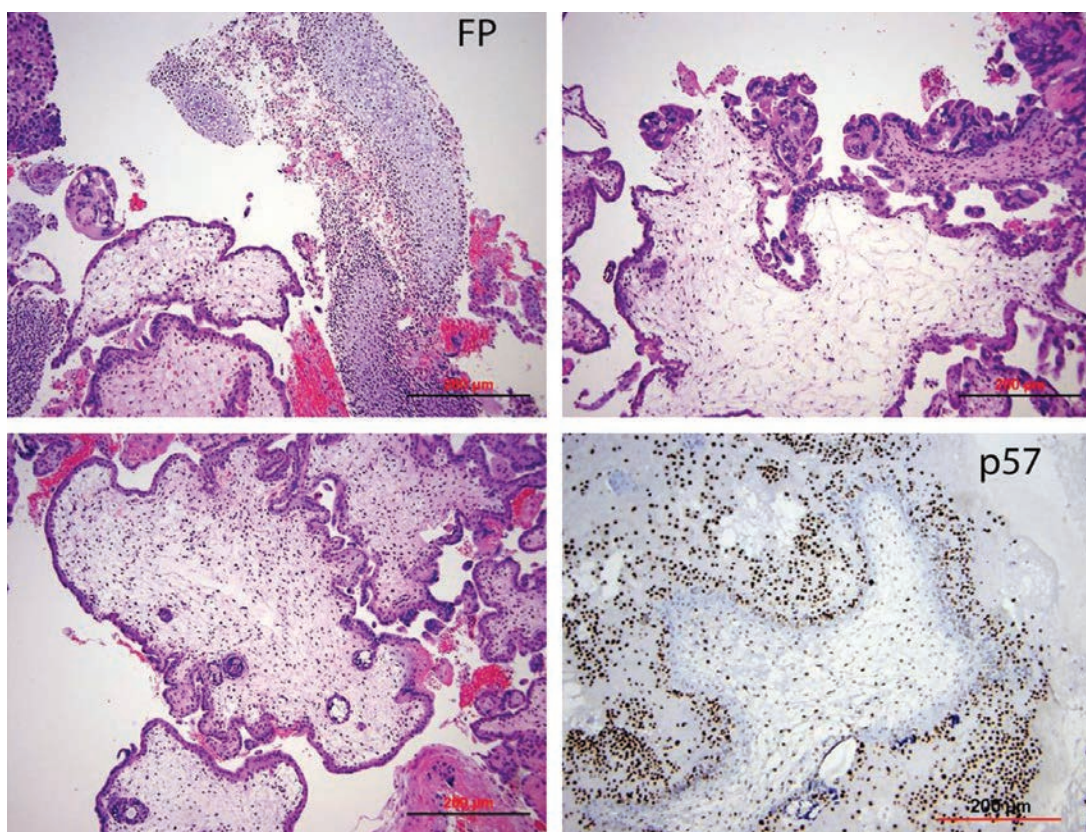


FIGURE 27.4. Partial hydatidiform mole. Upper left: large chorionic villi and fetal parts (FP); Upper right: large irregular contour and trophoblastic proliferation; lower left: large irregular contour with pseudoinclusion cysts; lower right: chorionic villous stromal cells stain positive for p57.

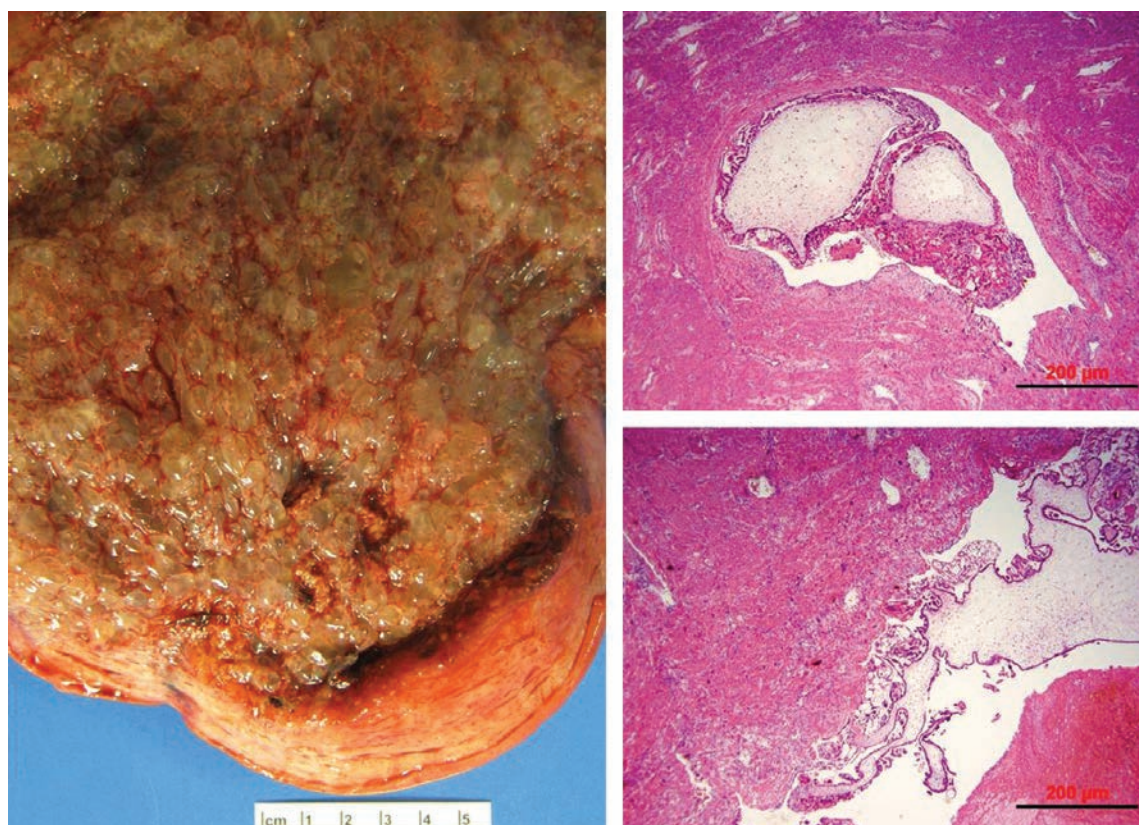


FIGURE 27.5. Invasive mole. Macrophotograph of molar product of conception that is occupying the entire endometrial cavity and invading into the myometrium (left panel). Photomicrographs show molar chorionic villi infiltrating into the myometrium (right panels).

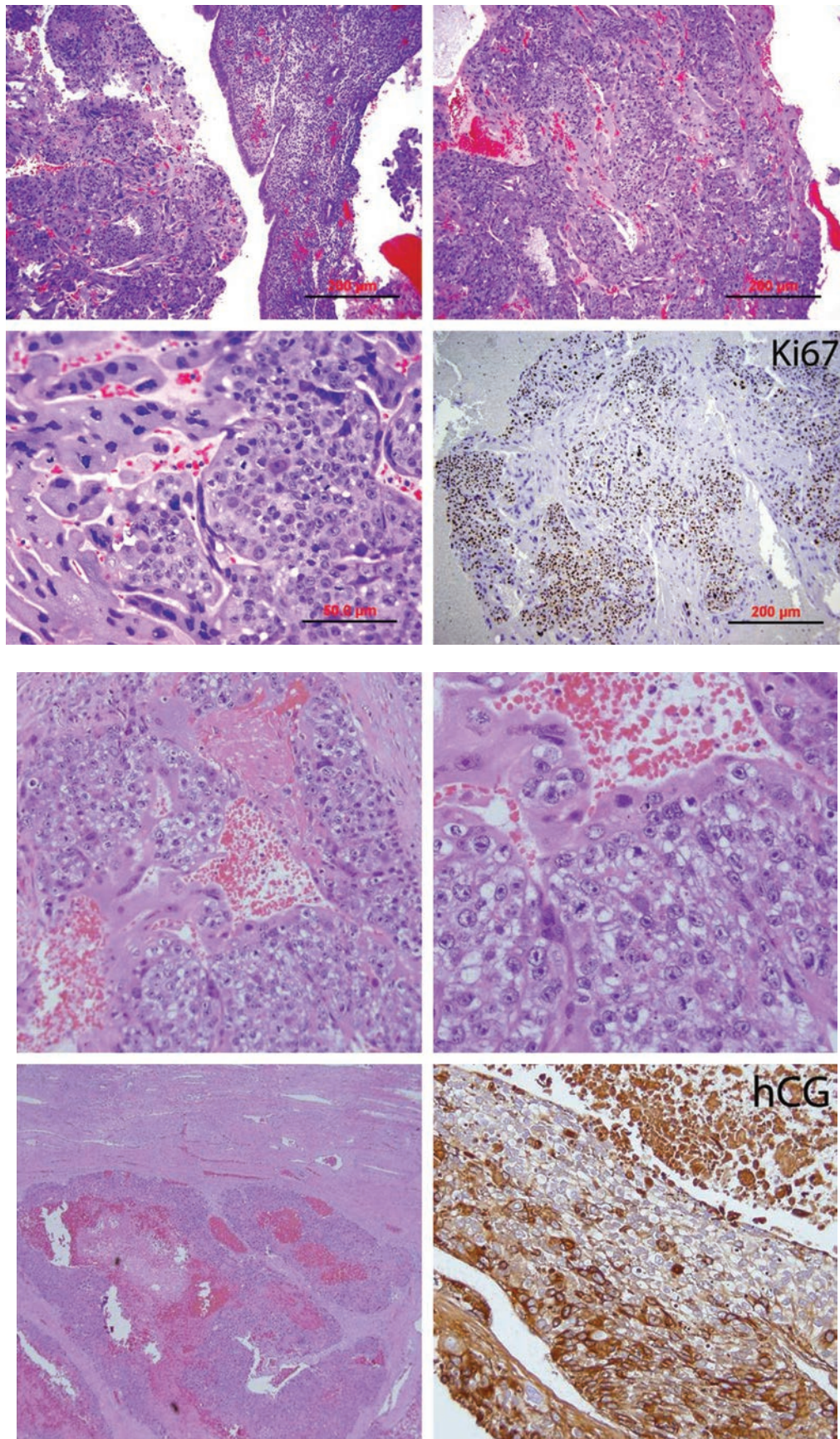


FIGURE 27.6. Choriocarcinoma. (A) Upper left: fragment of trophoblastic proliferation in the background of normal appearing endometrium; Upper right: sheath of cyto- and syncytiotrophoblastic proliferation with hemorrhage; Lower left: close view of biphasic cytotrophoblastic and syncytiotrophoblast cell proliferation; Lower right: Ki-67 index is >50% in tumor cells. **(B)** Upper panels: close view of biphasic cyto- and syncytiotrophoblastic proliferation; Lower left: tumor invasion into myometrium with characteristic hemorrhage; Lower right: immunostain for hCG is positive in most syncytiotrophoblast cells.

Table 27.3 Clinicopathologic Features of Gestational Trophoblastic Diseases

Disease	Pathologic Features	Clinical Features
Complete mole	• Diploid (46,XX and some 46,XY) • No fetus or embryo • Diffuse swelling of villi • Diffuse trophoblastic hyperplasia	• Vaginal bleeding • Large for date uterine size • Bilateral theca lutein cysts • hCG can be >100,000 mIU/mL
Partial mole	• Triploid (69,XXY; 69,XYY; 69,XXX) • Abnormal fetus or embryo • Focal swelling of villi • Focal trophoblastic hyperplasia with mild atypia	• Symptoms of incomplete or missed abortion • Vaginal bleeding • hCG rarely elevated >100,000 mIU/mL
Invasive mole	• Trophoblastic hyperplasia • Swollen villi • Myometrial invasion	• Irregular postmolar vaginal bleeding • Persistent hCG elevation • <15% symptoms of lung/vaginal metastases
Choriocarcinoma	• Mixture of cytotrophoblast and syncytiotrophoblast hyperplasia • No villi • Myometrial invasion and metastatic potential • Hemorrhage • Necrosis	• Irregular postmolar vaginal bleeding • Persistent hCG elevation • Metastases and associated symptoms
PSTT	• Diploid • IT hyperplasia • No villi • Less hemorrhage and necrosis • High potential for lymphatic invasion and metastasis • Focal hCG production	• Low serum hCG • Enlarged uterus • hCG levels normal to 1,000 mIU/mL • Metastases and associated symptoms
ETT	• IT nodules surrounded by hyalinized ECM • Extensive necrotic tissue • Preserved blood vessel structure • Hemorrhage and metastases rare	

hCG, human chorionic gonadotropin; IT, intermediate trophoblast; ECM, extracellular matrix; PSTT, placental site trophoblastic tumor; ETT, epithelioid trophoblastic tumor.

Source: Adapted from Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol.* 2010;203(6):531–539, with permission.

Table 27.4 The Changing Clinical Signs of Molar Pregnancy

Clinical Sign	Incidence (%)	
	1970s	2010s
Vaginal bleeding	100	90
Uterine enlargement	54	28
Toxemia	22	1
Hyperemesis	28	8
Hyperthyroidism	10	<1
Trophoblastic emboli	2	<1
Bilaterally enlarged ovaries	15	15
Absence of fetal heart sounds	100	100

MANAGEMENT OF MOLAR PREGNANCY

Clinical Presentation

Approximately 80% to 90% of women with complete hydatidiform mole present with vaginal bleeding, occurring at 6 to 16 weeks gestation. Women may also present with larger uterine size than expected for gestational date, toxemia, hyperemesis, and hyperthyroidism in the first or second trimester. However, the widespread use of ultrasonography in developed countries and accurate hCG tests to evaluate vaginal bleeding have led to earlier diagnosis of molar pregnancy, and other clinical signs and symptoms are seen less often (Table 27.4) (67). hCG levels can be greater than 100,000 mIU/mL in a complete molar pregnancy, and there are no fetal heart tones (Table 27.3); however, hCG levels vary widely in individual patients, and with earlier ultrasound detection, patients may not present with extremely elevated hCG. It should also be emphasized that a high hCG level alone is not sufficient for a diagnosis of hydatidiform mole, and a confirmatory ultrasound should be performed. In approximately 15% of women with complete hydatidiform mole, ultrasound imaging reveals the presence of bilateral theca lutein cyst enlargement of the ovaries (5,67–69).

Partial hydatidiform mole presents quite differently from complete mole. The vast majority of patients—greater than 90%—present with symptoms of incomplete or missed abortion. Vaginal bleeding occurs in 75% of patients with a partial molar pregnancy, and uterine enlargement, hyperemesis,

ETT tumor cells show diffuse expression of immunohistologic markers, including cytokeratin and inhibin α (Table 27.2) (64). Cyclin E staining is higher in ETT than placental site nodule and can help in differentiating between the two (64–66).

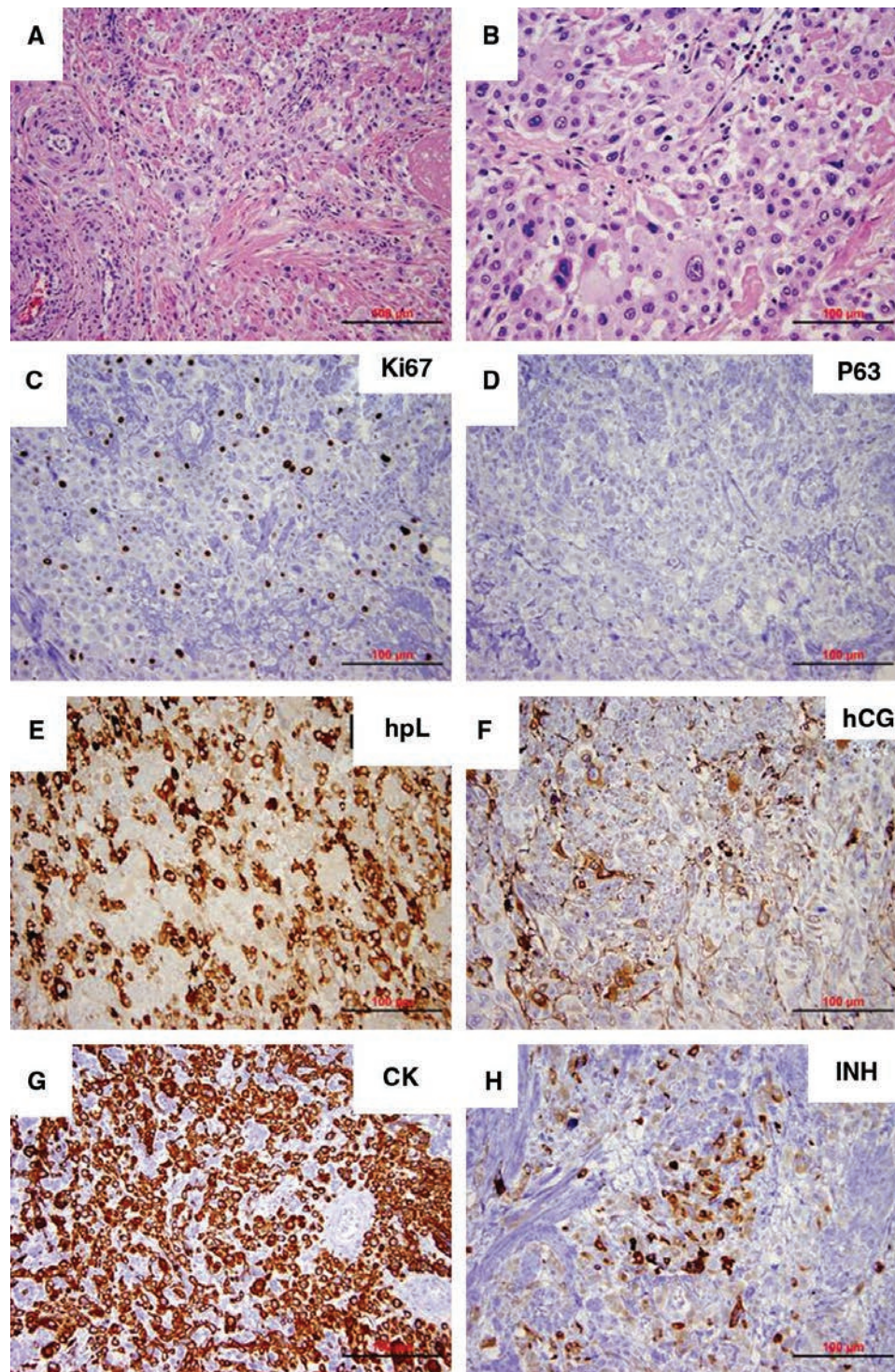


FIGURE 27.7. Placental site trophoblastic tumor (PSTT). (A, B) Histology shows mostly intermediate placental site trophoblastic cell proliferation and infiltration into the myometrium. (C) Tumor cells show moderate cytotrophic atypia and have an increased Ki-67 index (>20%). Tumor cells are also negative for p63 (D), which excludes a diagnosis of epithelioid trophoblastic tumor; are strongly and diffusely positive for human placental lactogen (E) and pan-cytokeratin (G); and are diffusely positive for hCG (F) and inhibin (H). CK, cytokeratin; hPL, human placental lactogen; INH, inhibin.

hypertension, hyperthyroidism, and theca lutein cysts are not often seen. Presenting hCG levels are higher than 100,000 mIU/mL in only 10% of patients (70–72).

Diagnosis

Ultrasonography is the primary means of preoperative diagnosis of molar pregnancy, and its introduction has made diagnosis

at much earlier stages possible (5,73–75). Ultrasound not only provides information on the type of molar pregnancy, but also determines involvement of the endometrial cavity or myometrium, assesses the risk of uterine perforation, and detects theca lutein cysts and vaginal metastases. The diffuse hydropic swelling of the chorionic villi in complete molar pregnancy is seen as a characteristic vesicular “snowstorm” pattern on ultrasound, with many holes within the placenta and the absence of a fetus (Fig. 27.9). However, as this pattern is also seen in women with

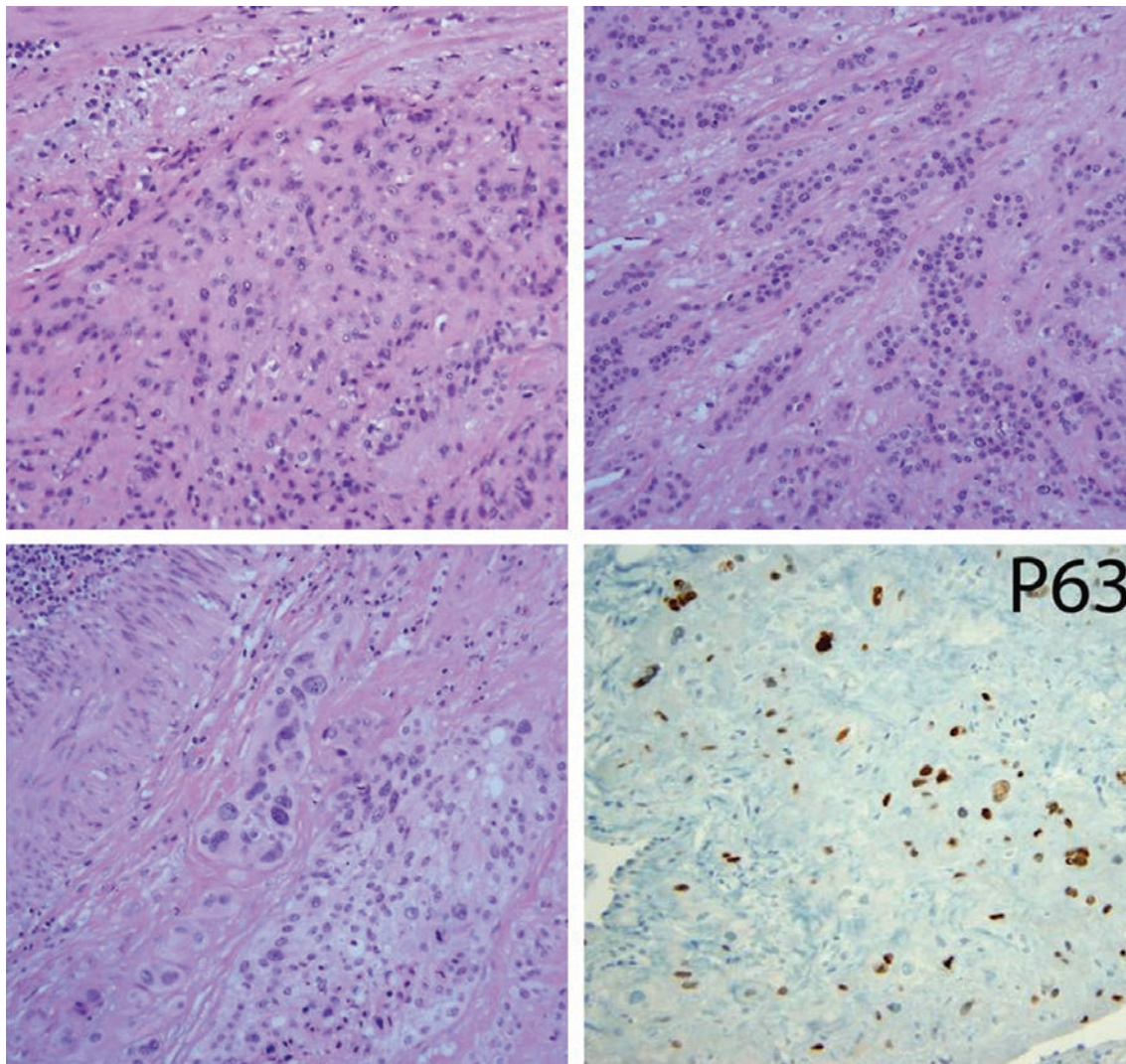


FIGURE 27.8. Epithelioid trophoblastic tumor. Tumor cell proliferation in sheets (*upper left*) or cords (*upper right*), and myometrial invasion (*lower left*). Tumor cells stain positive for p63.

missed abortion, hematometra, or uterine fibroids ultrasound diagnosis alone is not very specific. When ultrasound diagnosis is combined with elevated hCG and the absence of fetal heartbeat, molar pregnancy is the most likely diagnosis. For partial moles, ultrasonography can detect focal cystic spaces in the placental and the enlarged gestational sac (75). Ultrasound may show the snowstorm pattern and a viable fetus, which may also indicate threatened abortion, fibroid uterus, or twin gestation with a single missed abortion and a complete mole. Partial mole can be confirmed with chorionic villus sampling that shows triploidy.

The most accurate disease-specific marker of GTD is hCG, which is produced by hydatidiform moles and CCA and can be measured quantitatively in the blood and urine. Placental hCG is a glycoprotein of two subunits, a common α subunit that is similar to the α subunit of pituitary hCG and a placenta-specific β subunit. In a normal pregnancy, hCG is essential for maintaining placental vascular supply (76). As pregnancy progresses, hCG is secreted by syncytiotrophoblasts, increasing to approximately 60,000 mIU/mL at 10 weeks and then declining to a range of values around 12,000 mIU/mL through the remainder of the pregnancy (77). hCG molecules secreted by trophoblast-derived moles and GTN are more heterogeneous than in a normal pregnancy, with transformation of the trophoblast resulting in fragmentation of the hCG molecule, and several forms of hCG are present, including hyperglycosylated,

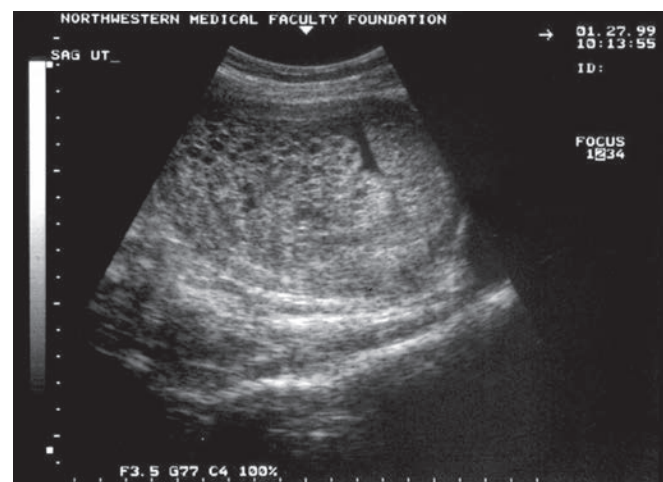


FIGURE 27.9. Ultrasound of complete hydatidiform mole. The characteristic vesicular “snowstorm” pattern of multiple echoes, appearing as holes within the placenta. No fetus is present.

nicked, C-terminal truncated β subunit, free β subunit, nicked free β subunit, and free α subunit (78). Normally, hyperglycosylated hCG is produced by cytotrophoblasts early in gestation and acts as an autocrine regulator of trophoblast invasion of the implantation site and establishment of the fetomaternal circulation. Hyperglycosylated β subunit is produced by GTN lesions and promotes the growth and invasion of the malignant trophoblasts (79).

It is, therefore, essential that quantitative assays used to diagnose or follow up GTD detect all forms of the hCG protein and its degradation products. In one study, Cole et al., compared several commercially available hCG tests and found significant variations in assay results related to differences in recognition of hCG variants (80). The most common hCG assay is a monoclonal antibody sandwich assay (81). Complete hydatidiform moles present with markedly elevated hCG, with half of patients having levels greater than 100,000 mIU/mL (82,83). Because hCG levels in a normal pregnancy are highest at the end of the first trimester, hCG measurements need to be taken at several times to differentiate a complete molar pregnancy from a normal gestation, multiple gestation, or pregnancy complicated by diseases that are associated with an enlarged placenta. By contrast, hCG levels greater than 100,000 mIU/mL are seen in only 10% of patients with partial moles (71,72).

Diagnosis of complete and partial moles may also include pathologic examination of curettage tissue; however, with the diagnosis of hydatidiform mole occurring earlier in gestation, histologic analysis can be challenging (84,85). Cytogenetic analysis can differentiate between complete mole (androgenetic diploidy), partial mole (diandritic triploidy), and hydropic abortus (biparental diploidy). A hydropic abortus can contain enlarged villi, but lacks proliferating trophoblast (57). Immunohistochemical analysis may also help to confirm a diagnosis of molar pregnancy; specifically, p57kip2 expression can differentiate between complete and partial hydatidiform moles (Table 27.2) (86–90). This protein is paternally imprinted and maternally expressed; therefore, the villous cytotrophoblast cells in complete moles, which lack maternal chromosomes, will stain negative for p57kip2, whereas partial moles and hydropic abortus will stain positive. Fluorescence in situ hybridization can be used to distinguish between p57kip2-positive partial moles (triploid) and hydropic abortus (diploid) (91). *PHLDA2* is another maternally imprinted gene that can be used to identify partial moles (92).

False-Positive hCG Tests

hCG measurements are a critical diagnostic tool for GTD, but some assays may produce false-positive or “phantom” hCG results (93). False-positive hCG tests, some as high as 800 mIU/mL, can lead to unnecessary surgery and chemotherapy in healthy patients (94). These false-positive results are due to the presence of nonspecific heterophilic antibodies that mimic hCG and can interfere with the hCG sandwich assay. These antibodies are present in 3% to 4% of healthy people. Because the antibody does not pass into the urine, false-positive hCG test results can be identified by determining hCG levels in the urine. In addition, serial dilution of the serum sample would not show a decrease in the detected antibody.

Luteinizing hormone (LH) can also cross-react with hCG assays, leading to falsely elevated hCG in women with elevated pituitary FSH, LH, or hCG. hCG normally increases with age, and perimenopausal and postmenopausal women may have low-level hCG test results. To determine whether the hCG detected in the serum is from the pituitary, women may be given oral contraceptive to suppress LH, followed by simultaneous measurement of LH and hCG (95,96).

Treatment

Suction evacuation and curettage is the preferred treatment for hydatidiform mole in patients who wish to preserve their fertility (Table 27.5) (97,98). Patients should undergo a preoperative evaluation including vital signs, laboratory tests, and electrocardiogram to identify any medical complications, such as anemia, preeclampsia, and hyperthyroidism. The patient’s blood type and hCG levels should also be measured preoperatively. If the patient is hemodynamically stable, the type of molar evacuation procedure can be selected (99,100). If the uterus is greater than 12-week size, ultrasound monitoring should be used to prevent uterine perforation and ensure complete removal of the molar tissue. Suction evacuation and curettage is performed under anesthesia, and the cervix is dilated to allow passage of a 12- to 14-mm suction cannula into the lower uterine segment. The cannula is rotated to remove the intrauterine contents. Intravenous oxytocin should be started at the onset of the procedure and continued postoperatively for several hours to enhance uterine contraction. Rh-negative patients will also need to receive Rh immunoglobulin during evacuation because the Rh D factor is expressed by trophoblastic cells (99,100). Gentle sharp curettage should be applied after suction evacuation. At least 2 units of blood should be available because of the risk of bleeding, which increases with uterine size. Postoperative respiratory distress may occur due to trophoblastic embolization, excessive fluid resuscitation, or massive oxytocin infusion. Attention to blood and crystalloid replacement reduces the risk of pulmonary complications, though all patients should be monitored with a pulse oximeter for at least 2 hours after surgery. Patient outcomes can be improved with the judicious use of equipment, ready access to blood products, careful monitoring during the procedure, and anticipation and treatment of complications.

For patients who have completed childbearing and do not wish to preserve their fertility, hysterectomy may be performed as an alternative to suction evacuation and curettage (Fig. 27.10). Hysterectomy removes the risk of local myometrial invasion, and focal disease can be ruled out in patients with

Table 27.5 Evacuation of Hydatidiform Mole

Preoperative evaluation and preparation

1. Chest X-ray
2. Complete blood count
3. Electrolytes
4. Baseline oxygen saturation
5. Type and cross 2 units of blood
6. Set up Rho (D) immunoglobulin (RhoGAM) if patient is Rh-negative

Surgical procedure (with ultrasound guidance if uterus is >12 wk size)

1. Premedication and paracervical anesthesia
2. Dilatation
3. Suction curettage—leave cannula at lower uterine segment until majority of molar tissue has been removed
4. Begin intravenous oxytocin infusion
5. Gentle sharp curettage

Postevacuation

1. Monitor respiratory status and uterine bleeding for at least 2 h
2. Give RhoGAM if Rh-negative
3. Prescribe contraceptive
4. Follow hCG levels every 2 wk until 2 consecutive normal results, then every month for 6 mo and every 3 mo twice

hCG, human chorionic gonadotropin.



FIGURE 27.10. In selected patients, hysterectomy may decrease the likelihood of postmolar GTN. This photograph shows a 16-week size uterus filled with complete hydatidiform mole.

persistent GTD. The high cost of this procedure and the risk of complications should limit the use of hysterectomy to those patients at high risk of postmolar GTD, including women over the age of 40, greater than gestational date uterine size, theca lutein cysts greater than 6 cm, hCG greater than 100,000 mIU/mL, and medical complications of pregnancy. However, metastatic disease may still be present after hysterectomy, with a 3% to 5% risk of postmolar GTN, and patients should be followed up with serial hCG testing (97).

Medical induction of labor and hysterotomy are not recommended, because of the increased risk of maternal morbidity, including blood loss, incomplete evacuation requiring surgical intervention, and the need for cesarean delivery in subsequent pregnancies. This approach also increases the risk of trophoblastic dissemination and development of postmolar GTN requiring chemotherapy (98).

Use of prophylactic chemotherapy—either methotrexate or actinomycin D—at the time of evacuation or immediately afterwards can reduce the risk of postmolar GTN from 15%–20% to 3%–8%. However, this approach exposes patients to chemotherapeutic toxicity but benefits only a small number of patients. Because all patients who are found to have persistent postmolar GTD with serial hCG testing can be cured with chemotherapy, the use of prophylactic chemotherapy should be limited to those patients who have a greater than normal risk of postmolar GTN or who are less likely to comply with serial hCG testing during follow-up (101–103).

Molar Pregnancy and Coexisting Fetus

Twin pregnancies of a complete mole and normal fetus occur approximately once in every 22,000 to 100,000 pregnancies and may be difficult to distinguish from partial mole. Ultrasound can usually differentiate between these two scenarios, though cytogenetics may help distinguish a normal viable fetus from a triploid nonviable fetus in a partial mole. Patients with a twin normal/complete mole pregnancy are at higher risk of hemorrhage and other complications as well as a higher risk of persistent GTD. Although suction evacuation and curettage are recommended to terminate the pregnancy, 40% of these pregnancies will result in a normal viable fetus if left untreated (104–106).

Follow-Up

Clinical findings of successful evacuation include prompt uterine involution, ovarian cyst regression, and cessation of bleeding.

Definitive follow-up after molar evacuation requires serial serum quantitative hCG measurements every 1 to 2 weeks until 3 consecutive normal tests, and then every 3 months for 6 months to 1 year after normalization. More than 50% of patients will achieve a normal hCG within 2 months of evacuation. Contraception is recommended for 6 months after the first normal hCG result so that any postmolar elevation in hCG that is detected can be distinguished from the hCG rise that occurs in a normal pregnancy. Oral contraceptives are preferred because they suppress LH and remove any interference with hCG assay measurements. Studies have shown that oral contraceptives do not increase the risk of postmolar GTN (107–109).

Prognosis

Disease-free survival and fertility is achieved in 80% of patients with hydatidiform mole, and compliant patients who are followed closely with serial hCG measurements are more likely to achieve cure. High-risk postmolar disease is more often seen after a term pregnancy or in patients who were lost to follow-up. There is a 1% to 2% increased risk of developing a second complete molar pregnancy (110), and a much lower risk of a second partial molar pregnancy (111).

Quiescent GTD

Some women with a history of GTD or spontaneous abortion may have a consistently low level of hCG (<200 mIU/mL for at least 3 months) but no detectable disease. There is also no hyperglycosylated hCG, which would indicate cytotrophoblastic invasion. This “quiescent GTD” does not respond to either surgery or chemotherapy. It is believed that the hCG being detected in these patients is produced by dispersed foci or individual slow-growing syncytiotrophoblast cells with no invasive potential in the absence of cytotrophoblast or intermediate trophoblast. Approximately one-quarter of patients with quiescent GTD go on to develop active GTN, with detectable increases in both hCG and hyperglycosylated hCG levels (112,113). These patients may secrete increased hyperglycosylated hCG within 5 years of the initial pregnancy event, weeks to months before a detectable rise in hCG or clinical evidence of GTN (114). To diagnose quiescent GTD, false-positive hCG testing should be ruled out and the patient examined for any evidence of disease. Patients should be monitored closely with periodic hCG testing and should avoid pregnancy (95). Chemotherapy and surgery

should be avoided unless a diagnosis of GTN can be made, based on either a sustained rise in hCG or the appearance of disease.

Pregnancy after Hydatidiform Mole

All women with a history of molar pregnancy have a higher risk of developing malignant disease in a subsequent pregnancy. After molar evacuation, women should wait at least 6 months from the time of hCG normalization to become pregnant. For all future pregnancies, pathologic examination of the placenta and other products of conception and measurement of hCG 6-weeks postpartum are recommended.

Persistent GTD/Postmolar GTN

Postmolar invasive mole or CCA occurs after 15% to 20% of complete and 1% to 5% of partial molar pregnancies, and invasive mole is seen more frequently (85% to 90%) than CCA (10% to 15%) (51,52,58,99,115–120). Approximately, half of all cases of CCA arise from a prior molar pregnancy, but only 2% to 3% of all hydatidiform moles will progress to CCA (121). A diagnosis of CCA after a partial mole has been reported as single cases in the literature (51,52,58,122–126). Of those with invasive mole, 15% will have metastatic disease to the lungs or vagina. Most PSTTs and ETTs arise after nonmolar pregnancies, sometimes years after the pregnancy event (64,127,128).

The likelihood of persistent GTD after a molar pregnancy is higher in women who initially presented with marked trophoblastic growth, as indicated by hCG levels greater than 100,000 mIU/mL, excessive uterine size (>20 weeks), and theca lutein cysts greater than 6 cm in diameter. Women who have at least one of these risk factors have a 40% chance of developing postmolar GTN, compared with a 4% risk in those with none of these factors. Other risk factors for postmolar GTN include age greater than 40 years, repeat molar pregnancy, aneuploidy mole, and medical complications of molar pregnancy, such as toxemia, hyperthyroidism, and trophoblastic embolization (99).

At the molecular level, studies have found that women who will develop postmolar disease are more likely to show telomerase activity (129). Conversely, apoptotic activity measured by various techniques is higher in hydatidiform moles that spontaneously regress versus those that go on to develop postmolar GTN (130,131). Other studies have found that hydatidiform moles that are more likely to progress to malignant disease have lower expression of the anti-apoptotic gene *Mcl-1* (132), ferritin light polypeptide (FTL), and IGFBP-1 (133).

Repeat curettage for persistent GTD is not recommended, except in patients with excessive uterine bleeding and intracavitary molar tissue on radiologic scans. In one retrospective study, although 9.4% of women who underwent repeat curettage avoided chemotherapy, there was a 2.4% risk of uterine perforation (134). Thus, the small benefit of repeat curettage in achieving remission or improving treatment outcomes does not outweigh the risk of uterine perforation and hemorrhage (134–137). A prospective phase II Gynecologic Oncology Group (GOG) trial is under way that will determine the utility of second curettage and whether benefit and risk vary with the depth of uterine infiltration (GOG 242, NCT00521118).

GTN, either invasive mole or CCA, presents as irregular bleeding after evacuation of a hydatidiform mole (usually a complete mole). Invasive mole is diagnosed clinically rather than pathologically, with persistent hCG elevation after molar evacuation. CCA occurs in association with any pregnancy event, with approximately 25% of cases occurring after abortion or tubal pregnancy, 25% after term or preterm gestation, and 50% after a molar pregnancy. Sometimes, a metastatic vaginal lesion may be disrupted during pelvic examination, which can lead to uncontrolled vaginal bleeding. Women with postmolar GTN may also present with an enlarged, irregular uterus and bilateral ovarian enlargement. There are no signs or symptoms that differentiate between postmolar GTN and GTN arising after a nonmolar pregnancy event, as these symptoms are related to the invasion and metastasis of the tumor. GTN should be considered in patients who present with postpartum bleeding and subinvolution, although other causes include endomyometritis, tumors in other organ systems, or another pregnancy. Uterine perforation and metastases can cause abdominal pain, hemoptysis, melena, or increased intracranial pressure that leads to headaches, seizures, or hemiplegia. Symptoms suggesting pulmonary involvement include dyspnea, cough, and chest pain (121), and early respiratory failure requiring mechanical ventilation may develop. A diagnosis of GTN should be considered for any women of reproductive age who presents with pulmonary symptoms. Symptoms of brain metastases include vomiting, seizures, headache, hemiparesis, and speech and visual disturbances. Liver and gastrointestinal metastases are rare, and usually are seen with simultaneous lung or brain involvement; these patients have the lowest survival rate (138). PSTT and ETT often present with irregular vaginal bleeding and an enlarged uterus, with hCG levels from normal to 1,000 mIU/mL, sometimes years after a previous pregnancy. PSTT may also present with liver, lung, or brain metastases, or complications such as neoplastic nephrotic syndrome. The risk of metastatic PSTT is higher in patients with more than 5 mitoses per 10 high-power fields.

Diagnosis

The International Federation of Gynecology and Obstetrics (FIGO) defined a set of criteria for diagnosing persistent GTD in 2002 (Table 27.6) (139). Postmolar GTN is usually diagnosed when hCG levels plateau or rise during follow-up after molar evacuation, without histologic diagnosis. An hCG plateau is defined as a less than 10% decline in 4 measurements taken over 3 weeks. A rise is defined as a greater than 20% increase in 3 measurements taken over 2 weeks. The presence of elevated hCG in addition to metastases usually indicates CCA, whereas with PSTT and ETT, serum hCG levels are only slightly elevated, making differential diagnosis particularly challenging (64,127,128). The free hCG β subunit may be the best biomarker for diagnosing PSTT, and the β core fragment for ETT (38,76). Although a diagnosis of GTN can be confirmed pathologically by examination of the curettage, or hysterectomy specimens, or the placenta, or biopsy of metastatic lesions, the risk of hemorrhage is too high, and biopsy of vaginal lesions should be avoided (140).

For any patient with suspected or established GTN, a metastatic workup and evaluation of risk factors is performed (3,32,110,141). A complete history, physical examination, and laboratory tests (including complete blood cell count, coagulation study, serum chemistries, blood type and antibody screening, and quantitative serum hCG level) should be taken. Radiologic studies should start with a chest X-ray; if abnormal, a CT or MRI of the chest should be performed to detect pulmonary metastases. CT scans of the abdomen and pelvis and MRI of the brain should also be performed. The vast majority of patients with brain involvement (94%) have associated lung metastases; conversely, 20% of patients with lung metastases also have brain metastases. Brain metastases tend to appear in

GESTATIONAL TROPHOBLASTIC NEOPLASIA

Clinical Presentation

The clinical presentation of GTN depends on the pregnancy event, the extent of disease, and histopathology. Postmolar

Table 27.6 FIGO 2000 Criteria for Diagnosis of Persistent GTD/Postmolar GTN

hCG plateau lasting for 4 measurements over a period of at least 3 wk (days 1, 7, 14, and 21)
Rise in hCG of 10% or more for 3 measurements over at least 2 wk (days 1, 7, and 14)
Persistence of elevated hCG 6 mo after mole evacuation
Presence of a histologic diagnosis of CCA

hCG, human chorionic gonadotropin; CCA, choriocarcinoma.

Source: From FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. *Int J Gynaecol Obstet.* 2002;77(3):285–287, with permission.

the parietal lobe, and on the right side of the brain (Fig. 27.11). If the physical examination and the chest X-ray are normal and there are no symptoms of metastasis, other sites of metastasis are rarely present. To detect brain involvement, hCG testing of the cerebrospinal fluid (CSF) may be helpful; a serum/CSF hCG ratio of less than 60:1 is a sensitive marker of CNS metastasis (142), although false positives can occur if measurements are taken when hCG levels are falling. Pelvic ultrasound and MRI may be useful to detect extensive uterine disease and identify patients who may benefit from hysterectomy. Biopsy of metastases is not recommended, as the associated risks of biopsy outweigh the benefits of confirming a diagnosis of metastatic disease.

Staging and Risk Scoring

In 2002, FIGO adopted a combined anatomic staging system and a modified version of the WHO risk factor scoring system for GTN (Tables 27.7 and 27.8) (143). The FIGO stage is designated by a Roman numeral and is followed by the modified WHO score designated by an Arabic numeral, separated by a colon. The risk score takes into account 8 criteria, each of which is given a score from 0 to 4. Treatment of GTN is based on the classification of patients into risk groups defined by the stage and risk factor scoring system (144). The FIGO system is essential for selecting initial therapy for patients with GTN that will ensure the best possible outcomes with the fewest side effects. A recent study found that most patients classified as low-risk but who have an initial level of hCG greater than 400,000 mIU/

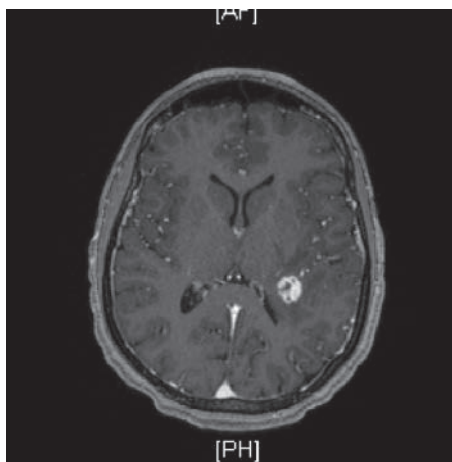


FIGURE 27.11. MRI of the brain. MRI showing right parietal lobe lesion with central hemorrhage.

Table 27.7 FIGO 2000 Staging for Gestational Trophoblastic Neoplasia

Stage	Description
I	Disease confined to uterus
II	Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)
III	Disease extends to lungs with or without genital tract involvement
IV	Disease involves other metastatic sites

Source: From FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. *Int J Gynaecol Obstet.* 2002;77(3):285–287, with permission.

Table 27.8 FIGO 2000 Risk Scoring System for Gestational Trophoblastic Neoplasia

Risk Factor	Score			
	0	1	2	4
Age, y	≤39	>39	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Pregnancy event to treatment interval, mo	<4	4–6	7–12	>12
Pretreatment hCG, mIU/mL	<10 ³	10 ³ –10 ⁴	10 ⁴ –10 ⁵	>10 ⁵
Largest tumor mass, including uterus, cm	<3	3–4	≥5	–
Site of metastases	–	Spleen, kidney	GI tract	Brain, liver
No. of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	≥2 drugs

Source: From FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. *Int J Gynaecol Obstet.* 2002;77(3):285–287, with permission.

mL will fail their initial chemotherapy, suggesting that perhaps these patients would benefit from multiagent chemotherapy (145). Patients with hCG levels between 100,000 mIU/mL and 400,000 mIU/mL will either respond to a single-agent regimen or require a change in regimen to achieve cure. Note that this staging and risk factor scoring system does not apply to either PSTT or ETT.

Recently, Cole et al. described a form of “minimally-aggressive GTN” that is chemorefractory, has a slow growth rate, and can be detected by low levels of hyperglycosylated hCG (<40% of total hCG) or by an hCG doubling rate greater than 2 weeks (146). Thus far, data are available on 24 patients with this type of GTN, who were treated successfully using a protocol that delays chemotherapy until hCG levels exceed 3,000 mIU/mL.

Management

The cure rate for high risk GTN—most commonly CCA—is currently greater than 90%, and for low-risk disease is approaching 100%, primarily due to the inherent sensitivity of trophoblastic

Table 27.9 Chemotherapy for Low-Risk Gestational Trophoblastic Neoplasia	
Regimen	Primary Remission Rate (%)
MTX 0.4 mg/kg (max 25 mg)/day IV or IM for 5 d; repeat every 2 wk	87–93
MTX 30–50 mg/m ² IM weekly	49–74
MTX 1 mg/kg IM days 1, 3, 5, and 7; folinic acid 0.1 mg/kg IM days 2, 4, 6, and 8; repeat every 15–18 d or as needed	74–90
MTX 100 mg/m ² IVP, then 200 mg/m ² in 500 mL D5W over 12 h; folinic acid 15 mg IM or PO every 12 h for 4 doses beginning 24 h after start of MTX; repeat every 18 d or as needed	69–90
Act D 10–13 mg/kg IV every day for 5 d; repeat every 2 wk	77–94
Act D 1.25 mg/m ² IV every 2 wk (max 2 mg/day)	69–90
Alternating MTX 0.4 mg/kg (max 25 mg)/day IV or IM for 5 d and Act D 10–13 mg/kg IV every day for 5 d	100

Act D, actinomycin D; D5W, dextrose 5% in water; IM, intramuscular; IV, intravenous; IVP, intravenous push; MTX, methotrexate; PO, by mouth.

neoplasms to chemotherapy, the effective use of hCG as a marker of early disease, the referral of patients to specialized centers, the identification of predictive factors of treatment response that has permitted individualization of therapy, and the use of combined surgery, radiation, and chemotherapy in the highest risk patients. Management of PSTT and ETT is more challenging because these neoplasms are often resistant to chemotherapy and hCG level is not a strong marker of these diseases.

Low-Risk GTN

Patients in the low-risk group are those with Stage I disease (nonmetastatic) or Stage II and III disease (metastatic) with a risk score of less than 7. These patients should undergo single-agent chemotherapy with either methotrexate or actinomycin D (147,148), which has achieved survival rates approaching 100%. Invasive mole is often treated with chemotherapy without a pathologic diagnosis (121). There are several different chemotherapy protocols for low-risk nonmetastatic GTN that have produced comparable results in nonrandomized, retrospective studies (Table 27.9). Taken together, these studies suggest that the 5-day methotrexate or actinomycin D protocols or the 8-day methotrexate-folinic acid protocol are more effective than either weekly intramuscular (IM) or intermittent intravenous (IV) infusion of methotrexate or the biweekly single-dose actinomycin D protocols. Remission rates with each protocol vary due to differences in drug doses, schedules, routes of administration, and patient factors. These studies also found that initial chemotherapy resistance is associated with older age, higher hCG, nonmolar antecedent pregnancy, histopathologic diagnosis of CCA, presence of metastases, and higher FIGO score. Common side effects of these regimens are stomatitis, mucositis of the GI tract, pleuritis, conjunctivitis, and skin rash.

Chemotherapy is continued until hCG values have returned to normal, and at least 1 course is administered after the first normal hCG level is achieved. A recent retrospective study compared relapse rates in women from the UK and the Netherlands with low-risk disease who were treated with methotrexate

Table 27.10 Treatment of low-risk GTN at the Brewer Trophoblastic Disease Center			
Regimens: MTX 0.4 mg/kg (max 25 mg)/day IV for 5 d, repeat every 2 wk; Act D 10–13 mg/kg IV every day for 5 d, repeat every 2 wk			
	Complete Remission Rate to Initial Single-Agent MTX	Required Multiagent Chemotherapy or Surgery	Cured
Lurain et al. (1995) (1962–1990) (150)	89.3% (226/253 nonmetastatic, low-risk GTN)	2%	100%
Roberts and Lurain (1996) (1962–1992) (182)	65.6% (40/61 metastatic, low-risk GTN)	3%	100%
Chapman-Davis et al. (2009) (1979–2009) (183)	81% (291/360 FIGO low-risk GTN ^a)	6%	100%

^aStage I disease (nonmetastatic) and Stage II and III disease (metastatic), risk score <7.

alternating with folinic acid (149). A greater number of patients relapsed with only two consolidation courses than those who received three consolidation courses after reaching the institutional normal hCG value of greater than 5 mIU/mL. If hCG levels plateau at a point above normal during treatment or if toxicity limits the ability to administer the chosen regimen, chemotherapy is changed to an alternative single-agent regimen. Multiagent chemotherapy is indicated in the event of a significant elevation in hCG, development of metastases, or resistance to sequential single-agent chemotherapy. While there are differences in primary remission rates with each of the chemotherapy protocols, the cure rate remains high and most patients are able to preserve their fertility.

The John I. Brewer Trophoblastic Disease Center reviewed 30 years' of experience treating GTN to determine the most effective therapy, evaluate toxicity, and identify the factors associated with treatment resistance (Table 27.10) (150). Of 253 patients who received initial therapy of single-agent methotrexate (0.4 mg/kg, maximum 25 mg) as an IV push for 5 days every 2 weeks, only 5 required subsequent multiagent chemotherapy (90% complete response), and all patients achieved permanent remission. Only 12 patients experienced significant side effects with methotrexate, most commonly stomatitis, leading to a change in therapy to another agent, and no life-threatening toxicities were noted. Resistance to the initial single-agent methotrexate regimen was associated with high pretreatment hCG, nonmolar antecedent pregnancy, and clinicopathologic diagnosis of CCA. These findings are consistent with those of other centers and suggest that the most effective treatment protocol for low-risk nonmetastatic GTN is methotrexate 0.4 mg/kg (maximum total dose 25 mg) IM or IV push given once daily for 5 days every other week (150–152).

Other regimens for low-risk nonmetastatic disease include methotrexate 1.0 to 1.5 mg/kg given every other day alternating with folinic acid (0.1 to 0.15 mg/kg) for 8 days, with at least 1 week between treatments. Though this regimen is associated with lower toxicity than the 5-day regimen, it is inconvenient and a greater number of patients require a change in chemotherapy to achieve remission (153–159). Yet another modification of a methotrexate regimen is a high-dose (100 mg/m²) IV push followed by a 12-hour infusion at 200 mg/m² with folinic acid

(160); with this regimen, the interval between doses is dependent on the posttreatment hCG level. However, this treatment often requires second-line therapy (159–162). Finally, a regimen of weekly IM doses of methotrexate 30 to 50 mg/m² has the lowest complete response rate, and although it is more convenient, less costly, and less toxic, it is not appropriate for treating GTN (163–165).

Two retrospective case studies compared 5-day IM methotrexate and 8-day methotrexate-folinic acid protocols in patients with low-risk nonmetastatic GTN; one study found that there was no difference in remission rates (76%) (156), and the other reported lower remission rates in patients receiving methotrexate-folinic acid (72%) than in patients receiving methotrexate alone (92%) (166). Gleeson et al. subsequently reported a 69% primary remission rate in patients with nonmetastatic postmolar GTN treated with weekly methotrexate alone and a 75% remission rate with methotrexate-folinic acid (167).

As an alternative to methotrexate, actinomycin D may be given as an IV push of 10 to 12 µg/kg daily for 5 days every other week or as a single 1.25 mg/m² IV dose every week (168–172). The primary remission rate for patients with nonmetastatic postmolar GTN was 88% for 5-day actinomycin D and 78% for pulsed actinomycin D (173). However, actinomycin D is more often used as a second-line therapy in patients with methotrexate resistance or with contraindications to methotrexate, as it is associated with higher toxicity, particularly alopecia, and produces local tissue injury in cases of IV extraversion (174).

Several studies have compared weekly methotrexate and biweekly actinomycin D regimens for treatment of low-risk, nonmetastatic GTN. Across three randomized clinical trials, IM methotrexate was associated with lower primary complete response rates (49% to 53%) than pulsed actinomycin D (69% to 90%) (175–177). In the phase III GOG study (177), there was a higher complete response for biweekly IV actinomycin D than for weekly IM methotrexate (70% vs. 53%; $p = 0.01$), and in patients with lower risk scores (<5), the response rate was 73% and 58%, respectively ($p = 0.03$). Both regimens were less effective in patients with risk scores of 5 or 6 or if the diagnosis was CCA (complete response: 42% and 9%, respectively). Actinomycin D was associated with a high incidence of grade 1 alopecia and grade 1 nausea (177). In another randomized study of patients with stage I nonmetastatic GTN, complete remission was achieved in 74% of women who received methotrexate-folinic acid and in 100% of women who received 5-day actinomycin D (178). In a retrospective study of patients with low-risk, mostly nonmetastatic GTN, Abrao et al. reported no significant difference in the complete remission rates with 5-day regimens of methotrexate or actinomycin D or combination therapy (69%, 61%, and 79%, respectively); however, the incidence of side effects was much higher in patients receiving the combination therapy than either single-agent regimen (179).

For patients with low-risk metastatic GTN (Stage II or III, score <7), single-agent chemotherapy with multi-day dosing of either methotrexate or actinomycin D is appropriate; however, the biweekly actinomycin D protocols used for nonmetastatic disease should not be used in these patients (Table 27.9). Three specialized trophoblastic disease centers in the U.S. have reported remission rates of 48% to 67% in patients with low-risk, metastatic GTN with single-agent chemotherapy, with 1% to 14% of patients requiring multi-agent therapy after failure of single-agent therapy with or without surgery (Table 27.10) (180–182). In this group of patients, resistance to single-agent therapy was associated with pretreatment hCG levels >100,000 mIU/mL, age older than 35 years, a FIGO score of 4, and the presence of large vaginal metastases.

At the Brewer Trophoblastic Disease Center, we recently examined risk factors for developing resistance to initial methotrexate therapy in 358 patients with low-risk GTN between 1979 and 2009 (Table 27.10) (183). Patients initially received

methotrexate 0.4 mg/kg (max 25 mg) IV push daily for 5 days every 14 days. Actinomycin D 0.5 mg IV push daily for 5 days every 14 days was used in 64 patients who developed resistance or toxicity to initial methotrexate chemotherapy, and multiagent regimens were used in 20 patients for whom either single-agent chemotherapy failed. The complete response rate to initial methotrexate chemotherapy was 81%, and the complete response rate to actinomycin D as secondary therapy was 75% (94% overall complete response rate to sequential single-agent chemotherapy). The remaining patients achieved permanent remission with multi-agent chemotherapy with or without surgery. Resistance to initial methotrexate chemotherapy was associated with increasing FIGO score ($p < 0.0001$), clinicopathologic diagnosis of CCA ($p = 0.028$), higher pretreatment hCG ($p = 0.001$), and presence of metastatic disease ($p = 0.018$).

In general, primary treatment failure occurs in 10% to 30% of patients with low-risk GTN, and in 30% to 50% of patients with low-risk, metastatic disease. Most patients who are resistant to the initial chemotherapy will be placed into remission after changing to another single-agent chemotherapy. Patients with low-risk disease will rarely require multiagent chemotherapy, and approximately 15% of patients with low-risk, metastatic GTN will require multi-agent chemotherapy with or without surgery. The higher rate of failure of initial single-agent therapy in patients with higher FIGO scores has led some to propose an intermediate risk group of patients who have metastatic disease with scores of 5 or 6. Ideally, treatment failure should be identified as early as possible to limit patient exposure to ineffective chemotherapy cycles. Several groups have tried to determine an hCG cutoff value that can predict treatment resistance to allow prompt changes in treatment (184–186). One group found that a cutoff value of 737 mIU/mL was able to predict resistance to 8-day methotrexate with a specificity of 97.5% (186,187). If treatment change is necessary, the risk score is recalculated to determine the most appropriate second-line regimen.

In patients with low-risk GTN who do not wish to preserve their fertility, adjuvant hysterectomy may be performed with the initiation of chemotherapy to reduce the length of treatment required to achieve remission (188). Other indications for hysterectomy in low-risk GTN include persistent, chemotherapy-resistant disease in the uterus or to treat uterine tumor hemorrhage.

High-Risk GTN

Chemotherapy

Patients in the high-risk group have metastatic GTN, either Stage IV disease or Stage II and III disease with a risk factor score greater than 7. These patients are treated more aggressively, with multiagent chemotherapy with or without adjuvant radiation or surgery (Table 27.11). With this approach, cure rates have reached 80% to 90%. Treatment delay or dose reduction due to side effects increases the likelihood of tumor resistance and treatment failure. Historically, a combination treatment of methotrexate, actinomycin D, and cyclophosphamide or chlorambucil (MAC) was used as first-line therapy for high-risk, metastatic GTN and achieved cure in 63% to 71% of patients (Table 27.12) (189,190). Over time, the chemotherapy regimen of choice shifted to a combination of cyclophosphamide, hydroxyurea, actinomycin D, methotrexate with folinic acid, vincristine, and doxorubicin (CHAMOCA) (Fig. 27.12). The primary remission rate in high-risk, metastatic GTN was reported to be 82% with this regimen (191). However, a subsequent randomized trial comparing MAC and CHAMOCA found that the primary remission rate and the cure rate were inferior for CHAMOCA, which also had a more toxic side effect profile (192). The addition of etoposide to a regimen containing high-dose methotrexate with folinic acid, actinomycin D,

Disease		1960s	1970s	1980s	1990s	
Low-Risk GTN		Methotrexate x 5d IV		—————→		
High	1 st Line	MTX	MAC	————→	CHAMOCA → EMACO	—————→
Risk GTN	2 nd			MAC → BEP	EMA-EP	————→
	3 rd				BEP	————→
	4 th					VIP → ICE
	5 th					TP/TE
PSTT	1 st			EMA-EP	————→	
	2 nd					TP/TE

FIGURE 27.12. Evolution of chemotherapy for GTN at the John I. Brewer Trophoblastic Disease Center. Chemotherapy regimens are shown for low-risk disease, as well as the first-line therapy and subsequent regimens for recurrent or resistant high-risk disease. For PSTT, chemotherapy may be used in patients with metastatic disease and in patients with nonmetastatic disease and poor prognostic factors.

Table 27.11 EMA-CO Chemotherapy for High-Risk Gestational Trophoblastic Neoplasia

Treatment Day	Regimen	
1	Etoposide	100 mg/m ² IV over 30 min
	Act D	0.5 mg IVP
	MTX	100 mg/m ² IVP, then 200 mg/m ² in 500 mL D5W over 12 h
2	Etoposide	100 mg/m ² IV over 30 min
	Act D	0.5 mg IVP
	Folinic acid	15 mg IM or PO every 12 h for 4 doses starting 24 h after start of MTX (on day 1)
8	Cyclophosphamide	600 mg/m ² IV
	Vincristine	1.0 mg/m ² IVP

Cycle repeats every 2 weeks (i.e., days 15, 16, and 22).

IV, intravenous; Act D, actinomycin D; IVP, intravenous push; MTX, methotrexate; D5W, dextrose 5% in water; IM, intramuscular; PO, by mouth.

and vincristine (EMA-CO) improved both primary remission and survival rates in patients with high-risk GTN (Table 27.12) (193,194). The efficacy of the EMA-CO regimen for high-risk GTN has been reported to achieve complete response rates between 71% and 78% and long-term survival rates of 85% to 94% (195–202). In our study series (199,200,203), we reported complete response rates of 76%, 67%, and 54% and overall survival rates of 92%, 93%, and 92% with EMA-CO treatment. Deaths occurred only in patients with FIGO stage IV disease with scores greater than 12, and no treatment-related deaths or severe toxicities were seen. Neutropenia was rare, though alopecia and anemia were common, and mild paresthesia and

stomatitis occurred in 20% of patients. Some centers may use the EMA-EP regimen for patients with scores greater than 12. In the United Kingdom, patients with brain metastases are treated with intrathecal methotrexate rather than whole-brain radiotherapy (204).

Though aggressive multiagent therapy is associated with high levels of toxicity, single-agent therapy is not appropriate for high-risk patients, as the success rate of secondary chemotherapy after failure of single-agent therapy is only 20% to 50%. Based on current evidence, EMA-CO is the initial treatment of choice for patients with high-risk, metastatic GTN. The regimen has high complete response rates and survival rates, as well as low toxicity that improves patient adherence to treatment and thus reduces the risk of drug resistance. Chemotherapy is continued for at least 2 to 3 courses after the first normal hCG level is achieved.

Radiation

For patients who present with brain metastases, whole brain radiation (3,000 cGy in 200 cGy fractions) or, in selected patients, surgical excision with stereotactic radiation, is indicated and is usually performed at the start of chemotherapy to lower the risk of hemorrhage (205,206). In these patients, the EMA-CO regimen is modified such that methotrexate is increased to 1 g/m² with 30 mg of folinic acid every 12 hours for 3 days, starting 32 hours after the start of infusion (207). Intrathecal and high-dose methotrexate may also be used in some centers. Patients are also treated with dexamethasone to decrease edema and phenytoin sodium to prevent seizure. During therapy, patients undergo serial CT scans or MRIs to monitor the lesions. Once a complete response has been achieved, hCG levels in the CSF should be measured, ideally by radioimmunoassay to detect low levels of protein. The plasma to CSF ratio of hCG should be less than 60. Patients with brain metastases have a cure rate of 50% to 80% depending on patient symptoms and the number, size, and location of brain lesions (204,208).

Surgery

Approximately 50% of patients with high-risk, metastatic GTN will require adjuvant surgical procedures, usually hysterectomy

and pulmonary resection for chemotherapy-resistant disease and to control hemorrhage and sepsis (209–220). Selected patients with focal disease may be candidates for partial lung, liver, or brain resection. Imaging with fluorodeoxyglucose PET, with CT for anatomic localization, may help with targeted surgery (221). For women with excessive vaginal bleeding, selective arterial embolization may be beneficial. We reviewed a series of 50 patients with high-risk GTN who were treated at the Brewer Trophoblastic Disease Center from 1986 through 2005 with EMA-CO as primary or secondary therapy. Twenty-four patients (48%) underwent 28 adjuvant surgical procedures, and 21 (87.5%) were cured. Fifteen of 17 patients who underwent hysterectomy; 4 of 5 patients who had resistant foci of CCA in the lung resected; all 4 patients who had suturing of the uterus, uterine artery embolization, small bowel resection, and salpingectomy for bleeding; and 1 patient who had uterine wedge resection for resistant CCA survived (213).

Second-Line/Salvage Therapy

Despite the use of multimodal primary therapy, approximately 30% of patients with high-risk GTN will have an incomplete response or will relapse from remission and will require secondary chemotherapy (222–225). Risk factors for relapse include the presence of multiple metastases to sites other than the lung and vagina and inadequate first-line chemotherapy. Salvage chemotherapy with the EMA-EP regimen, in which etoposide and cisplatin have been substituted for cyclophosphamide and vincristine in the EMA-CO regimen, is the most appropriate for patients who have not responded (plateaued low hCG levels) or experienced a relapse (re-elevation of hCG after a complete response) to first-line EMA-CO. This regimen is highly toxic and usually requires granulocyte colony-stimulating factor (G-CSF) support by the third cycle. Salvage chemotherapy combined with surgical excision of persistent tumor will result in cure for most of these high-risk patients (226–228). In patients who have developed resistance to methotrexate-containing protocols, drug combinations containing etoposide and platinum with bleomycin, ifosfamide, or paclitaxel have also been effective (222,229).

At the Brewer Trophoblastic Disease Center, we reported on 26 patients with persistent or relapsed high-risk GTN who received secondary platinum-based salvage chemotherapy. The overall survival was 61.5% (16/26). Of the 16 patients for whom primary therapy with methotrexate/actinomycin D-based chemotherapy without etoposide failed, 10 (63%) had complete clinical responses to bleomycin, etoposide, and cisplatin; etoposide, ifosfamide, and cisplatin; and ifosfamide, carboplatin, and etoposide; and 10 (63%) were cured. Of the 10 patients for whom primary therapy with EMA-CO failed, 9 (90%) had complete clinical responses to EMA-EP or bleomycin, etoposide, cisplatin, but only 6 (60%) subsequently achieved a lasting remission (222).

Most recently, we reviewed the effect of etoposide/platinum-based salvage therapy in 49 women (20 of whom were treated secondarily at our center) with high-risk GTN treated between 1986 and 2010 for whom initial multiagent therapy with EMA-CO had failed (Table 27.13) (228). Salvage therapy included etoposide and a platinum agent with methotrexate and actinomycin D (EMA-EP), bleomycin (BEP), ifosfamide (VIP, ICE) or paclitaxel (TP/TE). Of the 28 patients who had developed resistance to EMA-CO, 82% achieved lasting complete responses to salvage therapy. Three of four patients who received radiation therapy for brain metastases survived, and 82% of patients who required surgical procedures to remove metastases survived. High hCG level at the start of salvage therapy ($p < 0.001$), a higher number of metastatic sites ($p < 0.02$), and metastases to sites other than the lung and vagina ($p < 0.05$) were associated with lower survival in these patients. Patients with metastases in the brain, liver, and gastrointestinal tract have a 75%, 73%, and 50% survival rate, respectively (230).

Table 27.12 Treatment of High-Risk GTN at Brewer Trophoblastic Disease Center

Brewer (1968) (190)	MTX and/or Act D followed by MAC: 39% survival
	Initial MAC: 65% survival
Lurain and Brewer (1985) (1968–1982) (189)	MAC: 63% (29/46) complete remission
Schink et al. (1992) (1986–1991) (194)	EMA-CO: 83% (10/12) complete remission
Escobar et al. (2003) (1986–2001) (199)	EMA-CO: 76% (19/25) complete response rate
	92% (23/25) survival
Lurain et al. (2006) (200)	EMA-CO: 66.7% (20/30) complete response rate
	93.3% (28/30) survival
Lurain et al. (2010) (1986–2009, FIGO high-risk only ^a) (203)	EMA-CO: 54% (14/26) complete response rate
	92% (24/26) survival

^aStage II and III disease, risk score ≥ 7 and Stage IV disease.

Table 27.13 Secondary Treatment of EMA-CO-Resistant, High-Risk GTN

Regimen	Patients	Complete Response, No. (%)	Survival, No. (%)
EMA-EP	19	11 (58)	9 (47)
BEP	16	11 (69)	9 (56)
VIP	2	1 (50)	1 (50)
ICE	6	4 (67)	3 (30)
TP/TE	3	2 (67)	1 (33)
Totals	46	29 (63)	23 (82)

EMA-CO, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine; EMA-EP, etoposide, methotrexate, actinomycin D, platinum agent; BEP, bleomycin, etoposide, platinum agent; VIP and ICE, etoposide, platinum agent, ifosfamide; TP/TE, paclitaxel, platinum agent/paclitaxel, etoposide.

Source: Adapted from Lurain JR, Schink JC. Importance of salvage therapy in the management of high-risk gestational trophoblastic neoplasia. *J Reprod Med.* 2012;57(5–6):219–224, with permission.

PSTT and ETT

Because of the relative resistance of PSTT and ETT to chemotherapy and the high risk of lymphatic spread, hysterectomy with lymph node dissection is the recommended treatment. Prior to surgery, histologic diagnosis of PSTT with endometrial biopsy or curettage specimen should be confirmed with immunohistochemical staining for the presence of human placental lactogen and the absence of hCG. Chemotherapy may be used in patients with metastatic disease and in patients with non-metastatic disease and poor prognostic factors, including a long interval between last pregnancy and diagnosis (>2 years), deep

myometrial invasion, tumor necrosis, and mitotic count greater than 5/10 high-power fields (231,232). Though we do not know the optimal chemotherapy regimen for PSTT and ETT, the current treatment of choice is a platinum-containing regimen, such as EMA-EP or a paclitaxel/cisplatin–paclitaxel/etoposide (TP/TE) doublet. With hysterectomy and chemotherapy, the survival rate is approximately 100% for nonmetastatic disease and 50% to 60% for metastatic disease (233–235).

Reasons for Treatment Failure

We identified patients who were transferred to the Brewer Trophoblastic Disease Center after treatment failure elsewhere in order to determine the causes of treatment failure. We also compared our second-line treatment results from 1979 to 2006 with previous reports from 1962 to 1978 (Table 27.14) (236). The most common reasons for treatment failure for GTN were (1) use of single-agent chemotherapy for patients with high-risk disease; and (2) inappropriate use of weekly IM methotrexate chemotherapy for treatment of patients with metastatic disease, FIGO scores ≥ 7 , and/or non-postmolar CCA. Successful secondary GTN treatment in these patients improved from 59% during 1962 through 1978 to 93% during 1979 through 2006, most likely as a result of center experience and the use of more effective chemotherapy regimens. It is recommended that clinicians request advice from or referral for treatment to centers with expertise in management of GTN for patients who fail single-agent therapy for low-risk disease and for any patient with high-risk disease (237).

Follow-Up of GTN

After hCG has returned to normal levels and treatment has been completed, serum quantitative hCG levels should be obtained at 1-month intervals for 12 months. The risk of relapse is approximately 3% in the first year after completing therapy and drops to less than 1% thereafter. Physical examinations are performed at intervals of 6 to 12 months, and other testing is rarely indicated.

Pregnancy after GTN

Successful treatment of GTN with chemotherapy has allowed most women to preserve their fertility, despite exposure to drugs that are toxic to the ovary. Most women resume normal ovarian function after chemotherapy and exhibit no increase in infertility. Menopause may occur earlier, however (238). Contraception should be maintained during treatment and for 1 year after completion of chemotherapy, preferably using oral contraceptives, to allow for uninterrupted hCG follow-up and to permit the ovulation of eggs that may have been damaged by exposure to cytotoxic drugs.

Successful pregnancies have been reported after GTN, without an increased rate of abortion, stillbirth, congenital anomalies, prematurity, or major obstetric complications (22,239,240). There is no evidence for reactivation of disease with subsequent pregnancies, although patients who have had 1 trophoblastic disease episode have a 1% to 2% risk of a second GTD event, independent of previous chemotherapy. Therefore, pelvic ultrasound is recommended in the first trimester of any post-GTN pregnancy to confirm a normal gestation. The products of conception or placentas from future pregnancies should also be carefully examined histopathologically, and a serum quantitative hCG level should be determined 6 weeks after any pregnancy.

Table 27.14 Overall Results of Treatment of GTN at the Brewer Center 1962–2006

Treatment Site/Dates	Number	Survival
Primarily at Brewer Center	740	702 (95%) ^a
1962–1978	359	329 (92%)
1979–2006	381	373 (98%)
Secondarily at Brewer Center	64	47 (73%) ^a
1962–1978	37	22 (59%) ^b
1979–2006	27	25 (93%) ^b
Total	804	749 (93%)

^a $p < 0.05$.

^b $p < 0.005$.

Source: Adapted from Lurain JR, Hoekstra AV, Schink JC. Results of treatment of patients with gestational trophoblastic neoplasia referred to the Brewer Trophoblastic Disease Center after failure of treatment elsewhere (1979–2006). *J Reprod Med.* 2008;53(7):535–540, with permission.

Risk of Secondary Malignancies

Because of the relatively short exposure of patients with GTN to intermittent schedules of methotrexate and actinomycin D and the infrequent use of alkylating agents, there are few reports of increased susceptibility to the development of other malignancies. However, increased use of etoposide-containing drug combinations for treatment of GTN has led to an increased risk of secondary malignancies, including acute myelogenous leukemia, colon cancer, melanoma, and breast cancer (241). Because of this, and an association with alopecia and severe nausea, the use of etoposide-containing regimens is limited to patients with high-risk disease.

CONCLUSIONS

The more widespread use of ultrasound to evaluate patients who present with vaginal bleeding has led to earlier diagnosis of hydatidiform mole. While hCG is a disease-specific marker for complete molar pregnancy, levels vary widely in individual patients, and those who are diagnosed with earlier stage disease may not show highly elevated hCG. The majority of patients with molar pregnancy are successfully treated with suction evacuation and curettage, and the risk of a second molar pregnancy or development of postmolar neoplasia is low.

Cure rates for both nonmetastatic and low-risk, metastatic GTN should approach 100% with the use of initial single-agent methotrexate or actinomycin D chemotherapy. Approximately 20% of low-risk patients will develop resistance to the initial chemotherapeutic agent, but 90% will be cured by the use of sequential single-agent chemotherapy. Eventually, approximately 10% of patients will require multiagent chemotherapy with or without surgery to achieve remission. With aggressive, multimodality therapy—EMA-CO with adjuvant radiotherapy or surgery as indicated—cure rates for high-risk GTN have reached 80% to 90%. Though one-third of high-risk patients fail first-line therapy or experience a relapse from remission, salvage therapy with platinum-containing drug regimens with or without surgery will cure most patients with resistant GTN.

REFERENCES

- Hertz R, Li MC, Spencer DB. Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. *Proc Soc Exp Biol Med*. 1956;93(2):361–366.
- Berkowitz RS, Goldstein DP. Molar pregnancy and gestational trophoblastic neoplasms. In: Barakat RR, et al. ed. *Principles and Practice of Gynecologic Oncology*. 5th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009;875–895.
- Soper JT. Gestational trophoblastic disease. *Obstet Gynecol*. 2006;108(1):176–187.
- Bracken MB. Incidence and aetiology of hydatidiform mole: an epidemiological review. *Br J Obstet Gynaecol*. 1987;94(12):1123–1135.
- Soto-Wright V, Bernstein M, Goldstein DP, et al. The changing clinical presentation of complete molar pregnancy. *Obstet Gynecol*. 1995;86(5):775–779.
- Atrash HK, Hogue CJ, Grimes DA. Epidemiology of hydatidiform mole during early gestation. *Am J Obstet Gynecol*. 1986;154(4):906–909.
- Palmer JR. Advances in the epidemiology of gestational trophoblastic disease. *J Reprod Med*. 1994;39(3):155–162.
- Fukunaga M, Ushigome S, Endo Y. Incidence of hydatidiform mole in a Tokyo hospital: a 5-year (1989 to 1993) prospective, morphological, and flow cytometric study. *Hum Pathol*. 1995;26(7):758–764.
- Jeffers MD, O'Dwyer P, Curran B, et al. Partial hydatidiform mole: a common but underdiagnosed condition. A 3-year retrospective clinicopathological and DNA flow cytometric analysis. *Int J Gynecol Pathol*. 1993;12(4):315–323.
- Bagshawe KD, Dent J, Webb J. Hydatidiform mole in England and Wales 1973–1983. *Lancet*. 1986;2(8508):673–677.
- Takeuchi S. Incidence of gestational trophoblastic disease by regional registration in Japan. *Hum Reprod*. 1987;2(8):729–734.
- Smith HO, Qualls CR, Prairie BA, et al. Trends in gestational choriocarcinoma: a 27-year perspective. *Obstet Gynecol*. 2003;102(5 Pt 1):978–987.
- Berkowitz RS, Cramer DW, Bernstein MR, et al. Risk factors for complete molar pregnancy from a case-control study. *Am J Obstet Gynecol*. 1985;152(8):1016–1020.
- Parazzini F, La Vecchia C, Mangili G, et al. Dietary factors and risk of trophoblastic disease. *Am J Obstet Gynecol*. 1988;158(1):93–99.
- Fulop V, Mok SC, Berkowitz RS. Molecular biology of gestational trophoblastic neoplasia: a review. *J Reprod Med*. 2004;49(6):415–422.
- Acaia B, Parazzini F, La Vecchia C, et al. Increased frequency of complete hydatidiform mole in women with repeated abortion. *Gynecol Oncol*. 1988;31(2):310–314.
- Parazzini F, Mangili G, La Vecchia C, et al. Risk factors for gestational trophoblastic disease: a separate analysis of complete and partial hydatidiform moles. *Obstet Gynecol*. 1991;78(6):1039–1045.
- Parazzini F, La Vecchia C, Pampallona S. Parental age and risk of complete and partial hydatidiform mole. *Br J Obstet Gynaecol*. 1986;93(6):582–585.
- Sehire NJ, Fiskett M, Fisher RA, et al. Risk of partial and complete hydatidiform molar pregnancy in relation to maternal age. *BJOG*. 2002;109(1):99–102.
- Sand PK, Lurain JR, Brewer JI. Repeat gestational trophoblastic disease. *Obstet Gynecol*. 1984;63(2):140–144.
- Berkowitz RS, Im SS, Bernstein MR, et al. Gestational trophoblastic disease: Subsequent pregnancy outcome, including repeat molar pregnancy. *J Reprod Med*. 1998;43(1):81–86.
- Garrett LA, Garner EI, Feltmate CM, et al. Subsequent pregnancy outcomes in patients with molar pregnancy and persistent gestational trophoblastic neoplasia. *J Reprod Med*. 2008;53(7):481–486.
- Sehire NJ, Fisher RA, Fiskett M, et al. Risk of recurrent hydatidiform mole and subsequent pregnancy outcome following complete or partial hydatidiform molar pregnancy. *BJOG*. 2003;110(1):22–26.
- Tuncer ZS, Bernstein MR, Wang J, et al. Repetitive hydatidiform mole with different male partners. *Gynecol Oncol*. 1999;75(2):224–226.
- Kou YC, Shao L, Peng HH, et al. A recurrent intragenic genomic duplication, other novel mutations in NLRP7 and imprinting defects in recurrent biparental hydatidiform moles. *Mol Hum Reprod*. 2008;14(1):33–40.
- Wang CM, Dixon PH, Decordova S, et al. Identification of 13 novel NLRP7 mutations in 20 families with recurrent hydatidiform mole; missense mutations cluster in the leucine-rich region. *J Med Genet*. 2009;46(8):569–575.
- Moglabey YB, Kircheisen R, Seoud M, et al. Genetic mapping of a maternal locus responsible for familial hydatidiform moles. *Hum Mol Genet*. 1999;8(4):667–671.
- Messaed C, Chebaro W, Di Roberto RB, et al. NLRP7 in the spectrum of reproductive wastage: rare non-synonymous variants confer genetic susceptibility to recurrent reproductive wastage. *J Med Genet*. 2011;48(8):540–548.
- Murdoch S, Djuric U, Mazhar B, et al. Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans. *Nat Genet*. 2006;38(3):300–302.
- Fisher RA, Hodges MD, Newlands ES. Familial recurrent hydatidiform mole: a review. *J Reprod Med*. 2004;49(8):595–601.
- Berkowitz RS, Bernstein MR, Harlow BL, et al. Case-control study of risk factors for partial molar pregnancy. *Am J Obstet Gynecol*. 1995;173(3 Pt 1):788–794.
- Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. *Curr Opin Oncol*. 2007;19(5):486–491.
- Buckley JD, Henderson BE, Morrow CP, et al. Case-control study of gestational choriocarcinoma. *Cancer Res*. 1988;48(4):1004–1010.
- Stone M, Dent J, Kardana A, et al. Relationship of oral contraception to development of trophoblastic tumour after evacuation of a hydatidiform mole. *Br J Obstet Gynaecol*. 1976;83(12):913–916.
- Costa HL, Doyle P. Influence of oral contraceptives in the development of post-molar trophoblastic neoplasia—a systematic review. *Gynecol Oncol*. 2006;100(3):579–585.
- Palmer JR, Driscoll SG, Rosenberg L, et al. Oral contraceptive use and risk of gestational trophoblastic tumors. *J Natl Cancer Inst*. 1999;91(7):635–640.
- Osborne R, Dodge J. Gestational trophoblastic neoplasia. *Obstet Gynecol Clin North Am*. 2012;39(2):195–212.
- Shih IM, Kurman RJ. The pathology of intermediate trophoblastic tumors and tumor-like lesions. *Int J Gynecol Pathol*. 2001;20(1):31–47.
- Xu G, Guimond MJ, Chakraborty C, et al. Control of proliferation, migration, and invasiveness of human extravillous trophoblast by decorin, a decidual product. *Biol Reprod*. 2002;67(2):681–689.
- Xu G, Chakraborty C, Lala PK. Expression of TGF-beta signaling genes in the normal, premalignant, and malignant human trophoblast: loss of smad3 in choriocarcinoma cells. *Biochem Biophys Res Commun*. 2001;287(1):47–55.
- Berkowitz RS, Goldstein DP. Recent advances in gestational trophoblastic disease. *Curr Opin Obstet Gynecol*. 1998;10(1):61–64.
- Bentley RC. Pathology of gestational trophoblastic disease. *Clin Obstet Gynecol*. 2003;46(3):513–522.
- Shih I-M. Trophogram, an immunohistochemistry-based algorithmic approach, in the differential diagnosis of trophoblastic tumors and tumorlike lesions. *Ann Diagn Pathol*. 2007;11(3):228–234.
- Kale A, Soylemez F, Ensari A. Expressions of proliferation markers (Ki-67, proliferating cell nuclear antigen, and silver-staining nucleolar organizer regions) and of p53 tumor protein in gestational trophoblastic disease. *Am J Obstet Gynecol*. 2001;184(4):567–574.
- Shih IM, Kurman RJ. p63 expression is useful in the distinction of epithelioid trophoblastic and placental site trophoblastic tumors by profiling trophoblastic subpopulations. *Am J Surg Pathol*. 2004;28(9):1177–1183.
- Singer G, Kurman RJ, McMaster MT, et al. HLA-G immunoreactivity is specific for intermediate trophoblast in gestational trophoblastic disease and can serve as a useful marker in differential diagnosis. *Am J Surg Pathol*. 2002;26(7):914–920.
- Fulop V, Mok SC, Genest DR, et al. p53, p21, Rb and mdm2 oncoproteins: Expression in normal placenta, partial and complete mole, and choriocarcinoma. *J Reprod Med*. 1998;43(2):119–127.
- Fulop V, Mok SC, Genest DR, et al. c-myc, c-erbB-2, c-fms and bcl-2 oncoproteins: Expression in normal placenta, partial and complete mole, and choriocarcinoma. *J Reprod Med*. 1998;43(2):101–110.
- Hussein MR. Analysis of p53, BCL-2 and epidermal growth factor receptor protein expression in the partial and complete hydatidiform moles. *Exp Mol Pathol*. 2009;87(1):63–69.
- Petignat P, Laurini R, Goffin F, et al. Expression of matrix metalloproteinase-2 and mutant p53 is increased in hydatidiform mole as compared with normal placenta. *Int J Gynecol Cancer*. 2006;16(4):1679–1684.
- Szulman AE, Surti U. The syndromes of hydatidiform mole. I. Cytogenetic and morphologic correlations. *Am J Obstet Gynecol*. 1978;131(6):665–671.
- Szulman AE, Surti U. The syndromes of hydatidiform mole. II. Morphologic evolution of the complete and partial mole. *Am J Obstet Gynecol*. 1978;132(1):20–27.
- Kajii T, Ohama K. Androgenetic origin of hydatidiform mole. *Nature*. 1977;268(5621):633–634.
- Fisher RA, Newlands ES. Gestational trophoblastic disease. Molecular and genetic studies. *J Reprod Med*. 1998;43(1):87–97.
- Azuma C, Saji F, Tokugawa Y, et al. Application of gene amplification by polymerase chain reaction to genetic analysis of molar mitochondrial DNA: the detection of anuclear empty ovum as the cause of complete mole. *Gynecol Oncol*. 1991;40(1):29–33.
- Lawler SD, Fisher RA, Dent J. A prospective genetic study of complete and partial hydatidiform moles. *Am J Obstet Gynecol*. 1991;164(5 Pt 1):1270–1277.

57. Lage JM. Gestational trophoblastic diseases. In: Robboy SJ, Anderson MC, Russell P, eds. *Pathology of the Female Reproductive Tract*. Edinburgh, UK: Churchill Livingstone; 2001:759–781.
58. Lage JM, Mark SD, Roberts DJ, et al. A flow cytometric study of 137 fresh hydropic placentas: correlation between types of hydatidiform moles and nuclear DNA ploidy. *Obstet Gynecol*. 1992;79(3):403–410.
59. Gaber LW, Redline RW, Mostoufi-Zadeh M, et al. Invasive partial mole. *Am J Clin Pathol*. 1986;85(6):722–724.
60. Shih IM, Kurman RJ. Immunohistochemical localization of inhibin-alpha in the placenta and gestational trophoblastic lesions. *Int J Gynecol Pathol*. 1999;18(2):144–150.
61. Shih IM, Kurman RJ. Ki-67 labeling index in the differential diagnosis of exaggerated placental site, placental site trophoblastic tumor, and choriocarcinoma: a double immunohistochemical staining technique using Ki-67 and Mel-CAM antibodies. *Hum Pathol*. 1998;29(1):27–33.
62. Oldt RJ 3rd, Kurman RJ, Shih IM. Molecular genetic analysis of placental site trophoblastic tumors and epithelioid trophoblastic tumors confirms their trophoblastic origin. *Am J Pathol*. 2002;161(3):1033–1037.
63. Rhoton-Vlasak A, Wagner JM, Rutgers JL, et al. Placental site trophoblastic tumor: human placental lactogen and pregnancy-associated major basic protein as immunohistologic markers. *Hum Pathol*. 1998;29(3):280–288.
64. Shih IM, Kurman RJ. Epithelioid trophoblastic tumor: a neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma. *Am J Surg Pathol*. 1998;22(11):1393–1403.
65. Mao TL, Seidman JD, Kurman RJ, et al. Cyclin E and p16 immunoreactivity in epithelioid trophoblastic tumor—an aid in differential diagnosis. *Am J Surg Pathol*. 2006;30(9):1105–1110.
66. Bamberger AM, Aupers S, Milde-Langosch K, et al. Expression pattern of the cell cycle promoter cyclin e in benign extravillous trophoblast and gestational trophoblastic lesions: correlation with expression of Ki-67. *Int J Gynecol Pathol*. 2003;22(2):156–161.
67. Hou JL, Wan XR, Xiang Y, et al. Changes of clinical features in hydatidiform mole: analysis of 113 cases. *J Reprod Med*. 2008;53(8):629–633.
68. Curry SL, Hammond CB, Tyrey L, et al. Hydatidiform mole: diagnosis, management, and long-term followup of 347 patients. *Obstet Gynecol*. 1975;45(1):1–8.
69. Kohorn EI. Molar pregnancy: presentation and diagnosis. *Clin Obstet Gynecol*. 1984;27(1):181–191.
70. Szulman AE, Surti U. The clinicopathologic profile of the partial hydatidiform mole. *Obstet Gynecol*. 1982;59(5):597–602.
71. Czernobilsky B, Barash A, Lancet M. Partial moles: a clinicopathologic study of 25 cases. *Obstet Gynecol*. 1982;59(1):75–77.
72. Berkowitz RS, Goldstein DP, Bernstein MR. Natural history of partial molar pregnancy. *Obstet Gynecol*. 1985;66(5):677–681.
73. Santos-Ramos R, Forney JP, Schwarz BE. Sonographic findings and clinical correlations in molar pregnancy. *Obstet Gynecol*. 1980;56(2):186–192.
74. Benson CB, Genest DR, Bernstein MR, et al. Sonographic appearance of first trimester complete hydatidiform moles. *Ultrasound Obstet Gynecol*. 2000;16(2):188–191.
75. Fine C, Bundy AL, Berkowitz RS, et al. Sonographic diagnosis of partial hydatidiform mole. *Obstet Gynecol*. 1989;73(3 Pt 1):414–418.
76. Cole LA. Human chorionic gonadotropin and associated molecules. *Expert Rev Mol Diagn*. 2009;9(1):51–73.
77. Cole LA. Human chorionic gonadotropin tests. *Expert Rev Mol Diagn*. 2009;9(7):721–747.
78. Ozturk M, Berkowitz R, Goldstein D, et al. Differential production of human chorionic gonadotropin and free subunits in gestational trophoblastic disease. *Am J Obstet Gynecol*. 1988;158(1):193–198.
79. Cole LA, Khanlian SA. Hyperglycosylated hCG: a variant with separate biological functions to regular hCG. *Mol Cell Endocrinol*. 2007;260–262:228–236.
80. Cole LA, Shahabi S, Butler SA, et al. Utility of commonly used commercial human chorionic gonadotropin immunoassays in the diagnosis and management of trophoblastic diseases. *Clin Chem*. 2001;47(2):308–315.
81. Cole LA. hCG, its free subunits and its metabolites. Roles in pregnancy and trophoblastic disease. *J Reprod Med*. 1998;43(1):3–10.
82. Berkowitz R, Ozturk M, Goldstein D, et al. Human chorionic gonadotropin and free subunits' serum levels in patients with partial and complete hydatidiform moles. *Obstet Gynecol*. 1989;74(2):212–216.
83. Menczer J, Modan M, Serr DM. Prospective follow-up of patients with hydatidiform mole. *Obstet Gynecol*. 1980;55(3):346–349.
84. Fowler DJ, Lindsay I, Seckl MJ, et al. Histomorphometric features of hydatidiform moles in early pregnancy: relationship to detectability by ultrasound examination. *Ultrasound Obstet Gynecol*. 2007;29(1):76–80.
85. Sebire NJ, Rees H, Paradinas F, et al. The diagnostic implications of routine ultrasound examination in histologically confirmed early molar pregnancies. *Ultrasound Obstet Gynecol*. 2001;18(6):662–665.
86. Sarmadi S, Izadi-Mood N, Abbasi A, et al. p57KIP2 immunohistochemical expression: a useful diagnostic tool in discrimination between complete hydatidiform mole and its mimics. *Arch Gynecol Obstet*. 2011;283(4):743–748.
87. Castrillon DH, Sun D, Weremowicz S, et al. Discrimination of complete hydatidiform mole from its mimics by immunohistochemistry of the paternally imprinted gene product p57KIP2. *Am J Surg Pathol*. 2001;25(10):1225–1230.
88. Fisher RA, Hodges MD, Rees HC, et al. The maternally transcribed gene p57(KIP2) (CDNK1C) is abnormally expressed in both androgenetic and biparental complete hydatidiform moles. *Hum Mol Genet*. 2002;11(26):3267–3272.
89. Thaker HM, Berlin A, Tycko B, et al. Immunohistochemistry for the imprinted gene product IPL/PHLDA2 for facilitating the differential diagnosis of complete hydatidiform mole. *J Reprod Med*. 2004;49(8):630–636.
90. McConnell TG, Murphy KM, Hafez M, et al. Diagnosis and subclassification of hydatidiform moles using p57 immunohistochemistry and molecular genotyping: validation and prospective analysis in routine and consultation practice settings with development of an algorithmic approach. *Am J Surg Pathol*. 2009;33(6):805–817.
91. Chiang S, Fazlollahi L, Nguyen A, et al. Diagnosis of hydatidiform moles by polymerase deletion probe fluorescence in situ hybridization. *J Mol Diagn*. 2011;13(4):406–415.
92. Genest DR, Dorfman DM, Castrillon DH. Ploidy and imprinting in hydatidiform moles. Complementary use of flow cytometry and immunohistochemistry of the imprinted gene product p57KIP2 to assist molar classification. *J Reprod Med*. 2002;47(5):342–346.
93. Palmieri C, Dhillon T, Fisher RA, et al. Management and outcome of healthy women with a persistently elevated beta-hCG. *Gynecol Oncol*. 2007;106(1):35–43.
94. Rotmensch S, Cole LA. False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotropin concentrations. *Lancet*. 2000;355(9205):712–715.
95. Hancock BW. hCG measurement in gestational trophoblastic neoplasia: a critical appraisal. *J Reprod Med*. 2006;51(11):859–860.
96. Papapetrou PD, Anagnostopoulos NI. A gonadotropin and alpha-subunit suppression test for the assessment of the ectopic production of human chorionic gonadotropin and its subunits after the menopause. *J Clin Endocrinol Metab*. 1985;60(6):1187–1195.
97. Soper JT. Surgical therapy for gestational trophoblastic disease. *J Reprod Med*. 1994;39(3):168–174.
98. Tidy JA, Gillespie AM, Bright N, et al. Gestational trophoblastic disease: a study of mode of evacuation and subsequent need for treatment with chemotherapy. *Gynecol Oncol*. 2000;78(3 Pt 1):309–312.
99. Berkowitz RS, Goldstein DP. Clinical practice. Molar pregnancy. *N Engl J Med*. 2009;360(16):1639–1645.
100. Hancock BW, Tidy JA. Current management of molar pregnancy. *J Reprod Med*. 2002;47(5):347–354.
101. Kashimura Y, Kashimura M, Sugimori H, et al. Prophylactic chemotherapy for hydatidiform mole. Five to 15 years follow-up. *Cancer*. 1986;58(3):624–629.
102. Kim DS, Moon H, Kim KT, et al. Effects of prophylactic chemotherapy for persistent trophoblastic disease in patients with complete hydatidiform mole. *Obstet Gynecol*. 1986;67(5):690–694.
103. Limpongsanurak S. Prophylactic actinomycin D for high-risk complete hydatidiform mole. *J Reprod Med*. 2001;46(2):110–116.
104. Steller MA, Genest DR, Bernstein MR, et al. Clinical features of multiple conception with partial or complete molar pregnancy and coexisting fetuses. *J Reprod Med*. 1994;39(3):147–154.
105. Fishman DA, Padilla LA, Keh P, et al. Management of twin pregnancies consisting of a complete hydatidiform mole and normal fetus. *Obstet Gynecol*. 1998;91(4):546–550.
106. Sebire NJ, Foksett M, Paradinas FJ, et al. Outcome of twin pregnancies with complete hydatidiform mole and healthy co-twin. *Lancet*. 2002;359(9324):2165–2166.
107. Berkowitz RS, Goldstein DP, Marean AR, et al. Oral contraceptives and postmolar trophoblastic disease. *Obstet Gynecol*. 1981;58(4):474–477.
108. Curry SL, Schlaerth JB, Kohorn EI, et al. Hormonal contraception and trophoblastic sequelae after hydatidiform mole (a Gynecologic Oncology Group Study). *Am J Obstet Gynecol*. 1989;160(4):805–809; discussion 809–811.
109. Deicas RE, Miller DS, Rademaker AW, et al. The role of contraception in the development of postmolar gestational trophoblastic tumor. *Obstet Gynecol*. 1991;78(2):221–226.
110. Berkowitz RS, Goldstein DP. Current management of gestational trophoblastic diseases. *Gynecol Oncol*. 2009;112(3):654–662.
111. Rice LW, Lage JM, Berkowitz RS, et al. Repetitive complete and partial hydatidiform mole. *Obstet Gynecol*. 1989;74(2):217–219.

112. Cole LA, Butler SA, Khanlian SA, et al. Gestational trophoblastic diseases: 2. Hyperglycosylated hCG as a reliable marker of active neoplasia. *Gynecol Oncol.* 2006;102(2):151–159.
113. Khanlian SA, Cole LA. Management of gestational trophoblastic disease and other cases with low serum levels of human chorionic gonadotropin. *J Reprod Med.* 2006;51(10):812–818.
114. Cole LA, Khanlian SA. Inappropriate management of women with persistent low hCG results. *J Reprod Med.* 2004;49(6):423–432.
115. Lurain JR, Brewer JL, Torok EE, et al. Natural history of hydatidiform mole after primary evacuation. *Am J Obstet Gynecol.* 1983;145(5):591–595.
116. Feltmate CM, Batorfi J, Fulop V, et al. Human chorionic gonadotropin follow-up in patients with molar pregnancy: a time for reevaluation. *Obstet Gynecol.* 2003;101(4):732–736.
117. Hancock BW, Nazir K, Everard JE. Persistent gestational trophoblastic neoplasia after partial hydatidiform mole incidence and outcome. *J Reprod Med.* 2006;51(10):764–766.
118. Feltmate CM, Growdon WB, Wolfberg AJ, et al. Clinical characteristics of persistent gestational trophoblastic neoplasia after partial hydatidiform molar pregnancy. *J Reprod Med.* 2006;51(11):902–906.
119. Berkowitz RS, Goldstein DP, Bernstein MR. Evolving concepts of molar pregnancy. *J Reprod Med.* 1991;36(1):40–44.
120. Mosher R, Goldstein DP, Berkowitz R, et al. Complete hydatidiform mole: Comparison of clinicopathologic features, current and past. *J Reprod Med.* 1998;43(1):21–27.
121. Lurain JR. Gestational trophoblastic tumors. *Semin Surg Oncol.* 1990;6(6):347–353.
122. Paradinas FJ, Browne P, Fisher RA, et al. A clinical, histopathological and flow cytometric study of 149 complete moles, 146 partial moles and 107 non-molar hydropic abortions. *Histopathology.* 1996;28(2):101–110.
123. Sebire NJ, Fisher RA, Rees HC. Histopathological diagnosis of partial and complete hydatidiform mole in the first trimester of pregnancy. *Pediatr Dev Pathol.* 2003;6(1):69–77.
124. Heifetz SA, Czaja J. In situ choriocarcinoma arising in partial hydatidiform mole: implications for the risk of persistent trophoblastic disease. *Pediatr Pathol.* 1992;12(4):601–611.
125. Menczer J, Girtler O, Zajdel L, et al. Metastatic trophoblastic disease following partial hydatidiform mole: case report and literature review. *Gynecol Oncol.* 1999;74(2):304–307.
126. Gardner HA, Lage JM. Choriocarcinoma following a partial hydatidiform mole: a case report. *Hum Pathol.* 1992;23(4):468–471.
127. Allison KH, Love JE, Garcia RL. Epithelioid trophoblastic tumor: review of a rare neoplasm of the chorionic-type intermediate trophoblast. *Arch Pathol Lab Med.* 2006;130(12):1875–1877.
128. Baergen RN, Rutgers JL, Young RH, et al. Placental site trophoblastic tumor: a study of 55 cases and review of the literature emphasizing factors of prognostic significance. *Gynecol Oncol.* 2006;100(3):511–520.
129. Cheung AN, Zhang DK, Liu Y, et al. Telomerase activity in gestational trophoblastic disease. *J Clin Pathol.* 1999;52(8):588–592.
130. Wong SY, Ngan HY, Chan CC, et al. Apoptosis in gestational trophoblastic disease is correlated with clinical outcome and Bcl-2 expression but not Bax expression. *Mod Pathol.* 1999;12(11):1025–1033.
131. Chiu PM, Ngan YS, Khoo US, et al. Apoptotic activity in gestational trophoblastic disease correlates with clinical outcome: assessment by the caspase-related M30 CytoDeath antibody. *Histopathology.* 2001;38(3):243–249.
132. Fong PY, Xue WC, Ngan HY, et al. Mcl-1 expression in gestational trophoblastic disease correlates with clinical outcome: a differential expression study. *Cancer.* 2005;103(2):268–276.
133. Feng HC, Tsao SW, Ngan HY, et al. Differential expression of insulin-like growth factor binding protein 1 and ferritin light polypeptide in gestational trophoblastic neoplasia: combined cDNA suppression subtractive hybridization and microarray study. *Cancer.* 2005;104(11):2409–2416.
134. van Trommel NE, Massuger LF, Verheijen RH, et al. The curative effect of a second curettage in persistent trophoblastic disease: a retrospective cohort survey. *Gynecol Oncol.* 2005;99(1):6–13.
135. Schlaerth JB, Morrow CP, Rodriguez M. Diagnostic and therapeutic curettage in gestational trophoblastic disease. *Am J Obstet Gynecol.* 1990;162(6):1465–1470; discussion 1470–1471.
136. Pezeszki M, Hancock BW, Silcocks P, et al. The role of repeat uterine evacuation in the management of persistent gestational trophoblastic disease. *Gynecol Oncol.* 2004;95(3):423–429.
137. Garner EI, Feltmate CM, Goldstein DP, et al. The curative effect of a second curettage in persistent trophoblastic disease: a retrospective cohort survey. *Gynecol Oncol.* 2005;99(1):3–5.
138. Crawford RA, Newlands E, Rustin GJ, et al. Gestational trophoblastic disease with liver metastases: the charing cross experience. *Br J Obstet Gynaecol.* 1997;104(1):105–109.
139. FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. *Int J Gynaecol Obstet.* 2002;77(3):285–287.
140. Berry E, Hagopian GS, Lurain JR. Vaginal metastases in gestational trophoblastic neoplasia. *J Reprod Med.* 2008;53(7):487–492.
141. Lurain JR. Treatment of gestational trophoblastic tumors. *Curr Treat Options Oncol.* 2002;3(2):113–124.
142. Athanassiou A, Begent RH, Newlands ES, et al. Central nervous system metastases of choriocarcinoma: 23 years' experience at Charing Cross Hospital. *Cancer.* 1983;52(9):1728–1735.
143. Ngan HY, Bender H, Benedet JL, et al. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *Int J Gynaecol Obstet.* 2003;83(suppl. 1):175–177.
144. Lurain JR, Casanova LA, Miller DS, et al. Prognostic factors in gestational trophoblastic tumors: a proposed new scoring system based on multivariate analysis. *Am J Obstet Gynecol.* 1991;164(2):611–616.
145. McGrath S, Short D, Harvey R, et al. The management and outcome of women with post-hydatidiform mole 'low-risk' gestational trophoblastic neoplasia, but hCG levels in excess of 100 000 IU l⁻¹. *Br J Cancer.* 2010;102(5):810–814.
146. Cole LA. Minimally-aggressive gestational trophoblastic neoplasms. *Gynecol Oncol.* 2012;125(1):145–150.
147. Lurain JR. Pharmacotherapy of gestational trophoblastic disease. *Expert Opin Pharmacother.* 2003;4(11):2005–2017.
148. Alazzam M, Tidy J, Hancock BW, et al. First line chemotherapy in low risk gestational trophoblastic neoplasia. *Cochrane Database Syst Rev.* 2009;(1):CD007102.
149. Lybol C, Sweep FC, Harvey R, et al. Relapse rates after two versus three consolidation courses of methotrexate in the treatment of low-risk gestational trophoblastic neoplasia. *Gynecol Oncol.* 2012;125(3):576–579.
150. Lurain JR, Elfstrand EP. Single-agent methotrexate chemotherapy for the treatment of non-metastatic gestational trophoblastic tumors. *Am J Obstet Gynecol.* 1995;172(2 Pt 1):574–579.
151. Hammond CB, Borchert LG, Tyrey L, et al. Treatment of metastatic trophoblastic disease: good and poor prognosis. *Am J Obstet Gynecol.* 1973;115(4):451–457.
152. Hammond CB, Hertz R, Ross GT, et al. Primary chemotherapy for nonmetastatic gestational trophoblastic neoplasms. *Am J Obstet Gynecol.* 1967;98(1):71–78.
153. Bagshawe KD, Dent J, Newlands ES, et al. The role of low-dose methotrexate and folinic acid in gestational trophoblastic tumours (GTT). *Br J Obstet Gynaecol.* 1989;96(7):795–802.
154. Garrett AP, Garner EO, Goldstein DP, et al. Methotrexate infusion and folinic acid as primary therapy for nonmetastatic and low-risk metastatic gestational trophoblastic tumors: 15 years of experience. *J Reprod Med.* 2002;47(5):355–362.
155. Berkowitz RS, Goldstein DP, Bernstein MR. Ten year's experience with methotrexate and folinic acid as primary therapy for gestational trophoblastic disease. *Gynecol Oncol.* 1986;23(1):111–118.
156. Wong LC, Choo YC, Ma HK. Methotrexate with citrovorum factor rescue in gestational trophoblastic disease. *Am J Obstet Gynecol.* 1985;152(1):59–62.
157. McNeish IA, Strickland S, Holden L, et al. Low-risk persistent gestational trophoblastic disease: outcome after initial treatment with low-dose methotrexate and folinic acid from 1992 to 2000. *J Clin Oncol.* 2002;20(7):1838–1844.
158. Khan F, Everard J, Ahmed S, et al. Low-risk persistent gestational trophoblastic disease treated with low-dose methotrexate: efficacy, acute and long-term effects. *Br J Cancer.* 2003;89(12):2197–2201.
159. Growdon WB, Wolfberg AJ, Goldstein DP, et al. Evaluating methotrexate treatment in patients with low-risk postmolar gestational trophoblastic neoplasia. *Gynecol Oncol.* 2009;112(2):353–357.
160. Wong LC, Ngan HY, Cheng DK, et al. Methotrexate infusion in low-risk gestational trophoblastic disease. *Am J Obstet Gynecol.* 2000;183(6):1579–1582.
161. Berkowitz RS, Goldstein DP, Bernstein MR. Methotrexate infusion and folinic acid in the primary therapy of nonmetastatic gestational trophoblastic tumors. *Gynecol Oncol.* 1990;36(1):56–59.
162. Elit L, Covens A, Osborne R, et al. High-dose methotrexate for gestational trophoblastic disease. *Gynecol Oncol.* 1994;54(3):282–287.
163. Hoffman MS, Fiorica JV, Gleason NC, et al. A single institution experience with weekly intramuscular methotrexate for nonmetastatic gestational trophoblastic disease. *Gynecol Oncol.* 1996;60(2):292–294.
164. Homesley HD, Blessing JA, Rettenmaier M, et al. Weekly intramuscular methotrexate for nonmetastatic gestational trophoblastic disease. *Obstet Gynecol.* 1988;72(3 Pt 1):413–418.
165. Homesley HD, Blessing JA, Schlaerth J, et al. Rapid escalation of weekly intramuscular methotrexate for nonmetastatic

- gestational trophoblastic disease: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1990;39(3):305–308.
166. Smith EB, Weed JC Jr, Tyrey L, et al. Treatment of nonmetastatic gestational trophoblastic disease: results of methotrexate alone versus methotrexate–folinic acid. *Am J Obstet Gynecol.* 1982;144(1):88–92.
 167. Gleeson NC, Finan MA, Fiorica JV, et al. Nonmetastatic gestational trophoblastic disease: Weekly methotrexate compared with 8-day methotrexate–folinic acid. *Eur J Gynaecol Oncol.* 1993;14(6):461–465.
 168. Osathanondh R, Goldstein DP, Pastoride GB. Actinomycin D as the primary agent for gestational trophoblastic disease. *Cancer.* 1975;36(3):863–866.
 169. Petrilli ES, Morrow CP. Actinomycin D toxicity in the treatment of trophoblastic disease: a comparison of the five-day course to single-dose administration. *Gynecol Oncol.* 1980;9(1):18–22.
 170. Twigg LB. Pulse actinomycin D scheduling in nonmetastatic gestational trophoblastic neoplasia: cost-effective chemotherapy. *Gynecol Oncol.* 1983;16(2):190–195.
 171. Schlaerth JB, Morrow CP, Nalick RH, et al. Single-dose actinomycin D in the treatment of postmolar trophoblastic disease. *Gynecol Oncol.* 1984;19(1):53–56.
 172. Petrilli ES, Twigg LB, Blessing JA, et al. Single-dose actinomycin-D treatment for nonmetastatic gestational trophoblastic disease: A prospective phase II trial of the Gynecologic Oncology Group. *Cancer.* 1987;60(9):2173–2176.
 173. Kohorn EI. Decision making for chemotherapy administration in patients with low-risk gestational trophoblastic neoplasia. *Int J Gynecol Cancer.* 1996;6:279–285.
 174. Kohorn EI. Is lack of response to single-agent chemotherapy in gestational trophoblastic disease associated with dose scheduling or chemotherapy resistance? *Gynecol Oncol.* 2002;85(1):36–39.
 175. Gilani MM, Yarandi F, Eftekhari Z, et al. Comparison of pulse methotrexate and pulse dactinomycin in the treatment of low-risk gestational trophoblastic neoplasia. *Aust N Z J Obstet Gynaecol.* 2005;45(2):161–164.
 176. Yarandi F, Eftekhari Z, Shojaei H, et al. Pulse methotrexate versus pulse actinomycin D in the treatment of low-risk gestational trophoblastic neoplasia. *Int J Gynaecol Obstet.* 2008;103(1):33–37.
 177. Osborne RJ, Filiaci V, Schink JC, et al. Phase III trial of weekly methotrexate or pulsed actinomycin for low-risk gestational trophoblastic neoplasia: a gynecologic oncology group study. *J Clin Oncol.* 2011;29(7):825–831.
 178. Lertkongsuksak AA, Israngura N, Wilailak S, et al. Actinomycin d versus methotrexate–folinic acid as the treatment of stage I, low-risk gestational trophoblastic neoplasia: a randomized controlled trial. *Int J Gynecol Cancer.* 2009;19(5):985–988.
 179. Abrao RA, de Andrade JM, Tiezzi DG, et al. Treatment for low-risk gestational trophoblastic disease: comparison of single-agent methotrexate, dactinomycin and combination regimens. *Gynecol Oncol.* 2008;108(1):149–153.
 180. DuBeshter B, Berkowitz RS, Goldstein DP, et al. Management of low-risk metastatic gestational trophoblastic tumors. *J Reprod Med.* 1991;36(1):36–39.
 181. Soper JT, Clarke-Pearson DL, Berchuck A, et al. 5-day methotrexate for women with metastatic gestational trophoblastic disease. *Gynecol Oncol.* 1994;54(1):76–79.
 182. Roberts JP, Lurain JR. Treatment of low-risk metastatic gestational trophoblastic tumors with single-agent chemotherapy. *Am J Obstet Gynecol.* 1996;174(6):1917–1923; discussion 1923–1914.
 183. Chapman-Davis E, Hoekstra AV, Rademaker AW, et al. Treatment of nonmetastatic and metastatic low-risk gestational trophoblastic neoplasia: factors associated with resistance to single-agent methotrexate chemotherapy. *Gynecol Oncol.* 2012;125(3):572–575.
 184. Shigematsu T, Hirakawa T, Yahata H, et al. Identification of chemotherapeutic refractory cases based on human chorionic gonadotropin values among patients with low-risk persistent trophoblastic disease treated with 8-day methotrexate–folinic acid. *Eur J Gynaecol Oncol.* 2003;2(2):113–116.
 185. Rotmensch J, Rosenshein NB, Block BS. Comparison of human chorionic gonadotropin regression in molar pregnancies and post-molar nonmetastatic gestational trophoblastic neoplasia. *Gynecol Oncol.* 1988;29(1):82–86.
 186. van Trommel NE, Massuger LF, Schijf CP, et al. Early identification of resistance to first-line single-agent methotrexate in patients with persistent trophoblastic disease. *J Clin Oncol.* 2006;24(1):52–58.
 187. Kerkmeijer LG, Thomas CM, Harvey R, et al. External validation of serum hCG cut-off levels for prediction of resistance to single-agent chemotherapy in patients with persistent trophoblastic disease. *Br J Cancer.* 2009;100(6):979–984.
 188. Clark RM, Nevadunsky NS, Ghosh S, et al. The evolving role of hysterectomy in gestational trophoblastic neoplasia at the New England Trophoblastic Disease Center. *J Reprod Med.* 2010;55(5–6):194–198.
 189. Lurain JR, Brewer JI. Treatment of high-risk gestational trophoblastic disease with methotrexate, actinomycin D, and cyclophosphamide chemotherapy. *Obstet Gynecol.* 1985;65(6):830–836.
 190. Brewer JI, Torok EE, Webster A, et al. Hydatidiform mole: A follow-up regimen for identification of invasive mole and choriocarcinoma and for selection of patients for treatment. *Am J Obstet Gynecol.* 1968;101(4):557–563.
 191. Begent RH, Bagshawe KD. The management of high-risk choriocarcinoma. *Semin Oncol.* 1982;9(2):198–203.
 192. Curry SL, Blessing JA, DiSaia PJ, et al. A prospective randomized comparison of methotrexate, dactinomycin, and chlorambucil versus methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, and vincristine in “poor prognosis” metastatic gestational trophoblastic disease: a Gynecologic Oncology Group study. *Obstet Gynecol.* 1989;73(3 Pt 1):357–362.
 193. Newlands ES, Bagshawe KD, Begent RH, et al. Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumors, 1979 to 1989. *Br J Obstet Gynaecol.* 1991;98(6):550–557.
 194. Schink JC, Singh DK, Rademaker AW, et al. Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine for the treatment of metastatic, high-risk gestational trophoblastic disease. *Obstet Gynecol.* 1992;80(5):817–820.
 195. Bolis G, Bonazzi C, Landoni F, et al. EMA/CO regimen in high-risk gestational trophoblastic tumor (GTT). *Gynecol Oncol.* 1988;31(3):439–444.
 196. Bower M, Newlands ES, Holden L, et al. EMA/CO for high-risk gestational trophoblastic tumors: results from a cohort of 272 patients. *J Clin Oncol.* 1997;15(7):2636–2643.
 197. Kim SJ, Bae SN, Kim JH, et al. Risk factors for the prediction of treatment failure in gestational trophoblastic tumors treated with EMA/CO regimen. *Gynecol Oncol.* 1998;71(2):247–253.
 198. Matsui H, Suzuka K, Iitsuka Y, et al. Combination chemotherapy with methotrexate, etoposide, and actinomycin D for high-risk gestational trophoblastic tumors. *Gynecol Oncol.* 2000;78(1):28–31.
 199. Escobar PF, Lurain JR, Singh DK, et al. Treatment of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine chemotherapy. *Gynecol Oncol.* 2003;91(3):552–557.
 200. Lurain JR, Singh DK, Schink JC. Primary treatment of metastatic high-risk gestational trophoblastic neoplasia with EMA-CO chemotherapy. *J Reprod Med.* 2006;51(10):767–772.
 201. Turan T, Karacay O, Tulunay G, et al. Results with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy in gestational trophoblastic neoplasia. *Int J Gynecol Cancer.* 2006;16(3):1432–1438.
 202. Lu WG, Ye F, Shen YM, et al. EMA-CO chemotherapy for high-risk gestational trophoblastic neoplasia: a clinical analysis of 54 patients. *Int J Gynecol Cancer.* 2008;18(2):357–362.
 203. Lurain JR, Singh DK, Schink JC. Management of metastatic high-risk gestational trophoblastic neoplasia: FIGO stages II–IV; risk factor score ≥ 7 . *J Reprod Med.* 2010;55(5–6):199–207.
 204. Newlands ES, Holden L, Seckl MJ, et al. Management of brain metastases in patients with high-risk gestational trophoblastic tumors. *J Reprod Med.* 2002;47(6):465–471.
 205. Evans AC Jr, Soper JT, Clarke-Pearson DL, et al. Gestational trophoblastic disease metastatic to the central nervous system. *Gynecol Oncol.* 1995;59(2):226–230.
 206. Small W Jr, Lurain JR, Shetty RM, et al. Gestational trophoblastic disease metastatic to the brain. *Radiology.* 1996;200(1):277–280.
 207. Rustin GJ, Newlands ES, Begent RH, et al. Weekly alternating etoposide, methotrexate, and actinomycin/vincristine and cyclophosphamide chemotherapy for the treatment of CNS metastases of choriocarcinoma. *J Clin Oncol.* 1989;7(7):900–903.
 208. Bakri Y, Berkowitz RS, Goldstein DP, et al. Brain metastases of gestational trophoblastic tumor. *J Reprod Med.* 1994;39(3):179–184.
 209. Alazzam M, Hancock BW, Tidy J. Role of hysterectomy in managing persistent gestational trophoblastic disease. *J Reprod Med.* 2008;53(7):519–524.
 210. Doumplis D, Al-Khatib K, Sieunarine K, et al. A review of the management by hysterectomy of 25 cases of gestational trophoblastic tumours from March 1993 to January 2006. *BJOG.* 2007;114(9):1168–1171.
 211. Fleming EL, Garrett L, Growdon WB, et al. The changing role of thoracotomy in gestational trophoblastic neoplasia at the New England Trophoblastic Disease Center. *J Reprod Med.* 2008;53(7):493–498.
 212. Lim AK, Agarwal R, Seckl MJ, et al. Embolization of bleeding residual uterine vascular malformations in patients with treated gestational trophoblastic tumors. *Radiology.* 2002;222(3):640–644.

213. Lurain JR, Singh DK, Schink JC. Role of surgery in the management of high-risk gestational trophoblastic neoplasia. *J Reprod Med.* 2006;51(10):773–776.
214. Mutch DG, Soper JT, Babcock CJ, et al. Recurrent gestational trophoblastic disease: Experience of the Southeastern Regional Trophoblastic Disease Center. *Cancer.* 1990;66(5):978–982.
215. Newlands ES, Bower M, Holden L, et al. Management of resistant gestational trophoblastic tumors. *J Reprod Med.* 1998;43(2):111–118.
216. Pisal N, North C, Tidy J, et al. Role of hysterectomy in management of gestational trophoblastic disease. *Gynecol Oncol.* 2002;87(2):190–192.
217. Saitoh K, Harada K, Nakayama H, et al. Role of thoracotomy in pulmonary metastases from gestational choriocarcinoma. *J Thorac Cardiovasc Surg.* 1983;85(6):815–820.
218. Tomoda Y, Arii Y, Kaseki S, et al. Surgical indications for resection in pulmonary metastasis of choriocarcinoma. *Cancer.* 1980;46(12):2723–2730.
219. Vogelzang RL, Nemcek AA Jr, Skrtic Z, et al. Uterine arteriovenous malformations: primary treatment with therapeutic embolization. *J Vasc Interv Radiol.* 1991;2(4):517–522.
220. Xu LT, Sun CF, Wang YE, et al. Resection of pulmonary metastatic choriocarcinoma in 43 drug-resistant patients. *Ann Thorac Surg.* 1985;39(3):257–259.
221. Dhillon T, Palmieri C, Sebire NJ, et al. Value of whole body 18FDG-PET to identify the active site of gestational trophoblastic neoplasia. *J Reprod Med.* 2006;51(11):879–887.
222. Lurain JR, Nejad B. Secondary chemotherapy for high-risk gestational trophoblastic neoplasia. *Gynecol Oncol.* 2005;97(2):618–623.
223. Yang J, Xiang Y, Wan X, et al. Recurrent gestational trophoblastic tumor: management and risk factors for recurrence. *Gynecol Oncol.* 2006;103(2):587–590.
224. Ngan HY, Tam KF, Lam KW, et al. Relapsed gestational trophoblastic neoplasia: a 20-year experience. *J Reprod Med.* 2006;51(10):829–834.
225. Powles T, Savage PM, Stebbing J, et al. A comparison of patients with relapsed and chemorefractory gestational trophoblastic neoplasia. *Br J Cancer.* 2007;96(5):732–737.
226. Mao Y, Wan X, Lv W, et al. Relapsed or refractory gestational trophoblastic neoplasia treated with the etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EP-EMA) regimen. *Int J Gynaecol Obstet.* 2007;98(1):44–47.
227. Newlands ES, Mulholland PJ, Holden L, et al. Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors. *J Clin Oncol.* 2000;18(4):854–859.
228. Lurain JR, Schink JC. Importance of salvage therapy in the management of high-risk gestational trophoblastic neoplasia. *J Reprod Med.* 2012;57(5–6):219–224.
229. Wang J, Short D, Sebire NJ, et al. Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). *Ann Oncol.* 2008;19(9):1578–1583.
230. Hoekstra AV, Lurain JR, Rademaker AW, et al. Gestational trophoblastic neoplasia: treatment outcomes. *Obstet Gynecol.* 2008;112(2 Pt 1):251–258.
231. Bower M, Paradinas FJ, Fisher RA, et al. Placental site trophoblastic tumor: molecular analysis and clinical experience. *Clin Cancer Res.* 1996;2(5):897–902.
232. Chang YL, Chang TC, Hsueh S, et al. Prognostic factors and treatment for placental site trophoblastic tumor-report of 3 cases and analysis of 88 cases. *Gynecol Oncol.* 1999;73(2):216–222.
233. Papadopoulos AJ, Foksett M, Seckl MJ, et al. Twenty-five years' clinical experience with placental site trophoblastic tumors. *J Reprod Med.* 2002;47(6):460–464.
234. Hassadia A, Gillespie A, Tidy J, et al. Placental site trophoblastic tumour: clinical features and management. *Gynecol Oncol.* 2005;99(3):603–607.
235. Schmid P, Nagai Y, Agarwal R, et al. Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study. *Lancet.* 2009;374(9683):48–55.
236. Lurain JR, Hoekstra AV, Schink JC. Results of treatment of patients with gestational trophoblastic neoplasia referred to the Brewer Trophoblastic Disease Center after failure of treatment elsewhere (1979–2006). *J Reprod Med.* 2008;53(7):535–540.
237. Kohorn E. Regional centers for trophoblastic disease. *Am J Obstet Gynecol.* 2007;196(2):95–96.
238. Bower M, Rustin GJ, Newlands ES, et al. Chemotherapy for gestational trophoblastic tumours hastens menopause by 3 years. *Eur J Cancer.* 1998;34(8):1204–1207.
239. Woolas RP, Bower M, Newlands ES, et al. Influence of chemotherapy for gestational trophoblastic disease on subsequent pregnancy outcome. *Br J Obstet Gynaecol.* 1998;105(9):1032–1035.
240. Matsui H, Iitsuka Y, Suzuka K, et al. Early pregnancy outcomes after chemotherapy for gestational trophoblastic tumor. *J Reprod Med.* 2004;49(7):531–534.
241. Rustin GJ, Newlands ES, Lutz JM, et al. Combination but not single-agent methotrexate chemotherapy for gestational trophoblastic tumors increases the incidence of second tumors. *J Clin Oncol.* 1996;14(10):2769–2773.
242. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol.* 2010;203(6):531–539.

SECTION IV

SPECIAL MANAGEMENT TOPICS

CHAPTER

28

Breast Cancer

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INTRODUCTION

Breast cancer, a worldwide problem, remains the most common cancer diagnosis in women, affecting more than 1.2 million women diagnosed each year. Treatment paradigms require an understanding of the natural history of the disease, including the various patterns of metastases and recurrence, and both the prognostic and predictive factors that may influence both response to treatment and overall survival (OS). In addition, the complexities that govern medical and surgical decisions make the management of breast cancer far more complicated than that of other disease sites. This chapter will provide the essential information regarding breast cancer, with an emphasis on recent developments. It stresses an interdisciplinary view of disease management by providing the foundational aspects of breast disease and treatment.

EPIDEMIOLOGY

In 2012, an estimated 226,870 women and 2,190 men will be diagnosed with breast cancer in the United States (1). It is estimated that 1 in 8 women will be diagnosed with breast cancer in their lifetimes. Beginning in the late 1990s, a shift in the incidence of breast cancer in the United States was noted. The steady increase in breast cancer diagnoses seen in the 1950s started to decline in 1999 and continued to decline into 2003. The decline in the annual incidence between 2002 and 2003 was limited to women over 50 years of age. Whether the declining use of hormone replacement therapy following publication of the Women's Health Initiative study results, the utilization of mammographic screening, and earlier diagnosis of disease, or whether a combination of these factors, explains this trend continues to be an area of investigation. Mortality from breast cancer has been steadily declining since 1990, at a rate of 3.1% per year in women under 50 years of age and 2.1% per year in older women (1). Still, over 40,000 women will succumb to breast cancer this year, making it second only to lung cancer.

RISK FACTORS

Risk factors for breast cancer have been well characterized. Breast cancer is 100 times more frequent in women than in men. Factors associated with an increased exposure to estrogen have also been elucidated, including early menarche, late menopause, late age at first pregnancy, or nulliparity. The use of hormone replacement therapy has been confirmed as a risk factor, although mostly limited to the combined use of estrogen and progesterone, as demonstrated in the Women's Health Initiative (WHI) study (2). Analysis showed that the risk of breast cancer among women using estrogen and progesterone was increased by 24% compared to placebo. A separate arm of the WHI study randomized women with a prior hysterectomy to conjugated equine-estrogen (CEE) versus placebo, and in that study, the use of CEE was not associated with an increased risk of breast cancer (3). Unlike hormone replacement therapy, there is no evidence that oral contraceptive use (OCP) increases risk. A large population-based case-control study examining the risk of breast cancer among women who previously used or were currently using OCPs was conducted and included over 9,000 women 35 to 64 years of age (half of whom had breast cancer) (4). The reported relative risk was 1.0 (95% confidence interval [CI], 0.8–1.3) among women currently using OCPs and 0.9 (95% CI, 0.8–1.0) among prior users. In addition, neither race nor family history was associated with a greater risk of breast cancer among OCP users.

Apart from endocrine risk factors, sociodemographic risks have also been established. Breast cancer is an age-related phenomenon, with peak incidence after 40 years of age. Family history is also a strong epidemiologic risk factor. Clinical models can now be employed to predict the risk of breast cancer. Among those in common use are the Gail and Claus models (Table 28.1) (5,6). Although they have been widely used in the African-American population and other minority populations, they have not been validated sufficiently.

Beyond classification of risk based on family history (familial risk), the identification of genetic mutations that are passed in an autosomal dominant fashion (hereditary risk) has been

Table 28.1 Models for Estimating Risk for Breast Cancer

	Gail ^a	Claus ^b
Source	Breast Cancer Detection Demonstration Project (n = 284,780)	Cancer and Steroid Hormone Study (n = 9,418)
Personal Risk Factors	Age Age at menarche Prior breast biopsies Age at first live birth	Age
Family History	Number of <i>maternal</i> first-degree relatives with breast cancer	Number of relatives with breast cancer (beyond first-degree relatives) and ages of onset
Calculations	Absolute risk ^c at 5 years Lifetime risk up to 90 years old	Lifetime risk up to 80 years old
Limitations	Excludes paternal history Excludes ovarian cancer history Does not use pathological findings from breast biopsy Does not account for age of onset of breast cancer among family Not validated in other ethnic groups	Excludes other risk factors May underestimate risk in families with 3 or more family members with breast cancer

^aGail MH, et al. Projecting individualized probabilities of developing breast cancer for White females who are being examined annually. *J Natl Cancer Inst.* 1989;81(24):1879–1886.

^bClaus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer.* 1994;73(3):643–651.

^cRisk defined for invasive breast cancer only.

an important scientific finding. Among the most significant was the identification of mutations at *BRCA1*, localized to chromosome 17q21, and *BRCA2*, on chromosome 13q12–13, both of which confer a risk for breast cancer as high as 80% among carriers (7,8). A specific *BRCA1* mutation, 185delAG, has been identified in over 20% of Jewish women younger than 40 years of age at the time of breast cancer diagnosis. Other mutations known to carry an increased risk are those involving p53 in Li-Fraumeni syndrome (associated with other cancers, including sarcoma, leukemia, melanoma, gastrointestinal carcinomas, and brain tumors); *CHEK-2*, *PTEN* mutations associated with Cowden syndrome (associated with macrocephaly, intellectual disability and hamartomas with an increased incidence of endometrial cancer, benign and malignant thyroid disease, and noncancerous brain tumors); and *STK-11* mutations associated with Peutz-Jeghers syndrome (associated with hamartomatous polyps of the gastrointestinal tract, dark-colored spots on lips, mucous membranes and palms/soles, and an increased incidence of gastrointestinal, ovarian, and cervical malignancy).

Work evaluating the long-term effects of environmental factors has established prior radiation exposure as an additional risk factor. The therapeutic use of mantle-field radiation in women with Hodgkin's disease and the sequelae of the atomic bombing of Japan in World War II identified the heightened risks of breast cancer, particularly in young women (9,10).

Among modifiable risk factors, obesity, weight gain in later life, and the consumption of alcohol have been identified in

prospective observational studies (11). The association of environmentally found trace elements and breast cancer risk has also been evaluated, with unconvincing results in general.

An association has been made between breast cancer risk and breast findings. Among the best-described risk factors is the association between breast cancer and a history of biopsies for benign breast disease. In a study by Hartmann et al. the relative risk for breast cancer ranged from 1.27 for nonproliferative lesions, to 1.88 for proliferative lesions without atypia, to 4.24 in lesions with atypia, and this risk persisted for as long as 25 years after biopsy (12). A recent report from Worsham et al. evaluated the same risks in an intercity clinic and reported that African-American women with benign breast lesions faced similar risks in developing breast cancer (13). More recently, Boyd et al. reported on the association between risk and breast density (measured in percentage of the total breast). Using 1,112 matched case-control pairs, they determined the association between risk and reported that women with density of 75% or greater had a significantly increased risk of breast cancer (odds ratio, 4.7; 95% CI, 3.0–7.4), with younger women notably at greatest risk (14).

ANATOMY

The breast is a modified sweat gland composed of 2 components—the large ducts and the terminal duct-lobular unit (TDLU)—surrounded by adipose and fibrous tissue, lymphatics, nerves, and blood vessels. The surface of the breast is attached to the underlying fibrous tissue via Cooper's ligaments, and the mammary gland lies over the pectoralis major muscle extending vertically along the second to sixth ribs, and horizontally from the sternum to the anterior midaxillary line. The axillary tail comprises mammary tissue as well and extends laterally from the chest wall into the axilla. The large duct system of subsegmental, segmental, and lactiferous ducts converges and empties onto the nipple. The TDLU is the most distal part of this branching ductal system and is felt to be the site of origin of most pathologic entities of the breast, including fibrocystic changes, ductal hyperplasias, and the majority of carcinomas (15,16). It is connected to the subsegmental ducts and represents the secretory unit of the gland.

Mobility of the breast tissue over the chest wall is through the retromammary bursa that lies between the superficial and deep fascia. The lymphatic system of the breast is vast, comprising a network over the entire surface of the chest, neck, and abdomen, with increased density under the axilla. There are 3 main lymphatic pathways of the breast: (a) the axillary pathway, which drains the upper and lower halves of the breast into the lateral axillary nodal chain; (b) the transpectoral pathway, which drains into the supraclavicular nodes; and (c) the internal mammary pathway, draining the inner halves of the breast, into the nodes of the internal mammary chain.

NATURAL HISTORY OF BREAST CANCER

Breast cancer can occur with predictable features. For example, it is more likely to be diagnosed in the central or outer quadrants of the breast than in the inner regions (17). It has also been reported to be more commonly involving the left breast. One study of 2,139 cases of breast cancer in Iceland showed 13% more breast cancers occurred in the left breast versus the right (18).

Within the breast, cancer travels along ducts (intraductal carcinoma), and the process of invasion begins when the tumor

erodes through the basement membrane. Continued growth results as the tumor spreads along adjacent lobules, breast lymphatics, perineural tumors, and vascular spaces. When it involves the dermal lymphatics, the overlying dermis becomes edematous and red with the classic appearance of *peau d'orange*. Continued growth of the primary tumor can result in the involvement of the pectoralis and intercostal muscles, ribs, and the clavicle.

While less frequently encountered, locally advanced or metastatic disease at diagnosis still occurs in clinical practice. Tumor spread can occur locally by direct extension, lymphatically, or via intravascular means. Lymphatic spread of tumor from the breast travels to the locoregional nodes of the chest—the axillary, intramammary, and supraclavicular nodal basins—and increasing tumor size is a well-known predictor of nodal involvement. A medial or central lesion of the breast is more likely to metastasize to the internal mammary nodes than outer quadrant lesions, and this has been theorized to explain their worse prognosis compared to upper outer breast tumors (17). Vascular invasion can be observed, even with small tumors.

Metastatic disease from breast cancer can occur in any organ site. Lee reviewed the published autopsy series involving over 2,000 women who had died of breast cancer (19). The most commonly involved organs were the lungs, bones, nodes, and liver. The pleural space, adrenal glands, and brain represented the next most commonly involved sites. Bloom et al. compared a group of women with untreated breast cancer to a cohort of patients treated with radical or modified radical mastectomy, with or without irradiation, and reported an overall 10-year survival of 3.6% in the untreated cohort versus 34% in the treated group.

Theories on the spread of breast cancer have been used as a foundation for subsequent treatment and have evolved over time. Dr. William Halsted defined the notion that cancer arose from one location and travelled contiguously by lymphatics to reach local and distant locations. Hence, treatment with the *en bloc* resection of the breast and lymphatics was felt to present the best opportunity for cure. Still, it was clear that even with aggressive surgery and removal of the lymphatics from the breast, women still died of breast cancer. In a seminal paper by Valagussa et al., the OS was reported to be 60% among women with node-negative disease, 54% in those with up to 3 nodes positive, and 26% in those with more than 3 positive nodes. This showed that contiguous lymphatic spread alone could not explain survival outcomes (20).

The theory of breast cancer as a systemic disease was brought forward in 1980 by Dr. Bernard Fisher (21). Breast tumors were seen as a marker of this systemic syndrome, just as neuropathy would be a marker of advanced diabetes mellitus. Hence, nodal disease was not simply an extension of a primary breast cancer process, but rather a marker of disease already spread. This theory holds that achieving local control will not impact OS and argues for the use of systemic treatment in order to affect the best outcome. Recently, however, a meta-analysis on the use of adjuvant radiation by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has called this theory into question. In that analysis, the use of adjuvant radiation not only improved local control but also reduced annual mortality by 13% after the second year of follow-up (22).

It is likely that breast tumors express variable degrees of malignancy. Hellman argued that “synthesis” between Halsted and Fisher's theories was required (23). Recognizing that tumor size is proportional to the risk of metastases, he argued that small and large tumors behave differently, and carried different prognoses. Small tumors were a manifestation of a locoregional process and therefore were curable with treatment. Larger tumors, on the other hand, comprised cells more likely to proliferate and be more malignant—features that made them more likely to metastasize. As such, these were likely to be associated with systemic disease. Defining cure as “that proportion of the

treated group that has the same survival as an age-adjusted peer population,” he estimated that over 80% of women with tumors less than 1 cm in size were curable and that this was manifest at 10 years of follow-up. In summary, he once again stressed the importance of local control for small tumors, while emphasizing the importance of systemic control in breast cancer.

CLINICAL PRESENTATION OF BREAST CANCER

Today the most common presentation is with an abnormal mammogram, although patients continue to present with a painless or slightly tender breast mass. In younger women, a delay in diagnosis may be attributed to benign causes, such as recent trauma or changes with pregnancy, or due to breast-feeding. For those women presenting with a mass, the patient may ultimately present with breast tenderness, skin changes, bloody nipple discharge, or changes in the shape and size of the breast, with or without axillary adenopathy. Rarely will women present with axillary nodal disease but no evidence of a breast primary, otherwise known as occult breast carcinoma. Lastly, inflammatory breast cancer (IBC) presents as a tender, red, and swollen breast, often mistaken for mastitis. A crusting rash emanating from the nipple is *sine qua non* for Paget's disease of the breast, which is almost uniformly associated with an underlying malignancy. Fortunately, with the increase in screening following publication of the NIH Consensus Statement in 1978, patients rarely present with metastatic disease (24).

IMAGING STUDIES OF THE BREAST

Introduction

Breast imaging can be performed as a screening tool in asymptomatic women to detect early cancer, in high-risk women, or as a diagnostic examination in women suspected of having breast cancer or previously treated for breast cancer. Mammography, an X-ray examination of the breast obtained either by conventional film or by digital technique, remains the most widely used technique for screening and is the only modality proven to decrease mortality. The benefits of screening mammography and the differences between film and digital technique will be discussed. The reported benefits of digital mammography in selected groups of women will be presented. Computer-aided detection (CAD), a tool designed to help the radiologist improve the detection of breast cancer, is frequently used by interpreting radiologists; the benefits and consequences will be reviewed.

Modalities such as ultrasound (US) and magnetic resonance imaging (MRI) serve as adjunct tools in the diagnostic setting or high-risk screening. An emerging technology, breast tomosynthesis, has recently been approved by the United States Food and Drug Administration (FDA) for clinical use in patients. A review of this potentially revolutionary tool will be presented.

Mammography

The purpose of screening mammography is earlier detection of clinically unsuspected breast cancer in asymptomatic women. The efficacy has been widely established by multiple randomized controlled trials demonstrating absolute mortality reduction, achieved by mammography's ability to detect both ductal carcinoma *in situ* (DCIS) and invasive breast cancer at a smaller size and earlier stage than in unscreened groups of women. Screening mammography is associated with an 18% to 45% reduction in breast cancer mortality compared with unscreened

groups (1–3). Many of the trials were performed in Swedish populations, one study including analysis of 2,044 breast cancer deaths from 14,092 incident tumors, spanning over 7.5 million person-years (1). These studies have analyzed large-scale populations with and without screening over long time intervals.

For the past decade, based on these trials annual screening mammography in women beginning at 40 years of age has been recommended by the American Cancer Society (ACS), American College of Radiology (ACR), and most national medical societies (4). In November 2009, the United States Preventive Services Task Force (USPSTF) published a highly controversial statement with new recommendations for screening for breast cancer (5). Their new recommendations are:

Biennial screening mammography for ages 50 to 74, against routine screening mammography in women aged 40 to 49, with decision to start before age 50, based on individual risk factors, and to involve a discussion with a health care provider, against breast self-examination.

The new guidelines caused an upheaval in the medical community, with primary-care physicians unclear as how to guide their patients, and patients unsure of whether they should be screened at ages 40 to 49. The task force recommendations against routine screening at ages 40 to 49 are cited on the “harms” outweighing the benefits in this age group. Since there are fewer cancers in this age group, there are fewer lives saved with screening, with the “harms” of anxiety and distress over false-positive results, additional imaging studies, and biopsies said to be too significant to recommend routine screening. The USPSTF estimates the “number needed to invite for screening to extend one woman’s life” as 1904 for women aged 40 to 49, and 1,339 for women aged 50 to 59. The radiology community strongly disagrees with the USPSTF conclusion that there is not enough benefit in screening women in their 40s to warrant the “undue stress.”

Rebuttals by the radiology community, including the ACR and Society of Breast Imaging (SBI) as well as the American Congress of Obstetricians and Gynecologists (ACOG) and the National Cancer Institute (NCI) called the new recommendations “a step backward,” representing significant harm to women’s health, and raised concern that if adopted by the American public, they would result in needless deaths (6–8). Although the number needed to screen is higher in women in their 40s (1,904) than in their 50s (1,339), there is still sufficient benefit to those in their 40s to offer annual screening. At this time, screening based on risk is unfounded, since 75% of women diagnosed with breast cancer have no identifiable risk factors; screening only those with known risk factors will miss most of the women who will develop breast cancer (9).

Prior to 1997, controversy existed regarding screening mammography in women 40 to 49 years of age. This was largely due to most of the earlier trials not including enough women in this age group to demonstrate a statistically significant reduction in breast cancer mortality from screening. Subsequent studies (1,10) included a large enough population to demonstrate the benefit of screening this age group. The cost-effectiveness of age-related screening mammography has been assessed using the Markov model. The marginal cost per year-life saved (MCYLS) varies from \$18,800 to \$16,100 for age groups including women ages 40 to 79, within the range of other generally acceptable diagnostic and therapeutic medical procedures (10).

Therefore, current recommendations for screening remain unchanged: annual screening mammography for women beginning at age 40.

It is important to recognize that not all cancers will be found by mammography, the sensitivity being approximately 80% to 90%. Therefore, up to 10% to 20% of cancers will not be visible mammographically (11–13), largely because of insufficient contrast between normal and abnormal breast tissue. In a screening population, up to 10% of patients will be “recalled”

for additional imaging—either additional mammographic views, spot compression views to determine if the area represents superimposed tissue versus a true mass or magnification views to better characterize calcifications, or US evaluation to determine the solid or cystic nature of a mass. Of all positive screening examinations, approximately 5% to 10% will have a diagnosis of cancer. Of all recommended biopsies, 25% to 40% will be positive for cancer. It is anticipated that the addition of tomosynthesis to two-dimensional conventional mammography will effectively decrease the “recall” rate and positive screening rate, and decrease the anxiety caused to patients. It is also expected to increase the sensitivity of mammography.

Mammography Regulations and Reporting

Mammography practice in the United States is rigidly regulated by the FDA under the Mammography Quality Standards Act (MQSA) of 1992 (14). The MQSA tightly regulates mammography, requiring extensive follow-up and outcome monitoring of all facilities and interpreting radiologists. Recall rates, biopsy recommendations and results, and cancer detection rates must be analyzed for each interpreting radiologist. Cancer staging must be recorded to include histologic type, size, nodal status and grade. MQSA requires analysis of any known false-negative mammograms. Requirements include that the facility must send a letter to each patient informing her of the results of her mammogram, in addition to a formal report to the referring physician. It is federally mandated that the report include a final assessment category providing guidance and management recommendations.

The Breast Imaging Reporting and Data System (BIRADS), first published in 1993, is a lexicon developed by the ACR to standardize terminology used in reporting findings on mammograms (15). It includes terms for describing features of masses (shapes and margins) and calcifications (morphology and distribution). It defines final assessment categories to describe the radiologist’s level of suspicion about a mammographic abnormality, to comply with the federally mandated MQSA regulations (15). All mammograms must be assessed with a final BIRADS category of 0 to 6 (Table 28.2).

The report must include the date of comparison films, the indication for the examination (screening, recall, clinical finding, or follow-up), an assessment of overall breast composition to indicate the relative possibility that a lesion may be hidden by normal tissue limiting the sensitivity of the examination (Table 28.3), a description of any significant findings, and an overall summary impression.

Mammographic Technique and Findings

The screening mammogram is an X-ray of the breast, with two views of each breast obtained: a top-to-bottom, or cranio-caudad (CC) view, and an angled side-to-side, or mediolateral oblique (MLO), view. The breast is pulled away from the body, compressed, and held between two plates while the image is obtained. The images can be recorded on film or stored digitally on a computer. Two views of each breast are needed to optimize the amount of breast tissue included on each mammogram, to minimize overcalling disease because of superimposed tissue on a single view, and to decrease the likelihood of obscuring a cancer by overlapping tissue on a single view. In some patients, particularly those with larger breasts, more than 4 views are obtained by the technologist to ensure that all the breast tissue is included on the images.

A mammographic mass is defined as a space-occupying lesion seen in two projections, whereas an “asymmetry” is a potential mass seen only in a single projection. For masses, the shape, margins, and density may be described. Masses which are irregular in shape, with indistinct or spiculated margins, and

Table 28.2 BIRADS (Breast Imaging and Reporting Data System) Assessment Categories

Category	Interpretation
0	Mammographic assessment is incomplete Needs additional imaging evaluation and/or prior mammograms for comparison Used in screening situations
1	Negative No mammographic evidence of malignancy
2	Benign finding(s) “Normal” assessment, but describes a benign finding No mammographic evidence of malignancy
3	Probably benign finding—initial short interval follow-up suggested Finding with <2% risk of malignancy, not expected to change over interval
4	Suspicious abnormality—biopsy should be considered Findings do not have classic appearance of malignancy, but greater probability than Category 3
4A	Finding needs intervention but with low suspicion for malignancy
4B	Findings with intermediate suspicion for malignancy
4C	Findings with moderate suspicion for malignancy, but not classic
5	Highly suggestive of malignancy—appropriate action should be taken Finding had greater than 95% probability of being malignant
6	Known biopsy-proven malignancy—appropriate action should be taken Used for lesions identified on imaging studies with biopsy proof of malignancy prior to definitive therapy

Note: It is federally mandated that all mammography reports give a final assessment category.

Source: American College of Radiology BIRADS—Mammography. 4th ed. Reston, VA: American College of Radiology; 2003.

of high density are the most worrisome for malignancy, whereas round or oval masses with circumscribed (well-defined) margins are more likely benign. Calcifications can be described by type and distribution. Those that are larger, coarser, smoothly marginated, and more easily seen are likely benign, as opposed to those that are very fine, pleomorphic (varying in size and shape), or linear, which are more likely to be malignant. The distribution may be telling, as the diffuse and scattered calcifications are more likely innocent, and those grouped or clustered, arranged in a line (linear), or segmental fashion are more worrisome. The size of any abnormality, location by quadrant or clock-face, and depth should be included in the description. Associated findings suggestive of malignancy, or secondary signs of malignancy, are skin retraction, nipple retraction, skin thickening, trabecular thickening, axillary lymphadenopathy, and architectural distortion.

Table 28.3 Mammographic Assessment of Overall Breast Composition. The Overall Assessment of Volume of Attenuating Tissues in Breast, which Indicates the Relative Possibility that a Lesion is Hidden by Normal Tissue and Indicates the Sensitivity of the Examination

Mammographic Description	Glandular Proportion of Total Breast Tissue
The breast is almost entirely fat	<25%
Scattered fibroglandular densities present	25%–50%
The breast tissue is heterogeneously dense; this may obscure detection of small masses	51%–75%
The breast tissue is extremely dense; this may lower the sensitivity of mammography	>75%

Source: American College of Radiology BIRADS—Mammography. 4th ed. Reston, VA: American College of Radiology; 2003.

Diagnostic Mammography

Diagnostic mammography is reserved for women with clinical signs or symptoms that suggest breast cancer (palpable mass, skin thickening, nipple retraction, or nipple discharge). Recalls occur when patients are recalled for further mammographic evaluation because of an abnormal screening examination or personal history of breast cancer. Patients with breast augmentation may be considered diagnostic because of more effort and time involved with obtaining necessary views, but should be audited in the screening group.

Film versus Digital Mammography

Film mammography is extremely effective and has been widely accepted as a screening modality for the past 20 to 30 years. With this technique, the mammography images are recorded as hard copy on film and developed by the technologist, then presented to the radiologist for review. Digital mammography uses a digital detector to replace the screen-film of conventional mammography. Radiation transmitted through the breast is absorbed by an electronic detector, with a response faithful over a wide range of intensities. The recorded information can be displayed using computer image-processing techniques to allow arbitrary settings of image brightness and contrast without need for further exposure to patients. The lower system noise would be expected to enhance the visibility of subtle contrast differences between tumors and normal background tissue. The processes of image acquisition, storage, and display are separated, allowing optimization of each (16,17). The average patient dose of radiation is slightly lower than that of film mammography. Examination time for each patient is shorter, permitting increased patient throughput. Images are more easily archived and accessed in picture archiving and communication systems (PACS). The disadvantages of digital mammography are cost of equipment. The cost of a digital system is 1.5 to 4 times as much as a film system (18).

Early clinical trials showed only equivalent diagnostic accuracy between digital and screen-film mammography (19–24). The Senographe 2000D screening trial demonstrated a significantly significant decrease in recall rate for digital (11.8%) versus screen-film (14.9%), as well as a decrease in biopsy rate (19).

However, more recently, the results of the Digital Mammographic Imaging Screening Trial (DMIST) have been published in the *New England Journal of Medicine* demonstrating a benefit of digital over screen-film mammography in certain groups of women (18). In this study, 49,528 asymptomatic women presenting for screening mammography at 33 sites in the United States and Canada underwent both digital and film mammography, with the examinations interpreted independently by two radiologists. While in the entire population, the diagnostic accuracy of digital and film mammography was similar, the accuracy of digital mammography was significantly higher than that of film mammography in the following groups: women under the age of 50 years; women with heterogeneously dense or extremely dense breasts on mammography; and premenopausal or perimenopausal women. This is felt to be a significant study in the radiology community because the increased density seen on mammography is known to decrease the sensitivity of the technique in these patients (25,27), who have also been shown to have an increased risk of breast cancer because of their breast density (26–29). The results are understandable because the technical advantages of digital mammography permit X-ray transmission manipulation to enhance visualization of subtle changes in tissue over the entire breast. It is known that the major limitation of mammography is that cancer can be hidden by adjacent breast tissue; with digital mammography, the visibility of a mass or cancer present in an image can be increased if contrast is adjusted.

The effect of transition to digital mammography from film screen has been more recently studied (30). An audit of the practices data from baseline year of film screen, year 1 digital, year 2 digital, and year 3 digital was examined. In this practice, there was an increase in the recall rate with digital mammography (6.05 recall rate with film screen, to 7.1% to 8.5% with digital technique), which persisted as a higher rate even at year 3. However, the cancer detection rate also increased for at least 2 years after the transition to digital, suggesting that cancers were more often obscured with film screen mammography than were visible by digital technique. Overall, calcifications were significantly better seen by digital technique, an important point because calcifications often mark earlier, more treatable disease.

Computer-Aided Detection

CAD, approved by the FDA in 1998, identifies suspicious findings on mammograms to assist the radiologist's interpretation. Initial studies demonstrated increased sensitivity of cancer detection when CAD was added to screening programs, at a cost of increased recalls and increased rate of biopsy (31–33). Increased rates of cancer detection were reported at between 7.62% and 19.5% (34–37). Cupples et al. showed a particular improvement of small cancer detection by CAD, with a 164% increased cancer detection rate of invasive cancers less than 1 cm (37). Because of the reported improvement of breast cancer detection, Medicare and many insurers reimburse for use of CAD.

A larger-scale study conducted by Fenton et al. determined the association between use of CAD at mammographic facilities and performance of screening mammography during 1998 to 2002 (38,223,135); women were screened at 43 facilities in 3 states, with and without the assistance of CAD. The specificity of screening decreased from 90.2% without CAD to 87.2% with CAD, while the biopsy rate increased by 19.7% with CAD. There was no statistically significant change in sensitivity with or without CAD, although there was a trend towards an increase in sensitivity. Overall, the increased rate of biopsy resulting from use of CAD was not clearly associated with improved detection of invasive cancer. However, it should be noted that CAD was used more by community radiologists than academic radiologists in this study, which may account for some of the differences reported by others. Of the cancer detected by CAD, there was a trend towards more DCIS detection than invasive cancer,

which may be more clinically important as early detection may decrease mortality. Although there were a large number of women included in the study, the number of cancers was still relatively small, making it more difficult to judge whether the benefits of routine use of CAD outweigh its harms.

Ellis et al. (39) compared detection of small (less than 16 mm) invasive cancer by two different, FDA-approved CAD systems commercially available and demonstrated a statistically significant higher sensitivity for R2 than for iCAD Second Look.

Results from the Computer Aided Detection Evaluation Trial II (CADET II) study (40) demonstrate that double reading versus single reading plus CAD of mammographic exams are equivalent. This randomized, multicenter prospective study analyzed 227 cancers detected in 28,204 women by lesion type. Overall, there was no significant difference in the double reading regimen versus the single reading with CAD regimen for identification of masses or microcalcifications. However, more parenchymal deformities were detected in the double reading regimen, while more asymmetric densities were found by single reading plus CAD. In addition, there was a significant trend for improved cancer detection in women with dense breasts with double reading.

An analysis of prospectively overlooked CAD marks on prior screening mammograms in women subsequently diagnosed with breast cancer consisted of 50,100 screening mammograms over a 3-year time interval (41). A total of 75 mammograms of women subsequently diagnosed with breast cancer were analyzed by 3 radiologists. These mammograms were initially interpreted using CAD as negative. In 61%, the mammograms had visible findings in retrospect, with 46% determined actionable and 54% under-threshold; CAD correctly depicted 64% of these visible findings and also demonstrated a higher sensitivity for actionable findings (90%) than under-threshold (60%). CAD more often marked the actionable findings on both views (58%) versus under-threshold (27%). This suggests that when a finding on a screening mammogram shows a CAD mark on both the cranioaudad and MLO views, more attention should be paid.

The use of CAD has increased across the country by radiologists. An examination of the database of the nationwide Medicare Part B fee for service from 2004 to 2008 (42) found that by 2008, CAD was used in three-fourths of all screening and half of all diagnostic mammography examinations in the United States. CAD was used more often in the private office setting than in the hospital setting. "Double reading," demonstrated to increase cancer detection, is costly and time consuming; CAD may be a reasonable alternative. CAD is likely to continue to be used and may replace "double reading" currently in practice at some institutions.

Ultrasound

Ultrasonography is a valuable adjunct to mammography, largely due to being widely available and relatively inexpensive. It is usually used clinically as a targeted examination, most often to determine the cystic versus solid nature of a mass. It has been shown to be effective in determining features of masses to determine likelihood of benign versus malignant (43). Prevalence screening studies in women with radiographically dense breasts have shown that 3 to 4 cancers/1,000 women are detected by US only (43–48). However, the limitations of breast US as a screening tool are well known, as it requires a skilled operator, is labor intensive, and lacks standardized examination technique and interpretation criteria. Moreover, it does not detect microcalcifications, which can signal the earliest forms of cancer, the *in situ* disease. It has a high false-positive rate (44–47) and is less sensitive than breast MRI. Given these factors, it is unlikely that screening breast US will become widely used in the United States, particularly with the more sensitive breast MRI availability and recent FDA approval of tomosynthesis.

Tomosynthesis

Tomosynthesis is a 3-dimensional mammographic technique allowing better visualization of breast lesions by minimizing effects of overlapping tissue. The acquisition of images mimics conventional mammography with breast positioning and compression. Multiple low-dose images are obtained at different angles during a sweep of the X-ray tube, resulting in a digital data set which can be reconstructed into tomographic sections through the breast. Digital breast tomosynthesis (DBT) was approved for clinical use in February 2011.

A single vendor, Hologic, received FDA approval for Combo mode, requiring both conventional two-dimensional digital mammography in 2 projections (craniocaudal and MLO) to be obtained in the same compression with 3-dimensional tomosynthesis images. There is no additional positioning involved for the patient.

The limitations of conventional mammography are low-positive predictive value and low sensitivity, primarily because normal breast tissue elements outside of the plane of interest can obscure an abnormality, or superimposed tissue elements may give the appearance of an abnormality. It is expected that tomosynthesis will reduce false-positive mammograms, and thus decrease the recall rate, because it would minimize the effects of overlapping tissue.

Poplack et al. (49) compared the image quality of tomosynthesis with conventional mammography and estimated the recall rate of screening when tomosynthesis is used in addition to mammography. Ninety-eight women with 99 screening recalls were evaluated with tomosynthesis of the affected breast. The image quality of tomosynthesis was found to be equivalent in 52% and superior in 37% of patients. Also, many findings would not be recalled with tomosynthesis, allowing a reduction in recall of 40%. Masses were better seen on tomosynthesis because of recognition of tissue overlap. Calcifications were better seen on diagnostic mammography, accounting for most of the cases in which tomosynthesis was of inferior quality. This may be due to motion related blur due to the somewhat long (19 seconds) exposure time of the tomosynthesis, and also because in this study, the images were reconstructed at 1 mm slice thickness, which may be too thin to show the clustered distribution of calcifications. It will likely be needed to include a thicker reconstruction in the data set to permit better visualization of calcifications. It is believed that tomosynthesis will have more impact in women with dense breast tissue.

As currently approved for clinical use, tomosynthesis is performed in two projections. Rafferty (50) presented data on 34 patients scheduled for biopsy by performing tomosynthesis in both the CC and MLO projections, finding that most lesions (65%) were equally visible on both, but 9% were only seen on the CC view and would have been missed by the MLO view alone; all of these potentially missed lesions were malignant. The available data suggest tomosynthesis will require imaging in both projection for optimal lesion visualization.

Preliminary data suggest that tomosynthesis will improve screening mammography, and that it may also be an important diagnostic tool. In a subjective side-by-side review of 25 cases by 4 interpreting radiologists, Hakim et al. (51) compared the use of two-dimensional digital mammography with either tomosynthesis or additional spot compression views in the diagnostic setting. The combination of two-dimensional mammography with tomosynthesis was rated better or equivalent to conventional diagnostic workup in 81% of lesions observed. In 12% of cases, the use of tomosynthesis would eliminate the need for US. Noroozian et al. (52) evaluated the use of tomosynthesis in the diagnostic workup in 67 masses, comparing tomosynthesis to conventional spot compression views. Their preliminary findings suggest the additional mammographic views may not be necessary to characterize masses when tomosynthesis becomes

clinically integrated. The utility of additional mammographic views (recalls) was well established in the late 1980s and has been the mainstay of diagnostic breast imaging for mass characterization. These spot compression views reduce the superimposition of overlapping tissue, enhancing margin visibility and image detail. However, the recall examination induces much anxiety in many patients, causing criticism of traditional mammography over the years. The addition of tomosynthesis in the screening setting is expected to notably decrease the call-back rate.

Tomosynthesis is currently being implemented in larger imaging centers across the United States. It is expected that within a few years there will be more data available to better determine the utility of tomosynthesis. It is unknown whether there will be additional cost or reimbursement for the procedure. The technique as of now is being reimbursed as for two-dimensional digital mammography. However, the equipment is expensive and the reading time for the radiologist is increased, with additional images to be interpreted. As more breast imagers become adept at the technology, a clearer sense of the increased reading time will be available.

Given its ability to minimize the effects of overlapping tissue, tomosynthesis is expected to be more beneficial in women with dense breasts, and may not yield more information in women with fatty breast tissue, where lesions are less likely to be obscured by overlapping tissue. However, more large-scale trials will need to be performed to evaluate who will best benefit from the examination.

Breast MRI

MRI of the breast has evolved over the past 2 decades, from a research tool to the most sensitive imaging modality in the detection of breast cancer. Contrast-enhanced breast MRI is the most accurate modality in the clinical evaluation and staging of breast cancer (1). For breast lesion detection, intravenous injection of Gadolinium-based contrast enhancement allows visualization of breast cancer against the background of glandular tissue. This distinction relies on the determination that tumor angiogenesis and surrounding tissue permeability allow contrast uptake within cancer (2). That is, a significant number of invasive tumors demonstrate rapid wash-in of contrast by 2 minutes and wash-out with time (3). Significant overlap between the enhancement pattern of benign and malignant processes exists, which must be recognized, and which lowers the specificity of breast MRI. In addition, background enhancement works against lesion detection by obscuring abnormal areas of enhancement, particularly in premenopausal women, due to the hormonal effect on the glandular tissue. Therefore, to minimize this effect, it is recommended to image premenopausal women during days 7 to 14 of the menstrual cycle for routine breast MRI exams.

Variable protocols for MR imaging of the breast exist. However, technical standards have been set by the ACR for proper imaging, interpretation, and accreditation (4,5). MR imaging of the breast should be performed with a dedicated breast coil, using at least 1.5 T magnet, and imaging parameters should be instituted to optimize high spatial and temporal resolution. MR imaging with 3 T magnet is evolving and slowly spreading; however, its advantage over the more commonly used 1.5 T magnets is not known yet.

Technical advances in breast MRI have led to improved sensitivity for the detection of invasive breast cancer, currently reported to range from 89% to 100% (6,7). Although previous studies in DCIS showed low and variable sensitivities, with improved techniques, contemporary studies report higher sensitivity of up to 89% with a range of sensitivity between 60% and 100% (8,9,10). In that regard, MRI is superior to mammography

in delineating DCIS extent (10). Moreover, recent advances introduced the use of CAD in interpretation of breast MRI. This technology uses special software analysis of the lesion kinetics and performs post processing of the images, therefore, allowing the radiologist to determine the kinetic curve type. Some data suggest that CAD may improve discrimination between benign and malignant masses (11); however, a metaanalysis by Dorrius et al. showed little added value for experienced radiologists and may be more helpful for less-experienced readers (12).

Breast MR lesion characterization and assessment is based on the ACR BIRADS MR lexicon which incorporates terminology and specific descriptors of breast MRI findings, in addition to assigning a final BIRADS category in the assessment, similar to mammography. By definition, an enhancing focus is less than 5 mm. A mass is a space-occupying lesion, 5 mm or more in size. Non-mass-like enhancement (NMLE) can be clumped foci or ductal enhancement. Masses are evaluated based on shape, margin characteristics, internal enhancement, and kinetic analysis. To mention some descriptors of malignancy, an irregular mass, spiculated margins, heterogeneous/rim enhancement, and rapid wash-in and wash-out kinetics are characteristic of malignancy (Fig. 28.1). NMLE, which is more typical of DCIS, can be focal, linear, or ductal enhancement in a ductal or segmental distribution (Fig. 28.2) (13). As such, analysis of breast MR enhancing lesions involves analyzing both lesion morphology and kinetics of enhancement to provide the most specificity in lesion characterization (14).

Screening Breast MRI

Breast MRI is a validated screening modality in addition to mammography in patients at high risk for breast cancer, and the combination of the two screening tests has been shown to be the most accurate way to detect breast cancer in these patients (15). Cancer yield achieved by MRI alone was significantly higher compared to the yield from mammography or US in a prospective multicenter cohort trial by Kuhl et al. (16). In a study by Morris et al., mammographically occult breast cancer was detected by screening breast MRI in 4% of high-risk women, with a positive predictive value (PPV) of 24% (17). For women with *BRCA1* gene mutations, MRI is a very sensitive screening tool when used in conjunction with mammography. In a multicenter multimodality prospective trial by Sardanelli et al., which looked at screening in women with genetic-familial risk for breast cancer, MRI sensitivity of 94% and PPV of 63% were found (18). Many studies confirm that breast MRI is a validated

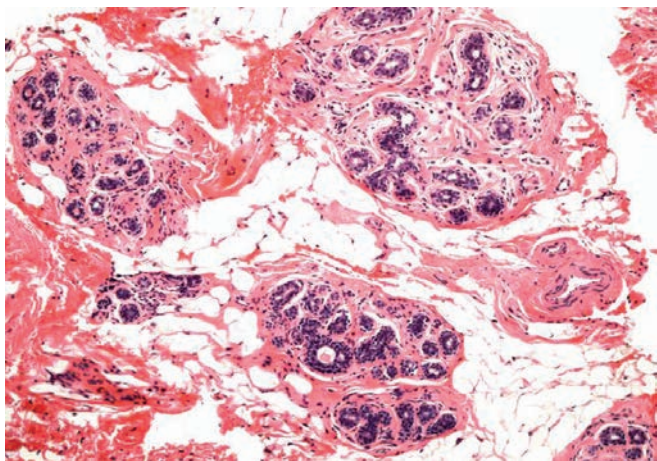


FIGURE 28.1 Normal breast lobules. Three terminal duct-lobular units are surrounded by adipose and fibrous tissue.

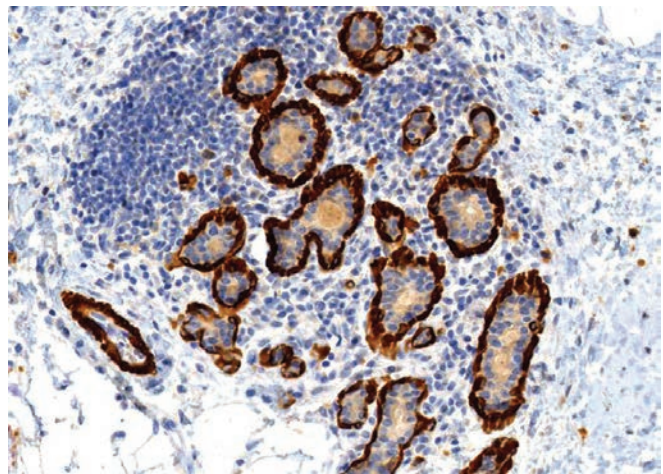


FIGURE 28.2 Normal breast lobule. The presence of myoepithelial cells is illustrated by positive staining for smooth muscle myosin heavy chain.

screening tool in selective women at high risk for breast cancer (19–22).

In 2007, the ACS published new guidelines for high-risk screening with MRI based on scientific evidence and expert opinion (Table 28.4) (23). According to these new guidelines, high risk is defined as a lifetime risk of 20% to 25% or more, *BRCA* gene mutation carrier or first-degree relative of *BRCA* carrier, women treated at early age with chest radiation, and hereditary syndromes that place women at high risk for breast cancer. Currently, not enough data exist to support or refute annual breast MRI in women with a personal history of breast cancer or with high-risk lesions, and these patients are to be assessed on a case-to-case basis.

Breast MRI also serves to screen the contralateral breast in women with recently diagnosed breast cancer. A recent multicenter prospective trial evaluating contralateral breast cancer in women with recently proven breast cancer found clinically and mammographically occult breast cancer in 3.1% of 969 women, with a sensitivity of 91% and a negative predictive value (NPV) of 99% (24).

Diagnostic Breast MRI

Preoperative Evaluation of Breast Cancer

There are several clinical scenarios in which breast MRI is useful in addition to mammography, with the most common indication being preoperative staging of a newly diagnosed invasive cancer or DCIS. Breast MRI can delineate clinically and mammographically occult additional disease, including *in situ* disease associated with invasive cancer, and can detect non-calcified DCIS. In that regard, MRI is superior to mammography or US in defining local extent of the disease and can identify additional sites of disease in 14% to 27% (25). Liberman et al. found that 48% of women who underwent preoperative MRI of the breast had additional foci of disease unsuspected by mammography (26). In a study by Girardi et al. additional mammographically occult cancer was detected in 9% of patients staged with MRI preoperatively (27). As such, the addition of breast MRI can aid in surgical planning, including decisions regarding the role of mastectomy or the consideration for neoadjuvant chemotherapy. In one study by Braun et al. looking at the influence of preoperative MRI on surgical management, clinical management was changed in 27.5% of patients (28). It is advisable to biopsy additional suspicious foci detected by MRI

Table 28.4 Indications for Annual Breast MRI Screening in Association with Mammography**Evidence-Based Recommendations:**Confirmed *BRCA* mutation carrier statusUntested but with first-degree relative with positive *BRCA* mutation status

Estimated lifetime risk of developing disease >20% (based on risk models)

Expert Opinion:*Recommended*

Prior radiotherapy to the chest wall (between ages 10 and 30)

Patients (and first-degree relatives) with predisposing cancer syndromes:

Li-Fraumeni Syndrome

Cowden Syndrome

Bannayan-Riley-Ruvacalba Syndrome

No recommendation (for or against)

Estimated lifetime risk 15% to <20% (based on risk models)

Lobular proliferative disease (LCIS or ALH)

Atypical ductal hyperplasia

Mammographic heterogeneity or density

Women with personal history of breast cancer (including DCIS)

Not recommended

Estimated lifetime risk <15%

Source: Hellman S. Karnofsky Memorial Lecture. Natural history of small breast cancers. *J Clin Oncol*. 1994;12(10):2229–2234.
 LCIS, lobular carcinoma *in situ*; ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma *in situ*

to avoid overestimation of disease and unnecessary mastectomy. With that in mind, the debate over the usefulness of MRI preoperatively continues. Opponents of MRI staging consider that additional foci of disease are treated with radiation and that the MRI-detected cancers may not be biologically important. Following the European Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial published in 2010, which concluded that MRI did not decrease surgical negative margins and led to unnecessary mastectomies, selective patients are referred for preoperative MRI, and many others are not being staged with MRI. Preoperative MRI should still be considered in women less than 50 years of age, in women with dense breasts, and with histological diagnosis of invasive lobular cancer. The effect of MRI staging on patient mortality outcome is still unknown. To date, breast MRI remains the most accurate tool to delineate extent of disease of breast cancer; however, radiologists have to be aware that additional multicentric foci may not necessarily validate mastectomy as most foci may be treated by radiation. Additional studies are needed to elucidate outcome of patients in terms of recurrence and mortality.

MRI is not the best test for the exclusion of malignancy in the work-up of mammographic calcifications or other mammographic abnormality, and suspicious findings should undergo core biopsy. A helpful role of MRI in such clinical scenarios would be to delineate the extent of disease and to rule out an underlying occult invasive component. For women presenting

with suspicious clinical findings for breast cancer and negative conventional imaging tests, MRI of the breast has an added value. These instances include a woman with a palpable suspicious mass, women with metastatic axillary lymph nodes but no mammographically defined breast primary cancer, and those with pathological unilateral nipple discharge or Paget's disease, and a negative mammogram and US.

MRI: Other Indications

In patients presenting with an increasing mammographic density at the lumpectomy site following breast-conserving therapy (BCT), MRI is better than mammography or US for recurrent disease with high specificity and NPV. In addition, MRI has a role in determining the response to neoadjuvant chemotherapy, and it is more reliable than mammography or US in that respect. However, while MRI may not show residual enhancement following chemotherapy, it is not 100% accurate in the detection of residual disease, and a 23% risk of underestimation has been reported (29).

MRI-Guided Core Biopsy

MR evaluation of the breast should not be offered as a service without the capability for MRI-guided breast biopsy. The procedure is performed for MRI-only detected suspicious abnormalities which do not have a correlate on conventional imaging. MR biopsy procedure has been widely applied in Europe and the United States, and is an accurate and safe test with an NPV of 93% and PPV of 100% (30). The outcome of positive MR breast biopsy has been evaluated, with a trend towards DCIS in most positive biopsies found across several studies. Upgrade rates of DCIS to invasive cancer of 17% were found by Lee et al. (31) and of ADH to cancer in up to 38% (32,33). Therefore, pathology and imaging correlation by the radiologist is key to the management recommendation of a biopsied lesion with MRI.

BREAST PATHOLOGY

The breast is a modified sweat gland composed of 2 components: the large ducts and the TDLU, surrounded by adipose and fibrous tissue. The large duct system of subsegmental, segmental, and lactiferous ducts converge and empty onto the nipple. The TDLU is the most distal part of this branching ductal system. It is connected to the subsegmental ducts and represents the secretory unit of the gland (Fig. 28.1). Normal ducts and lobules are lined by a single layer of epithelium with an underlying layer of myoepithelial cells (Fig. 28.2). The TDLU is felt to be the site of origin of most pathologic entities of the breast, including fibrocystic changes, ductal hyperplasias and the majority of carcinomas (16).

Fibrocystic Changes

The breast ducts and lobules can show a wide range of benign nonproliferative and proliferative epithelial lesions. Nonproliferative lesions include cysts (macroscopic and microscopic), duct ectasia, fibrosis, and apocrine metaplasia. Proliferative lesions were first separated into different risk categories based on the work of Dupont and Page (NEJM, 1985). Patterns associated with a mildly increased risk (~two-fold) of subsequent breast carcinoma are considered proliferative changes, and include usual ductal epithelial hyperplasia (Fig. 28.3), lobular hyperplasia, sclerosing adenosis, radial scars, and intraductal papillomas (25). Both sclerosing adenosis and radial scars (Figs. 28.4 and 28.5) show distortion of normal breast architecture, and

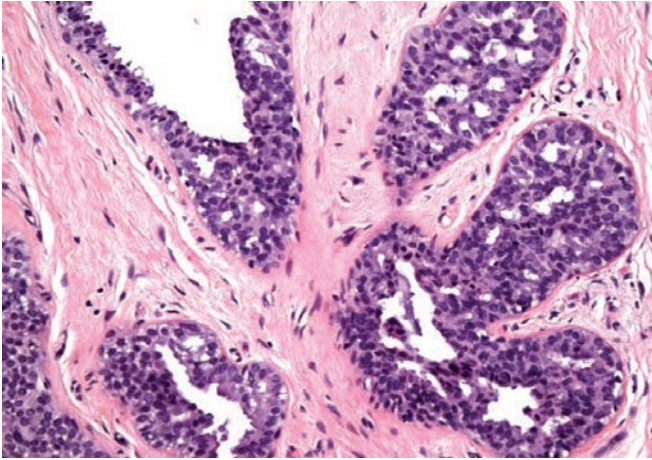


FIGURE 28.3. Usual ductal hyperplasia. Slightly expanded ducts are filled with hyperplastic ductal epithelial cells and myoepithelial cells in an irregular fenestrated growth pattern.

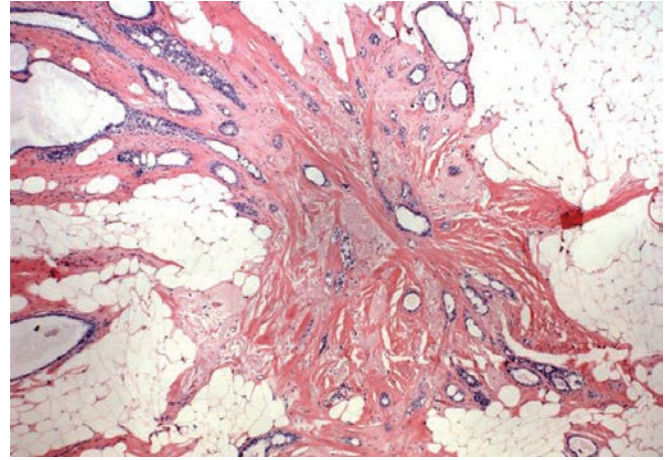


FIGURE 28.5. Radial scar: A stellate lesion with irregular ducts radiating from the elastotic center; the entrapped glands may mimic an invasive ductal carcinoma.

this irregular gland pattern may mimic an invasive carcinoma. These benign proliferations maintain a normal myoepithelial cell layer, which can be highlighted by immunohistochemical stains. Intraductal papillomas have fibrovascular cores lined by myoepithelial cells and one or more layers of epithelial cells (Fig. 28.6). Papillomas involving large ducts near the nipple may cause a bloody nipple discharge.

Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) are associated with a higher increased risk of subsequent breast cancer, about five-fold in most studies (25). ADH is characterized by architectural patterns approaching that of *in situ* carcinoma, while ALH shows expansion of the lobule by a loose, monomorphic cell population (Figs. 28.7 and 28.8). Reproducibility of the diagnosis of ADH is still problematic, but more uniform criteria are now used by most pathologists (26). There is still controversy as to whether size criteria should be used to separate ADH from low-grade DCIS (2 completely involved ducts or 2 mm). Excision is recommended for ADH found on core biopsy, as up to 30% of cases will have carcinoma (*in situ* or invasive) found on evaluation of the surrounding tissue (27). ADH can also involve a radial scar or intraductal papilloma.

A newly appreciated group of lesions are columnar cell change, columnar cell hyperplasia, and flat epithelial atypia (Figs. 28.9 and 28.10). These lesions were originally described by Azzopardi (ref 431, added to the end of the ref list) and their significance has been reappraised due to their frequent association with mammographically detected microcalcifications (28). More recently, it has been noted that flat epithelial atypia (Fig. 28.11) has a high association with low-grade DCIS (29) and invasive tubular carcinoma (30). Molecular studies may be able to further characterize these lesions and their role in breast carcinogenesis. Currently, excision is recommended for any of these atypical lesions identified on needle core biopsy.

In Situ Carcinoma

Ductal Carcinoma In Situ

DCIS, or intraductal carcinoma, is a heterogeneous group of lesions with the proliferation of malignant cells confined within the ductal system. Traditionally, DCIS was classified on the basis of its architectural pattern, often dichotomized as comedo and

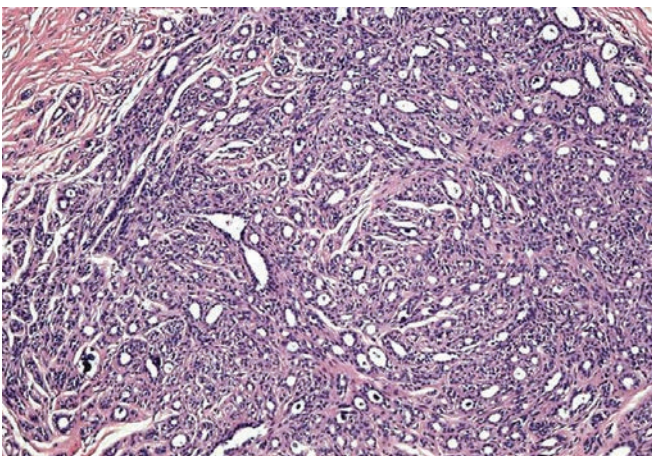


FIGURE 28.4. Sclerosing adenosis. A well-developed lobulocentric distribution of dilated ducts and overgrowth of spindly myoepithelial cells may be mistaken as malignancy in core biopsy or frozen section.

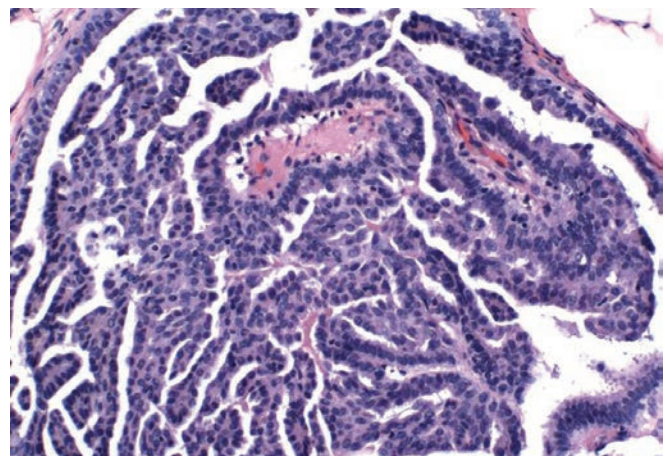


FIGURE 28.6. Intraductal Papilloma. A well-circumscribed papillary proliferation fills a dilated duct. The presence of fibrovascular core of the papillae indicates benignity.

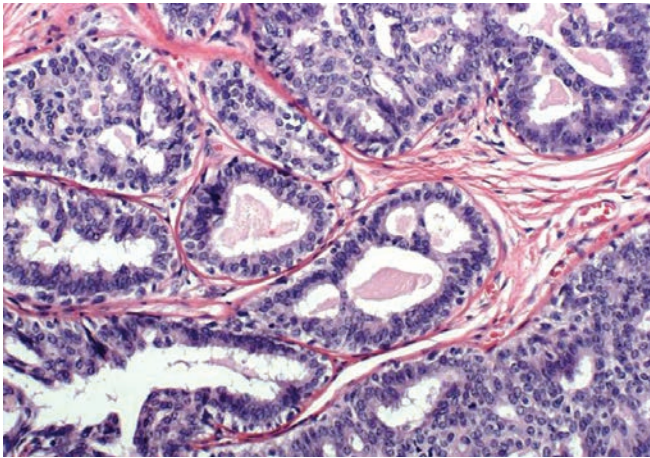


FIGURE 28.7. Atypical ductal hyperplasia. The proliferation has a cribriform growth pattern approaching that of a ductal carcinoma *in situ*, but the microlumens are more irregular in sizes and shapes.

noncomedo types. Noncomedo patterns include solid, cribriform, micropapillary, clinging, and papillary types. Combinations of these patterns are not uncommon in a biopsy. Several grading schemes incorporating both architectural and nuclear features have been proposed, but the Holland version, where nuclear features predominate, was most reproducible in one study (31,32). The presence of intraluminal necrosis and calcifications is usually noted, along with the nuclear grade and pattern(s).

Comedo-type DCIS (comedocarcinoma) shows a solid proliferation of large, pleomorphic nuclear grade 3 epithelial cells, with numerous mitoses and central necrosis containing cellular debris, so-called “comedo-necrosis” (Fig. 28.12). The necrotic material often becomes calcified, and these coarse calcifications have a distinctive mammographic appearance outlining the ductal system (“casting calcifications”). Periductal fibrosis and inflammation is common in comedo-type DCIS and can be a diagnostic problem, as microinvasion is a feature more frequently associated with comedo-type DCIS than other patterns (33,34). Extension of the large pleomorphic cells into the distal lobular unit is a pattern known as “cancerization of lobules.”

The solid, cribriform, papillary, and micropapillary patterns of noncomedo DCIS are usually composed of uniform low-grade or intermediate-grade nuclei. Cribriform patterns show smooth, rounded, “punched-out” spaces (Fig. 28.13). The micropapillary

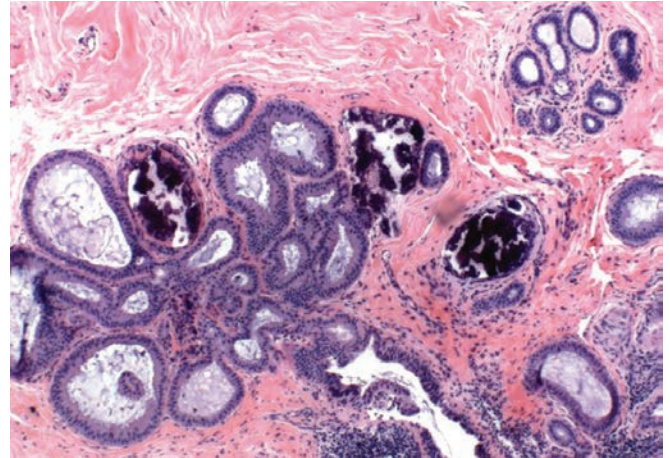


FIGURE 28.9. Columnar cell change with microcalcifications.

subtype does not contain fibrovascular cores, whereas papillary DCIS does (Fig. 28.14). The “clinging” or “flat” type of DCIS may have either low- or high-grade nuclei. Microcalcifications may be associated with these noncomedo patterns and may be detected by mammography. Their pattern of distribution is less specific than that of the comedo DCIS and may be similar to that seen in benign conditions.

DCIS is currently treated by wide local excision or mastectomy, similar to invasive carcinoma. Breast conservation is typically followed by radiation. Margin status and size of the lesion appear to be significant factors related to risk of recurrence (35,36). Silverstein et al. (37) created the Van Nuys Prognostic Index (VNPI) by combining pathologic classification (non-high-grade nuclei without necrosis; non-high-grade nuclei with necrosis; high-grade nuclei), tumor size, and closest margin width. The VNPI score, by combining these features (range, 3 to 9) stratifies the risk of local recurrence after breast-conserving surgery (BCS). Lesion size is often problematic by pathologic evaluation, as most DCIS is not grossly evident. It is not practical to submit all tissue from an excisional biopsy for microscopic evaluation, so sectioning is guided by the type of lesion and radiographic findings. Mammography can often give a more accurate size of the lesion, but only in tumors that are entirely marked by calcifications. Margin width is most easily measured microscopically

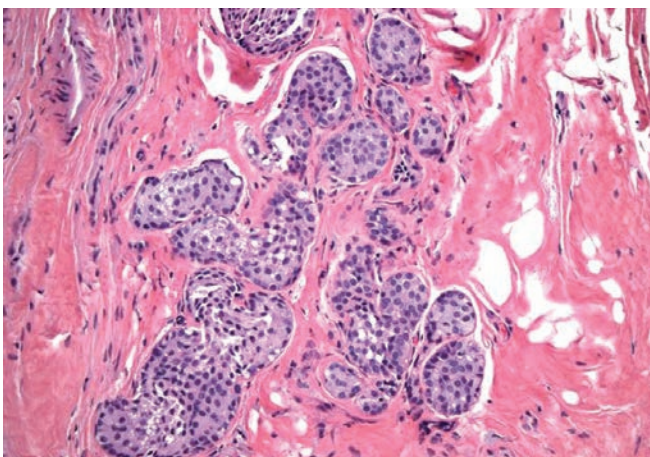


FIGURE 28.8. Atypical lobular hyperplasia. The lobular glands are somewhat expanded, with a loose monomorphic cell population.

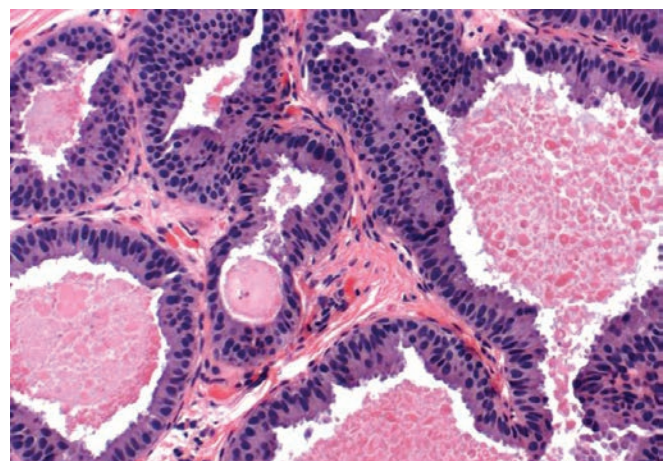


FIGURE 28.10. Columnar cell hyperplasia.

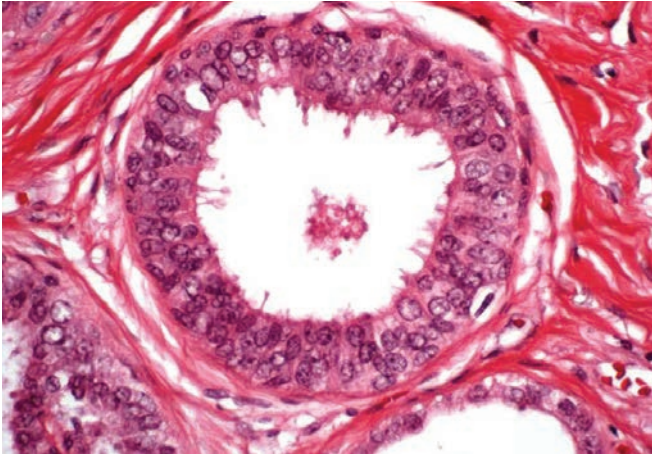


FIGURE 28.11. Flat epithelial hyperplasia. This is a columnar lesion characterized by mildly atypical epithelial cells, which may represent a precursor of or the earliest morphologically recognizable form of low-grade ductal carcinoma *in situ*.

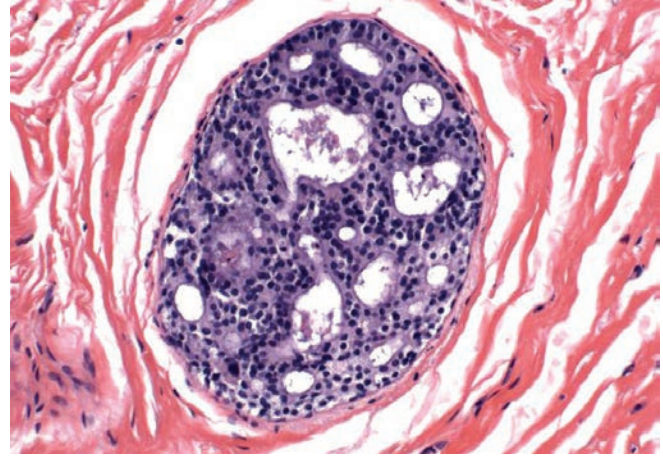


FIGURE 28.13. Cribriform ductal carcinoma *in situ*. Expanded duct is filled with low- to intermediate-grade neoplastic cells forming secondary rigid cribriform microlumens.

in perpendicular sections, which requires the presence of colored inks for unique identification of each margin.

Paget's Disease of the Nipple

Paget's disease of the nipple reflects direct extension of DCIS, usually high grade, into the lactiferous ducts and adjacent skin. Clinically, the nipple appears excoriated. The DCIS may or may not be accompanied by invasive carcinoma. Histologically, the Paget cells are large round cells with prominent nucleoli and pale cytoplasm. They occur singly within the layers of the epidermis, or may form groups at the dermal-epidermal junction, mimicking malignant melanoma (Fig. 28.15). Lesional cells of Paget's disease are positive for carcinoembryonic antigen (CEA) or cytokeratin 7 (CK7), and negative for Melan-A and HMB-45 (Fig. 28.16). Treatment is dictated by whether the underlying tumor is *in situ* or invasive.

Lobular Carcinoma *In Situ*

Lobular carcinoma *in situ* (LCIS) was first described by Foote and Stewart in 1941 and has been an enigma ever since. It is a multicentric lesion, with no identifying features on gross or

radiographic evaluation, and is often found as an incidental finding in biopsies performed for another reason. Histologically, in classic LCIS, the lobule is distended by a monomorphic population of small uniform cells with round nuclei and scant cytoplasm (Fig. 28.17). The cells may extend into the adjacent duct, growing beneath the normal ductal epithelium, a pattern known as “pagetoid spread.” There is continuing controversy as to whether LCIS is an obligate precursor of invasive lobular carcinoma, or just a marker of overall increased cancer risk in either breast (38). Certainly, LCIS is often found adjacent to invasive lobular carcinoma. The term “lobular neoplasia” is often used to encompass both LCIS and ALH, which have identical cytologic features, but minor differences in architecture. Recent studies suggest that the diagnosis of either LCIS or ALH on a needle core biopsy should lead to a surgical excision, with 14% to 38% of patients found to have a carcinoma, either DCIS, invasive ductal carcinoma, or invasive lobular carcinoma (27,39,40).

Pleomorphic Lobular Carcinoma *In Situ*

This pattern of *in situ* disease involves larger ducts and mimics the solid pattern of DCIS (41). The cells are evenly spaced,

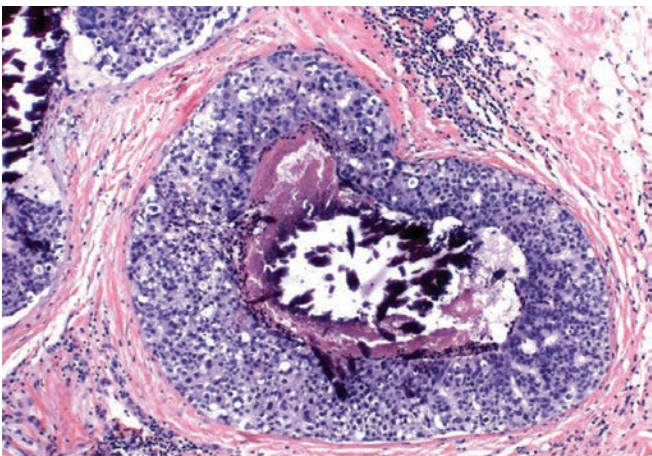


FIGURE 28.12. Comedo-type ductal carcinoma *in situ*. Markedly expanded ducts are filled with high-grade neoplastic ductal cells with central necrosis and calcifications.

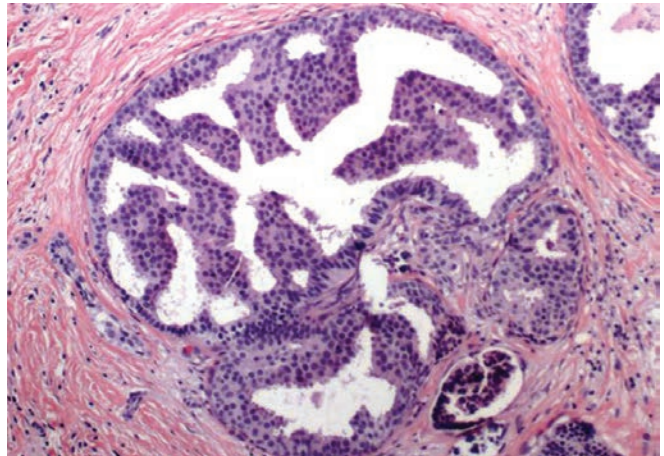


FIGURE 28.14. Micropapillary ductal carcinoma *in situ*. Low-grade neoplastic ductal cells form papillary fronds in an expanded duct. The papillary fronds lack fibrovascular core.

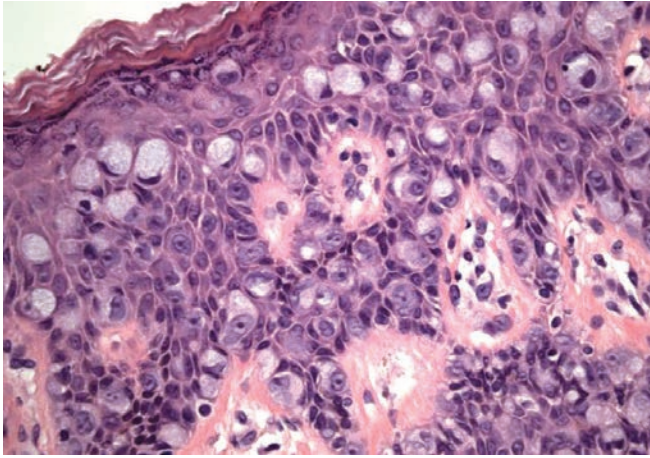


FIGURE 28.15. Paget's disease. Large, round, pale neoplastic cells occur singly within the epidermis, mimicking malignant melanoma.

slightly dyscohesive and may have visible intracytoplasmic lumina (Fig. 28.18). Immunohistochemistry for E-cadherin demonstrates loss of this membrane protein (Fig. 28.19). Treatment should be similar to DCIS, as this pattern of LCIS is considered a precursor lesion of invasive carcinoma, rather than just a risk factor for subsequent disease (42).

Invasive Carcinoma

Invasive carcinoma of the breast is defined by the presence of stromal invasion, usually manifest by a fibrotic, desmoplastic stromal reaction around the invading cells. Tumor may be microinvasive (<1 mm) within an area of DCIS, or may form an obvious tumor mass, clinically or radiographically. Tumors are classified by the pattern of growth into ductal and lobular forms. Breast carcinoma is surgically staged using the AJCC staging system based on the size of the invasive component. Synoptic checklist reporting using templates devised by the College of American Pathologists aids in ensuring that all-important pathologic features are documented. DCIS may be focally present adjacent to the invasive component or intermixed with invasive tumor. The term “EIC” denotes a tumor with an

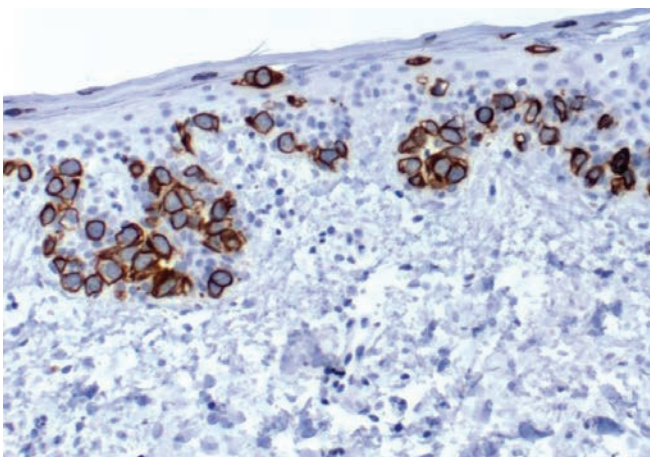


FIGURE 28.16. Paget's disease. Paget's disease cells are positive for CEA or CK7, and negative for Melan-A and HMB-45.

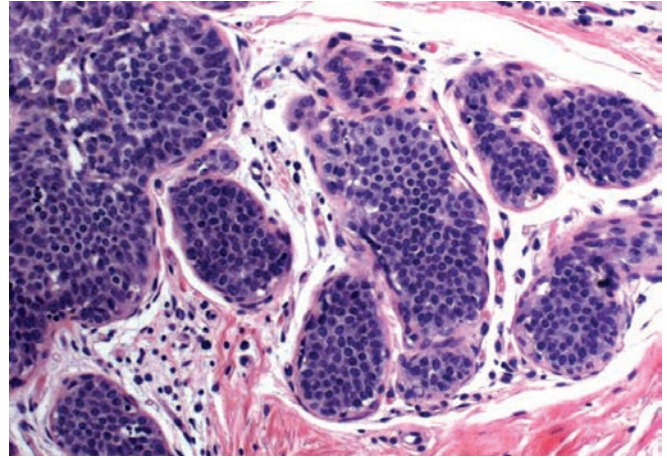


FIGURE 28.17. Lobular carcinoma *in situ*. An expanded lobule is markedly distended by a monomorphic population of small uniform cells. The underlying lobular architecture is still recognizable.

extensive *in situ* component, defined as at least 25% of the tumor mass.

Invasive Ductal Carcinoma

The majority of invasive tumors of the breast are ductal and have varying morphologic patterns that have led to several subclassifications. Most of the special types listed below are distinguished because they have an extremely good prognosis. The majority of tumors (~75%) have no specific features and are designated carcinoma, not otherwise specified (NOS), or carcinoma of no special type (NST). These tumors may be composed of small glands, tubules, solid cords, or nests of cells with varying degrees of cytologic atypia surrounded by a reactive (desmoplastic) fibrous stroma (Fig. 28.20). The recommended grading system is the Nottingham modification of the Bloom-Richardson system, which is based on adding scores for architectural pattern, nuclear pleomorphism and mitotic count (43) (Table 28.5). Grade 1 tumors (well differentiated) have 3 to 5 points, Grade 2 tumors (moderately differentiated) have 6 to 7 points and Grade 3 tumors (poorly differentiated) have 8 to 9 points. While initially applied only to invasive ductal carcinoma, this system can also be applied to invasive lobular carcinomas and has been validated in numerous studies (44).

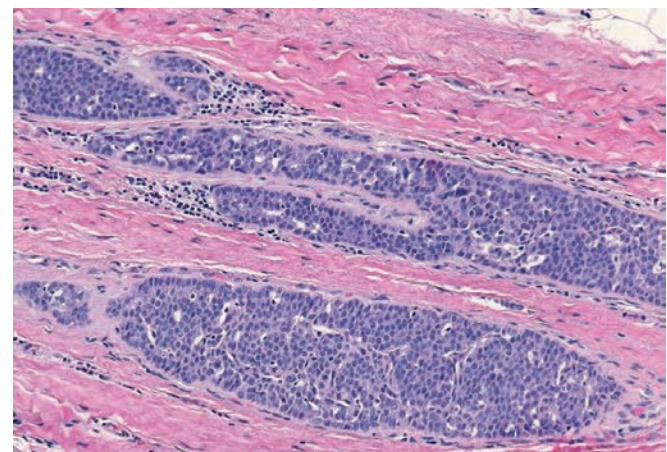


FIGURE 28.18. Pleomorphic lobular carcinoma *in situ*. This pattern of lobular carcinoma *in situ* involves larger ducts with evenly spaced and slightly dyscohesive tumor cells, mimicking solid pattern of ductal carcinoma *in situ*.

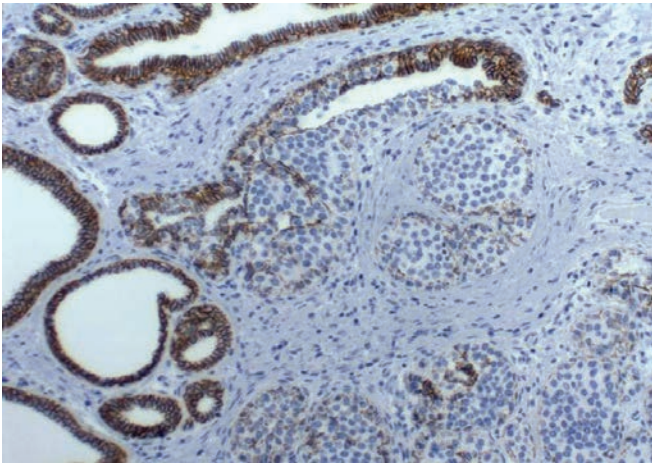


FIGURE 28.19. Lobular carcinoma *in situ*. Loss of E-cadherin staining of lobular carcinoma *in situ* in contrast with adjacent normal ducts with positive staining.

Special Types

Mucinous Carcinoma

Mucinous (or colloid) carcinoma usually occurs in postmenopausal women. The tumor is well circumscribed and may have a gelatinous gross appearance. Microscopically, nests of uniform small cells are surrounded by pools of mucin (Fig. 28.21). The *in situ* component is minimal, but may also show intraductal mucin production. Pure mucinous tumors are low grade and have an excellent prognosis with a low rate of lymph node metastasis (45). This is not true, however, of mixed carcinomas with a prominent nonmucinous, usual invasive ductal carcinoma component.

Tubular Carcinoma

Tubular carcinoma is a well-differentiated invasive carcinoma composed of small glands or tubules that can be difficult to distinguish from some benign lesions, especially radial scars. The tubules are arranged haphazardly, often with a surrounding cellular stroma. They are somewhat angular with open lumens

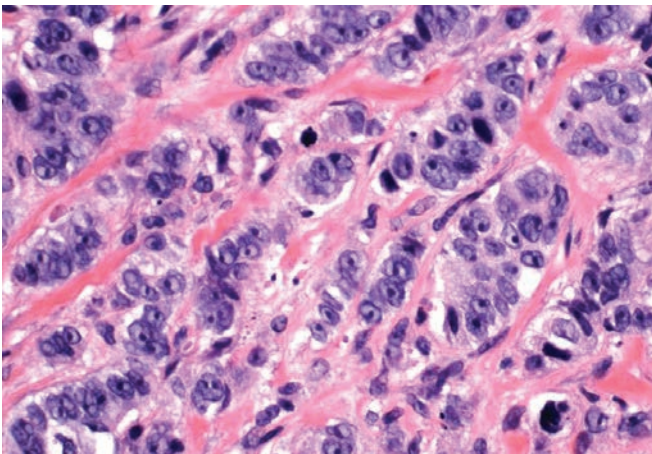


FIGURE 28.20. Invasive ductal carcinoma. Small solid cords of neoplastic cells with moderate to severe cytologic atypia are surrounded by a fibrous stroma.

Table 28.5 Modified Bloom-Richardson Grading Scheme

	Score
Tubule and Gland Formation	
Majority of tumor (>75%)	1
Moderate degree (10%–75%)	2
Little or none (<10%)	3
Nuclear Pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic Count (0.152 mm Field Area)^a	
0–5	1
6–10	2
>11	3

^aAdjust for different field areas.

and are lined by a single layer of monomorphic epithelial cells (Fig. 28.22). Myoepithelial cells are absent, and immunohistochemistry for myoepithelial markers (smooth-muscle myosin heavy chain, calponin, p63, and/or CD10) is helpful in confirming the diagnosis on needle biopsy. In order to have an excellent prognosis, the tumor must be composed of at least 75% tubules and have grade 1 nuclei (46). Invasive tubular carcinoma is often associated with a low-grade micropapillary or cribriform DCIS or adjacent atypical columnar cell lesions (30). Tubular carcinomas are small, usually less than 1 cm, and are frequently detected by screening mammography. Tumors with a component of usual invasive ductal carcinoma should not be included in this category. Invasive cribriform carcinoma, which also has a good prognosis, may be mixed with tubular carcinoma.

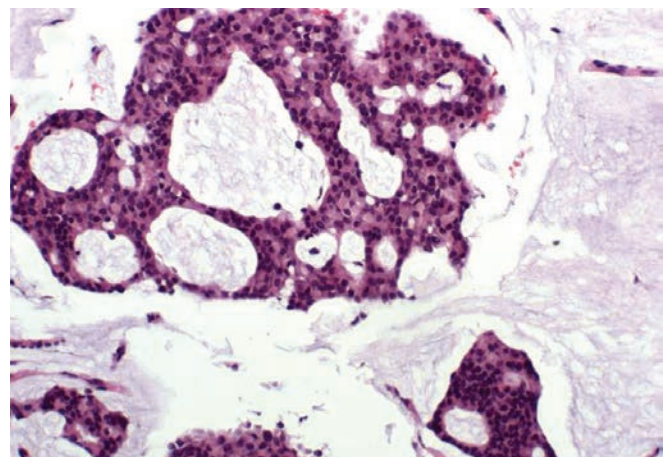


FIGURE 28.21. Mucinous carcinoma. Nests of low-grade neoplastic cells in a cribriform pattern are surrounded by a large pool of mucin.

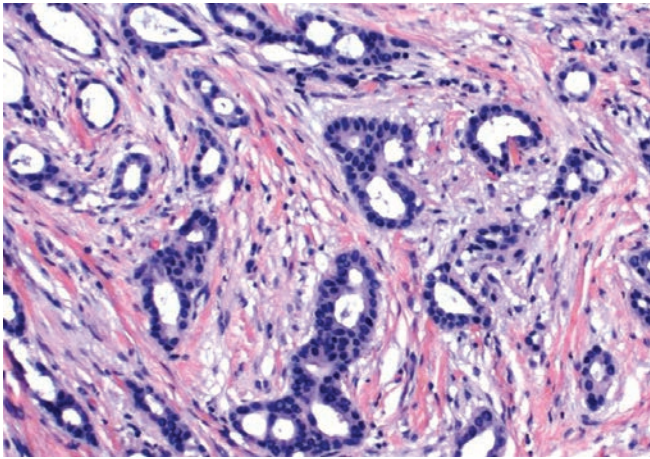


FIGURE 28.22. Tubular carcinoma. Well-formed angular, oval, and tubular glands with a single layer of neoplastic ductal cells diffusely infiltrate a desmoplastic fibrous stroma.

Medullary Carcinoma

Medullary carcinomas occur more commonly in women under 50 years of age and have a higher frequency in *BRCA1* mutation carriers. Clinically, the tumor is well circumscribed and may mimic a fibroadenoma. Microscopically, the tumor is composed of solid syncytial sheets of large anaplastic cells with pleomorphic nuclei, prominent nucleoli, and abundant mitotics (Fig. 28.23). Gland formation is absent. The tumor has a pushing border and is surrounded by a dense lymphoplasmacytic infiltrate. Only tumors with this strict morphology and no component of typical invasive ductal carcinoma have a good prognosis.

Micropapillary Carcinoma

Micropapillary carcinoma is a recently described entity with a characteristic morphology, high incidence of positive nodes at presentation despite small tumor size, and poor OS (47,48). The tumor is composed of small clusters of malignant cells floating within small clear spaces resembling lymphatic channels (Fig. 28.24). Most tumors have high nuclear grade and true

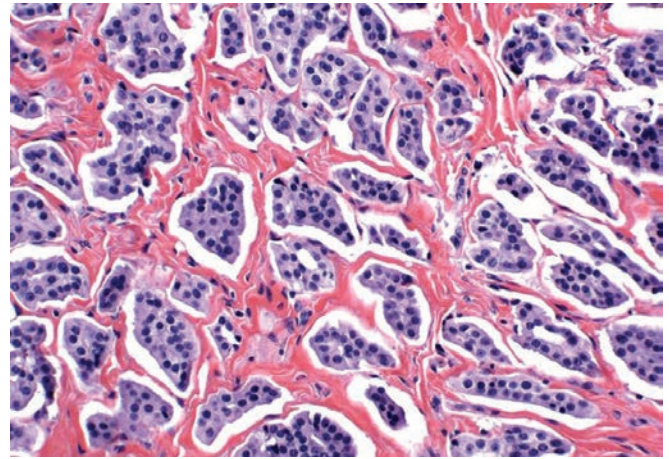


FIGURE 28.24. Invasive micropapillary carcinoma. Small clusters of intermediate-grade neoplastic cells lie within small clear spaces of a fibrocollagenous stroma mimicking tumor cells in lymphatic spaces.

lymphatic space invasion. A component of usual invasive ductal carcinoma may be present.

Papillary Carcinoma

Papillary carcinoma is a rare subtype. Several different entities are encompassed within this terminology. Solid papillary carcinoma and encapsulated (intracystic or encysted) papillary carcinoma have indolent behavior like a DCIS, although they lack surrounding myoepithelial cells (49,50) (Fig. 28.25). Encapsulated papillary carcinoma forms a well-circumscribed mass and may have DCIS present in adjacent ducts. Invasive papillary carcinomas have evidence of destructive stromal invasion adjacent to larger solid nests.

Inflammatory Carcinoma

The term “inflammatory carcinoma” originated as a clinical term to describe a patient presenting with a reddened edematous breast suggesting mastitis. Skin biopsies from such patients often show tumor thrombi in dermal lymphatic channels (Fig. 28.26), but this is not true in every case.

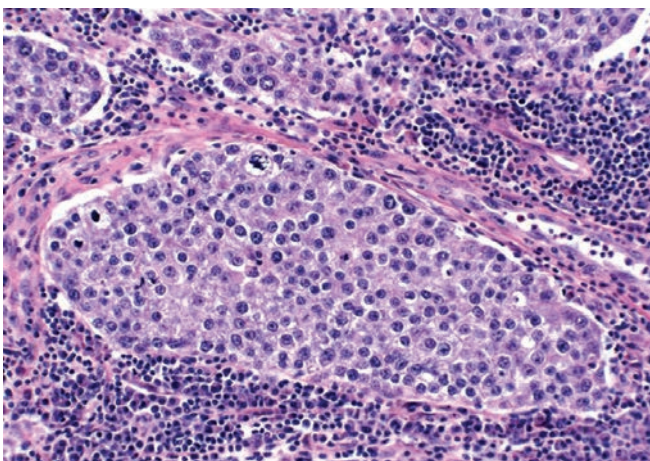


FIGURE 28.23. Medullary carcinoma. Highly pleomorphic neoplastic cells in a syncytial pattern are surrounded by a diffuse lymphocytic infiltrate.

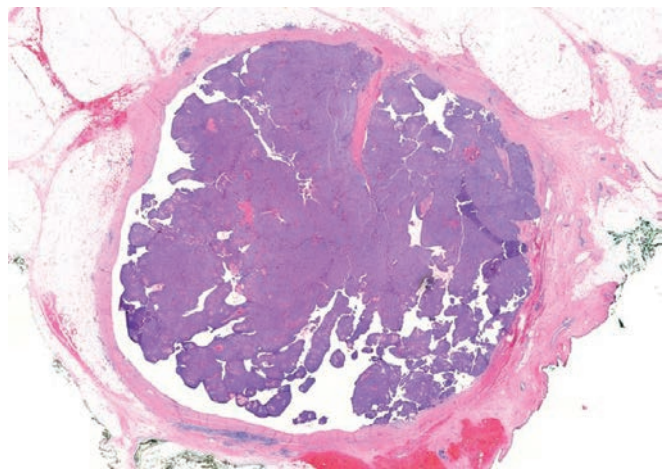


FIGURE 28.25. Solid or intracystic papillary carcinoma. Low power shows a well-circumscribed tumor with branching network of fibrovascular stroma. A cystic formation is not necessary for the diagnosis.

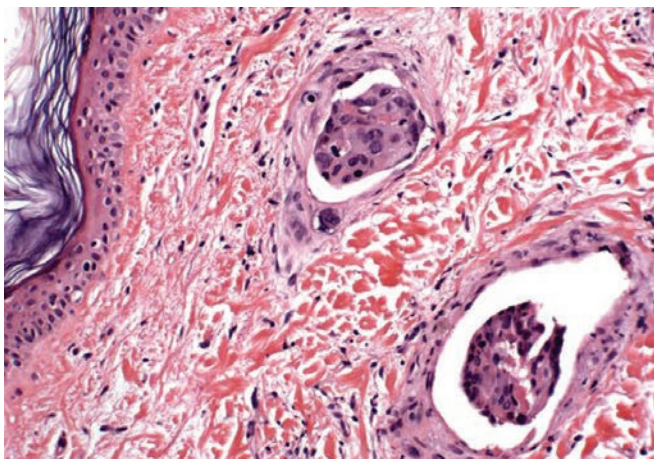


FIGURE 28.26. Inflammatory carcinoma. Carcinomatous emboli are present in dilated dermal lymphatics.

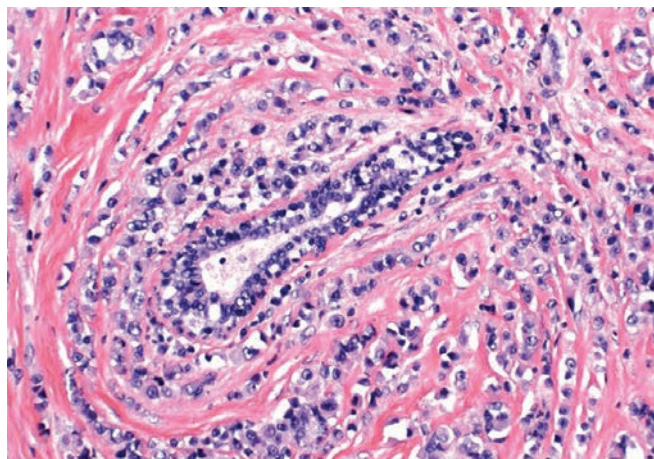


FIGURE 28.28. Invasive lobular carcinoma. Tumor cells infiltrate in a concentric pattern around a normal duct.

Invasive Lobular Carcinoma

Invasive lobular carcinoma comprises about 10% of all breast cancers. The classic form of invasive lobular carcinoma is composed of small monotonous tumor cells with scant cytoplasm growing in linear columns ("Indian file") or in concentric ("targetoid") patterns around normal ducts and lobules (Figs. 28.27 and 28.28). A mild stromal desmoplastic reaction may be present around the tumor cells, but many invasive lobular carcinomas do not form a discrete tumor mass. This diffuse growth pattern can be a problem when attempting conservative surgical excision, and tumors are frequently upstaged after surgery (51).

Variant forms of invasive lobular carcinoma include alveolar, solid, and trabecular patterns composed of the same monomorphic small cells. Signet ring cell carcinoma (Fig. 28.29), in which the cells contain prominent intracytoplasmic vacuoles, is considered a variant of invasive lobular carcinoma due to its similar growth patterns. Another variant is pleomorphic lobular carcinoma, where the columns of cells show marked nuclear atypia.

Stage for stage, the prognosis of patients with invasive lobular carcinoma is no different from invasive ductal carcinoma. However, the patterns of metastatic disease are different, with lobular carcinomas having a propensity to metastasize to the

meninges, and peritoneal and pleural surfaces. Invasive lobular carcinomas, and mixed lobular and ductal invasive carcinomas appear to be more frequent in postmenopausal women taking combination hormone replacement therapy (52).

Tubulo-lobular Carcinoma

This tumor shows a mixture of invasive lobular and tubular carcinoma growth patterns with low-grade nuclei. The mixed architectural pattern parallels the expression of markers of ductal and lobular differentiation, and these tumors appear to have a good prognosis.

Other Tumors

Metaplastic Carcinoma

The term "metaplastic carcinoma" is used to describe tumors with prominent morphologic patterns different from usual ductal and lobular patterns. The term encompasses epithelial tumors (carcinomas) showing squamous cell differentiation, monophasic spindle cell carcinoma, and biphasic tumors with both epithelial and mesenchymal elements (Fig. 28.30). Spindle

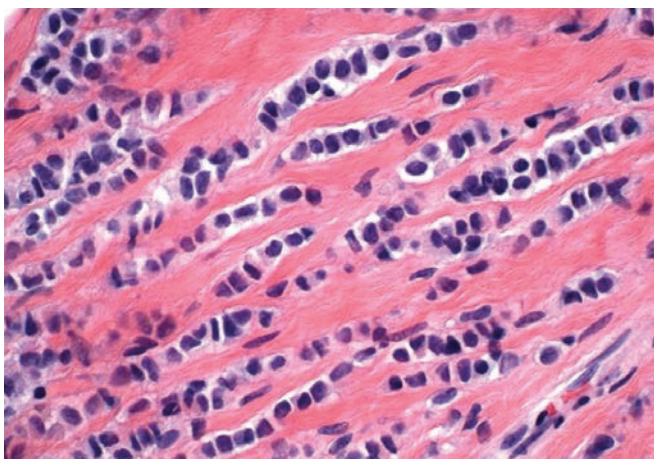


FIGURE 28.27. Invasive lobular carcinoma. Small monotonous tumor cells invade in linear "Indian file" pattern.

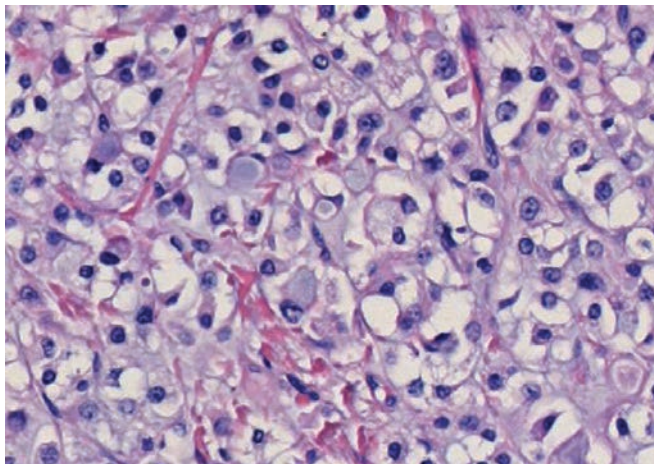


FIGURE 28.29. Signet ring cell carcinoma. Tumor cells contain large amounts of intracytoplasmic mucin, which pushes the nuclei to the cell periphery, thus resembling signet rings.

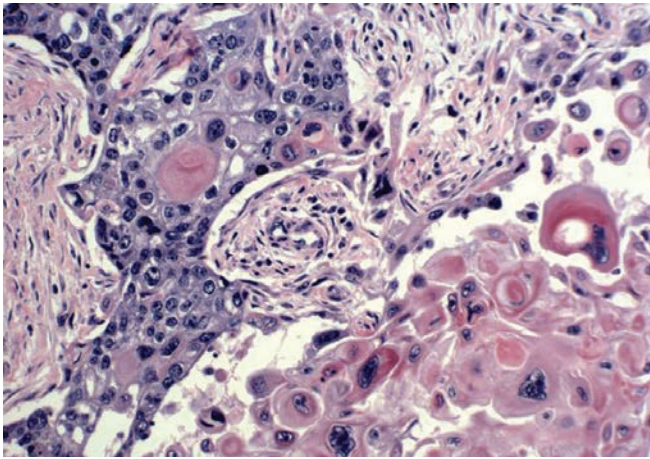


FIGURE 28.30. Metaplastic carcinoma. The area to the right of this poorly differentiated invasive breast carcinoma shows squamous differentiation.

cell (sarcomatoid) carcinomas express epithelial markers (cytokeratins) despite their spindle cell morphology and are aggressive tumors with a high rate of extranodal metastases. Biphasic tumors (biphasic sarcomatoid carcinoma or carcinosarcoma) may contain heterologous elements, such as malignant cartilage or bone (Fig. 28.31). These are also aggressive tumors that tend to metastasize as well as recur (53).

Phyllodes Tumors

Phyllodes tumors, formerly known as “cystosarcoma phyllodes,” are biphasic tumors similar to fibroadenomas with a spectrum of morphology and biologic behavior. The median age is 45 years, which is several decades higher than for fibroadenoma. These tumors are grossly well circumscribed, but are infiltrative on microscopic examination. They are composed of benign glandular elements with a prominent stromal component showing varying degrees of hypercellularity, nuclear atypia, and mitotic activity (Fig. 28.32). The older term “cystosarcoma phyllodes” refers to the leaf-like architectural pattern with intervening cystic spaces. While features such as

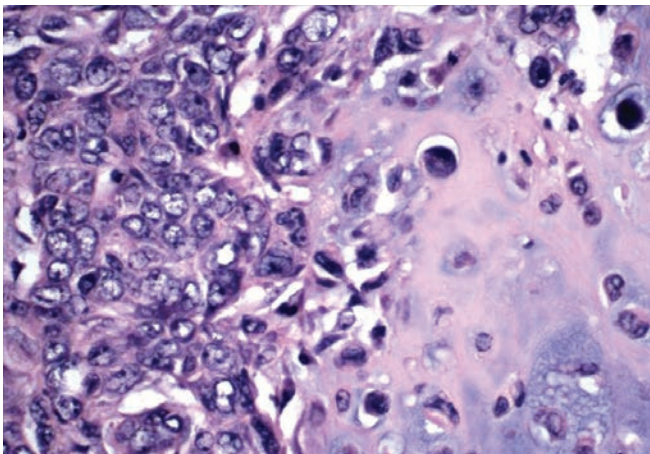


FIGURE 28.31. Metaplastic carcinoma. A well-developed cartilaginous focus is seen in this poorly differentiated invasive carcinoma with chondroid differentiation.

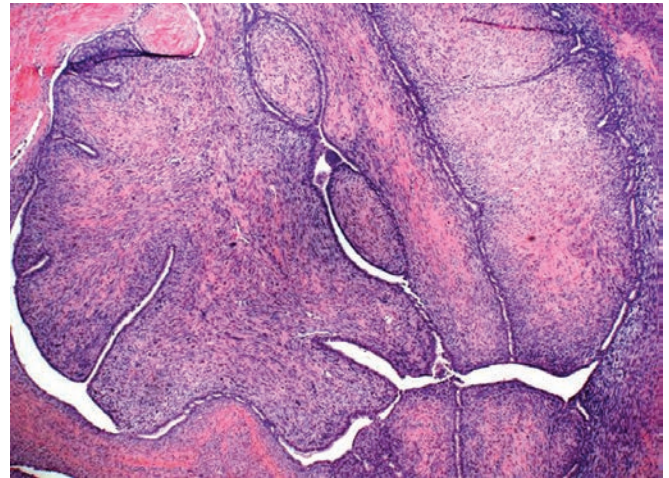


FIGURE 28.32. Phyllodes tumor: Phyllodes tumors have leaf-like architectural pattern with intervening cystic spaces. They are composed of benign glandular elements with a prominent stroma showing varying degrees of hypercellularity, nuclear atypia, and mitotic activity.

size, mitotic activity, and cellular atypia correlate with clinical behavior, attempts to reliably divide these tumors into benign and malignant forms are not always successful. The lower grade tumors tend to recur, especially if incompletely excised due to the subtle infiltrative margin. Obvious malignant tumors may have stromal overgrowth, which portends a worse prognosis (54,55). Overall, lymph node metastases are uncommon and surgery is the primary treatment.

Angiosarcoma

Angiosarcoma is the most common primary sarcoma of the breast and may be associated with previous radiation therapy. The tumors are composed of anastomosing vascular channels lined by endothelial cells, which range from mildly atypical to frankly malignant. The distinction between a benign angiosarcoma and a low-grade angiosarcoma can be difficult on a small biopsy. Overall 5-year survival is around 60% with multimodality therapy (56,57). Other histologic patterns of primary breast sarcoma also occur.

CLASSIFICATION OF BREAST CANCER

Estrogen interacting with nuclear estrogen receptors (ER) regulates cell growth, proliferation, and differentiation of normal breast epithelium, and those carcinomas that express ER. Measurement of ER in breast cancers is performed in order to predict the response of an invasive tumor to endocrine therapy, or the benefit of hormonal therapy for risk reduction in cases of *in situ* carcinoma. Progesterone receptor (PR) is an ER-regulated gene product with similar prognostic implications. Hormone receptors can be measured biochemically by ligand binding assays, or by immunohistochemical (IHC) techniques using monoclonal antibodies directed against the receptor protein (Fig. 28.33). Correlation between the two techniques is high (58). With today's smaller tumors usually diagnosed by needle core biopsy, IHC is the preferred method of analysis. This method also allows distinction between invasive tumor, *in situ* tumor, and nontumor elements. The American Society of Clinical Oncology and College of American Pathologists recently published a joint guideline containing an algorithm for testing, interpretation, and reporting,

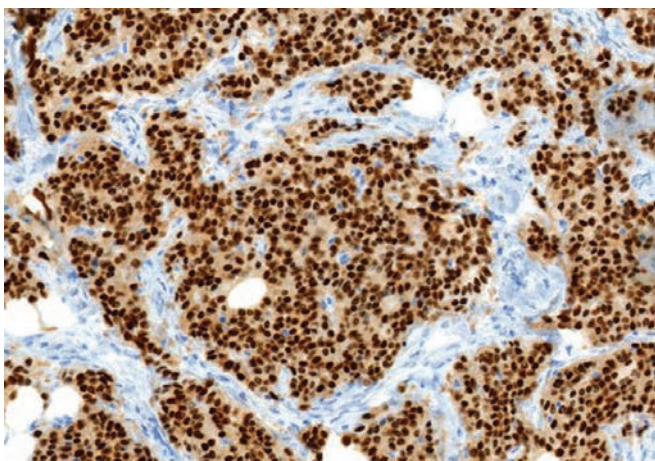


FIGURE 28.33. Positive estrogen receptor: More than 90% of tumor cells of this invasive ductal carcinoma are strongly positive for estrogen receptor.

as well as requirements for standardization and validation of testing techniques (59). Both the percentage of cells stained and the intensity of the staining should be reported. A positive result is defined as more than 1% of cell nuclei staining positive.

HER2/Neu

HER2/neu or c-erbB2 is an oncogene whose protein product is a membrane receptor tyrosine kinase. Amplification of *HER2/neu* is seen in most cases of comedo-type DCIS and in about 20% to 30% of invasive ductal carcinoma, usually of high grade. It can be detected by immunohistochemistry for the protein product or by gene amplification techniques, such as fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH). Increased copy number is closely associated with elevated protein expression. Amplification of *HER2/neu* identifies a subset of patients with a poor prognosis who benefit from treatment with trastuzumab, a monoclonal antibody directed against the *HER2/neu* receptor (60,61). The American Society of Clinical Oncology and College of American Pathologists published a joint guideline containing an algorithm for testing, interpretation and reporting, as well as requirements for standardization and validation of testing techniques (62). A positive *HER2/neu* result is 3+ IHC staining, defined as uniform intense membrane

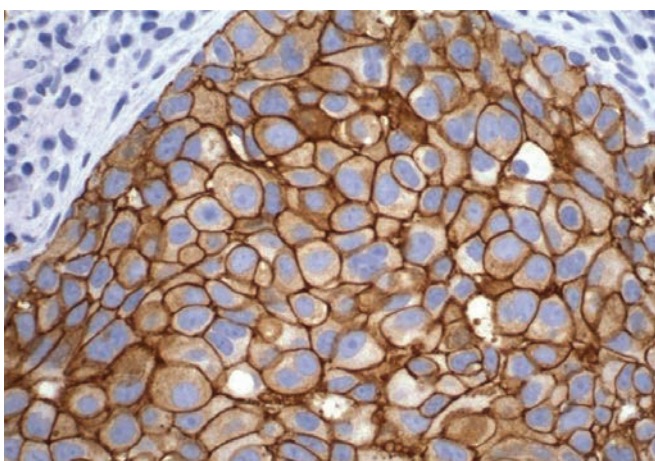


FIGURE 28.34. Positive *HER2/neu*. Strong (3+) *HER2/neu* membrane immunoreactivity is seen in this invasive ductal carcinoma.

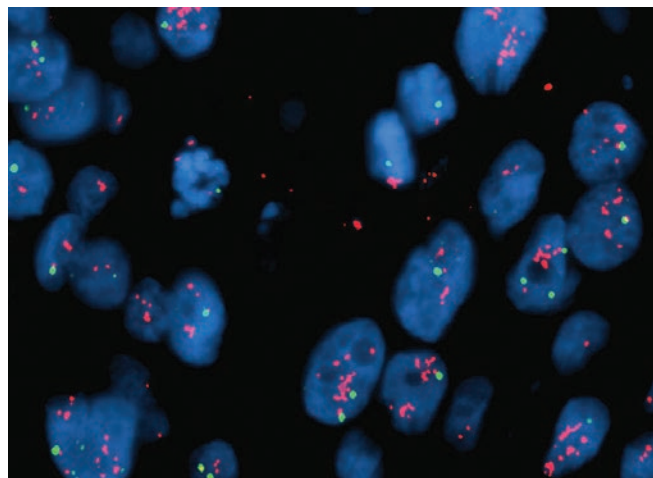


FIGURE 28.35. Amplification of *HER2/neu* gene (red dots) by fluorescence *in situ* hybridization.

staining of greater than 30% of invasive tumor cells (Fig. 28.34) or a FISH result of more than 6 *HER2* gene copies per nucleus OR a FISH ratio (*HER2* signals to chromosome 17 signals) of more than 2.2 (Fig. 28.35). Implementation of these guidelines will result in more reproducible results between laboratories.

Triple Negative Tumors

A subset of breast carcinomas is negative for the usual markers ER, PR, and *HER2/neu*. These tumors express cytokeratin 5/6, which denotes a basal phenotype, in contrast to the luminal cell phenotype of most breast carcinomas (63,64). These tumors typically are high grade with a central hyalinized scar or necrosis (65), occur in younger women, and are associated with poor survival (66). Many metaplastic carcinomas fall into this group of tumors. Most triple negative tumors are positive for epidermal growth factor receptor (EGFR), which may provide a target for future therapy (63).

BRCA1 and BRCA2

Histologically, tumors associated with either *BRCA1* or *BRCA2* are typically invasive ductal carcinomas. *BRCA1*-mutation associated breast cancers are usually triple negative and express basal markers (67). This is in contrast to *BRCA2*-mutation associated tumors, which are usually ER positive (ER+) and express a luminal A phenotype (44).

Other Markers

Proliferation rate measured by flow cytometry (S-phase fraction), DNA image cytometry, or IHC (Ki67 MIB-1 antibody) has a relation to clinical outcome (68). However, these and other markers suffer from problems with standardization of results between laboratories. A recent working group has addressed Ki67 assessment (69). Newer techniques using protein or gene microarrays to identify putative markers are more exciting. One panel of 22 genes has been used to predict the likelihood of recurrence in ER+ node-negative tumors (70).

Molecular Profile of Breast Cancer

Based on the results of microarray analysis, breast cancers can be broadly classified into 5 subgroups: luminal A, luminal B,

normal breast-like, HER2-positive (HER2+), and basal-like. The molecular features have some correlate with histologic grade and expression of hormone receptors (71). While, in general, these different groups have different prognoses, the basal-like group is most heterogeneous, containing medullary carcinoma, metaplastic carcinoma, and rare tumor types, such as adenoid cystic carcinoma (72).

GENERAL MANAGEMENT OF BREAST CANCER—SURGICAL CONSIDERATIONS

Historical Perspective

Early descriptions of breast disease date back to ancient Chinese and Egyptian civilizations, and those of breast malignancy date back to Hippocrates and Celsus. The predominating theories of Hippocrates and Galen's 4 bodily humours were taken as dogma until the 1700s, when LeDran proposed the revolutionary concept of lymphatic spread. Evolutions in surgical treatment of breast cancer, however, awaited the introduction of anesthesia and Listerian antiseptics.

Faced with a high incidence of local recurrence and the understanding that cancer growth and spread occurred in an "orderly sequential process," the radical mastectomy was championed as an attempt to get at "the roots" of the tumor. At the same time, surgeons suggested that the axillary nodes be removed as part of the operation on breast cancer, given the propensity of nodal involvement.

The earliest description of the mastectomy was by Jean Petit, but Charles Moore and Sir Joseph Lister are credited with advocating the more radical approach by incorporating the division of the pectoral muscles when performing a mastectomy, which allowed for improved exposure of the axillary contents. The subsequent ground work by Pancoast, Gross, and Moore of London lead to the reports of Willie Meyer and William Halsted, who simultaneously published papers advocating the systematic removal of nodes in continuity with the primary cancer in 1894 (73,74). These papers presented a systemically applied approach to the radical mastectomy and offered a standardized technique of lymphadenectomy in breast cancer in an anatomically logical and exact manner. Technically, the procedure involved an *en bloc* resection of the breast, the pectoralis major and minor, and a full axillary dissection, levels I to III. In so doing, the local recurrence rate dropped from nearly 50%–80%, to 6%, and the reported 3-year cure rate was 38.3% (75). So successful was this operation that it became the yardstick against which all other interventions would be measured. Even

with this breakthrough, Halsted recognized that node negativity did not ensure survival.

The extension of the operation was explored by surgeons in Europe and the U.S., including operations that involved resection of the supraclavicular nodes (Halsted) or the internal mammary nodes (Handey), and extension of surgery into the neck and/or mediastinum (Urban and Wangenstein) (76,77). However, these increasingly extensive surgeries did not improve OS, but did increase operative mortality, and thus, were largely abandoned. Simultaneously, Sir Geoffrey Keynes first described the role of radiation therapy (RT) in local control of cancer in 1930, and Robert McWhirter first demonstrated that axillary radiation was effective in locoregional control in breast cancer (78). This presaged the controversy regarding surgical resection versus radiotherapy for locoregional control and its relationship to survival.

Advances in medicine and public health between 1880 and the mid-1900s led to improvements in breast cancer detection and smaller tumors, which led surgeons to explore options beyond the radical mastectomy. It was not until the 1970s, however, that the surgical trend for breast cancer management was deliberately directed toward less-aggressive approaches (79).

Modern History

Over a decade after the first randomized clinical trial, evaluating the outcomes of breast conservation combined with postoperative radiation versus mastectomy, revealed no difference in either OS or in breast recurrence between treatment groups, the National Surgical Breast and Bowel Project (NSABP) launched a series of trials where the underlying construct was that breast cancer was systemic at origin and therefore, the technique of surgery was less important than systemic therapy. Under their dogma of "systemic disease controls survival," the group accepted negative margins delineated as "no tumor at ink," and this qualification would distinguish NSABP trials from other investigations. In total, 6 major prospective randomized trials were initiated between 1972 and 1983, and are summarized in Table 28.6.

The NSABP B-06 trial compared modified radical mastectomy to lumpectomy/axillary dissection with or without breast irradiation in 1,851 patients with stage I–II breast cancer (80). At 20 years of follow-up, there was no significant difference in either disease-free survival (DFS) or OS. Additionally, whole breast irradiation was found to reduce local recurrence in patients who received breast conservation. With these results, BCT was rightfully accepted as standard of care for nonmulticentric breast cancer. A similar trial was reported by Veronesi for the National Tumor Institute of Milan (81). Over 700

Table 28.6 Randomized Trials of Breast-Conserving Therapy and Mastectomy

Study	No. of Patients	Median Follow-up (years)	In-Breast Failure BCS + XRT Mastectomy		Overall Survival BCS + XRT Mastectomy	
IGR (83)	179	15	9%	14%	73%	65%
Milan (81)	701	20	9%	2%	42%	41%
NCI (84)	237	18	22%	6%	59%	58%
EORTC (85)	824	10	20%	12%	65%	66%
Danish (82)	904	6	3%	4%	79%	82%
NSABP B6 (7)	1219	20	14%	10%	46%	47%

IGR, Institut Gustave_Roussy; NCI, National Cancer Institute; EORTC, European Organization for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; BCS, breast-conserving surgery; XRT, radiation therapy.

women with tumors under 2 cm were randomized to mastectomy versus quadrantectomy with axillary dissection followed by radiotherapy. Adjuvant chemotherapy using cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) was administered to all patients with node-positive disease. With 20 years of follow-up, the actuarial DFS and OS were similar in both groups.

The Danish Cooperative group conducted a similar study of 895 patients and once more showed that with 6 years of follow-up, equivalent rates of local recurrence and OS were achieved (82). Finally, Arriagada et al. reported the results of a randomized trial involving 179 patients treated at the Institut Gustave-Roussy and once more demonstrating an equivalent DFS and OS (83). Notable studies from the NCI and EORTC showed a higher risk for local recurrences with breast conservation compared to mastectomy, but these studies were flawed for either inadequate margin assessment or frank margin involvement, respectively (84,85).

In the final analysis, the weight of evidence supports equivalence of BCT versus radical or modified radical mastectomy for early-stage breast cancer. The NSABP trials rigorously and systematically both challenged and advanced breast cancer surgical technique and systemic therapy. Ongoing debate about which patients were candidates for BCT continued for decades, ultimately landing at the determination based on the breast-tumor volume ratio, absence of multicentric disease, and eligibility for postlumpectomy radiation (86).

The NSABP applied similar methodology in evaluating the benefit of surgery and radiation in the management of ductal carcinoma *in situ* (DCIS). From the NSABP B-17 and B-24 trials, we learned that lumpectomy with radiation achieved the lowest rate of local recurrence but did not affect OS, and that tamoxifen could decrease not only ipsilateral recurrence but also contralateral new disease (87). NSABP B-32 compared axillary dissection to sentinel node biopsy in the management of the clinically negative axilla and demonstrated the success of sentinel node biopsy in predicting axillary involvement (88). Most recently, the American College of Surgeons Oncology Group Z-11 trial has suggested that verification of axillary involvement is adequate, and completion axillary dissection is not associated with improved survival in limited (1–2) node-positive disease.

In Situ Disease

In the past, DCIS was managed, like any breast cancer, by mastectomy. This was effective from a cancer point of view and resulted in a local recurrence rate of only 1% (89). Interestingly, at a time when breast-conservation surgery was being advocated for invasive breast cancer, total mastectomy was still the standard of care for DCIS. Current therapies have since evolved based on extrapolation of the trials of BCT with total mastectomy in invasive breast cancer, although there are no phase III studies comparing BCT with total mastectomy in DCIS.

Currently, most DCIS can be treated by wide local excision and radiotherapy. Margin status and size of the lesion appear to be significant factors related to risk of recurrence (35,36). Silverstein et al. created the VNPI by combining pathologic classification (non-high-grade nuclei without necrosis; non-high-grade nuclei with necrosis; high-grade nuclei), tumor size, and closest margin width (90). The VNPI score ranges from 4 to 12 and has been shown to stratify the risk of local recurrence after BCS, and has been used to identify a cohort where radiation may be safely omitted. However, the prospective randomized trial failed to validate a wide margin can be substituted for radiotherapy (91). Furthermore, both the NSABP and the EORTC trials demonstrated a 50% invasive component in the local recurrences in the nonradiated patients (92).

The indications for mastectomy for DCIS are: (1) persistent positive margins; (2) multicentric disease, that is, DCIS involving more than one quadrant; (3) cosmetically unacceptable breast-conservation surgery due to a large DCIS process in a comparatively small breast (93). For these cases, a total or skin-sparing mastectomy with sentinel lymph node biopsy is recommended. Sentinel node biopsy is performed to ensure the opportunity for lymphatic mapping will not have been sacrificed should occult invasive disease be identified on final pathology.

The role of sentinel node biopsy in DCIS treated with lumpectomy is less clear. Some have advocated for sentinel node biopsy in DCIS treated by lumpectomy when the diagnosis is based on a core needle biopsy since the risk of an invasive cancer at definitive excision ranges between 10% and 20%. In the largest series of sentinel node biopsy for pure DCIS, a 5% rate of nodal metastasis was described; however, 70% of these metastases were detected only by IHC staining (94). Others have suggested stratifying the risk of invasion based on retrospective studies, acknowledging that the implications of IHC positive nodes is unclear, especially in the context of known disease-specific survival from DCIS of 99% (95). Taking into account the published literature, consideration of lymphatic mapping is reasonable for a span of DCIS greater than 4 cm or a mass on mammography, palpable DCIS, high-grade DCIS, and in the presence or question of microinvasion (96).

Early Invasive Disease

Early invasive breast cancer is almost uniformly diagnosed by imaging modalities. While breast MRI has emerged as a valuable adjunct in the diagnostic evaluation of breast cancer, its widespread use as a screening tool has largely yet to be realized. Therefore, the majority of patients will present with lesions that have been identified by mammography.

Once the diagnosis of invasive cancer is established in early-stage disease, surgical planning commences. A thorough history, including family history, and physical examination is essential to establish both the patient's presentation and extent of clinically apparent disease, to screen for contraindications to BCT, classical multicentricity, or poor breast-tumor volume ratio, or contraindications to adjuvant radiation therapy, such as certain connective tissue disorders, pregnancy, or prior irradiation. Particular attention to the location of the tumor, its palpability, fixation to the skin or underlying chest wall, cutaneous changes, nipple irregularities, and regional nodal assessment are paramount. When there is a concern regarding family history, a referral to a genetic counselor for consultation regarding hereditary mutations is recommended.

Breast MRI has been employed in the evaluation of extent of disease with indeterminate success. While disease extent may be better delineated by MRI, and mammographically occult disease outside the operative field has been described (97), the only prospective randomized studies have failed to show any advantage to preoperative breast MRI, such as reduced positive margins, decreased local recurrence, or improved survival; yet an increased rate of unnecessary mastectomy due to false-positive MRI findings has been documented (98). However, the COMICE trial was underpowered, and the patients were across the full age and breast density spectrums. Furthermore, patients were taken to mastectomy with un-biopsied MRI findings. Prospective studies limited to the patients where MRI seems to realize the greatest benefit, the young with dense breasts, are unavailable.

Breast-conservation surgery should aim to resect the primary tumor with clear margins. This can be achieved either with the needle localization technique or one of the many other techniques that have been described in the literature to localize the lesion, such as intraoperative US localization or radioisotope guided resection (99,100). The ideal margin for breast cancer

in a wide local excision has been a well-published challenge; after all, an acceptable margin for one pathology may not be appropriate for another. In an recent review (101), Morrow references the exhaustive review of the technique and significance of the surgical margin for invasive breast cancer by Singletary, who analyzed 38 representative studies examining the impact of surgical margin on local recurrence (102). While it is difficult to discern a distinction between the significance of 1, 2, 3, or greater than 5 mm margins in patients with invasive breast cancer treated with whole breast irradiation with tumor bed boost, an increased local recurrence rate was demonstrated in patients with positive margins. Young age, large tumor size, positive lymph nodes, and the absence of systemic chemotherapy or endocrine therapy were identified as significant independent predictors of locoregional recurrence. The impact of the biology of the underlying cancer continues to be realized as research focuses on the impact of genomic analysis. The time-dependent nature of recurrence is further elaborated by Neuschatz et al. who showed that graded tumor-bed escalation in breast irradiation may establish equivalence in local recurrence for involved margins initially, but that after 5 years of follow-up, the local failure in the close/positive margin groups becomes apparent (103). While local failure was initially viewed as recoverable by mastectomy without impact on OS, the meta-analysis showed a survival disadvantage, with one mortality associated with every 4 recurrences at 15 years of follow-up (104).

Intraoperative margin analysis to ensure adequacy has been explored primarily using frozen section analysis, touch imprint cytology, or intraoperative imaging. A promising technique of treating potential positive margins is the use of intraoperative radiofrequency ablation, where a multipronged probe is deployed into the surrounding breast tissue at the completion of the lumpectomy before wound closure (105). Ablation is performed under US visualization for 15 minutes. Twenty-five percent of patients avoided returning for re-excision due to close margins evident on final pathologic analysis. However, longer follow-up is needed to ensure that the local recurrence remains low. A prospective randomized double-armed trial of the margin probe, a newer handheld device that utilizes radiofrequency signals to analyze the lumpectomy margin, reports a 56% reduction in re-excision with a positive margin rate of 5.6% in the probe group and 12.7% in the control arm (106).

Locally Advanced Breast Cancer

Locally advanced breast cancer is variously defined as primary tumor size greater than 3 to 5 cm, involvement of the chest wall, skin ulceration or satellitosis, and/or positive axillary nodes (107,108). Approximately 6% of breast cancers in the United States present as locally advanced breast cancer (LABC). These patients are candidates for neoadjuvant chemotherapy or endocrine therapy, which results in a higher rate of breast conservation, without a reduction in either DFS or OS (109). Additionally, neoadjuvant therapy has not been shown to increase the complication rate of surgery or delay the onset of further postoperative treatment. From a biological standpoint, neoadjuvant therapy provides the opportunity to assess the chemosensitivity of breast tumors *in vivo*. The use of neoadjuvant chemotherapy does result in a 30% and 40% decrease in the incidence of axillary nodal involvement, and up to a 20% complete response in responding patients (110–112). While neoadjuvant chemotherapy has not been shown to improve survival in LABC, it has demonstrated that up to 80% patients have significant breast tumor shrinkage, and only 2% to 3% will have progression of disease (108,109).

Approximately 25% of patients not candidates for breast conservation before treatment were able to conserve their breast after the administration of neoadjuvant chemotherapy. Data

from the NSABP B-18 trial demonstrated that patients who achieved a pathological complete response (pCR) have better survival than those who were partial responders (110). Kuerer et al. also demonstrated that the presence of residual disease in the axillary lymph nodes was a predictor of poor outcome and was associated with higher incidence of locoregional (14% vs. 5% in patients achieving a pCR in the nodes) and distant metastases (41 vs. 15%) (112). In this study, the eradication of nodal metastases was associated with improved survival. In addition, a pathologic complete response to neoadjuvant therapy has been more commonly noted in younger patients and in tumors that are ER negative (ER-), high-grade, ductal, and HER2/neu positive if treated with trastuzumab. Cancers with a high proportion of intraductal cancer and lobular carcinomas are also less likely to attain a complete pathologic response. Yet, the prognostic implications of failure to attain pCR do not seem to translate to the luminal A hormone positive and luminal B HER2/neu negative breast cancers (113). Neoadjuvant endocrine therapy has been used mainly in older women with ER+ disease; aromatase inhibitors are more effective than tamoxifen in inducing a local response but pCR is rare with endocrine therapy alone. The ACOSOG Z-1031 trial showed equivalent response rates to anastrozole, letrozole, and exemestane, with 51% patients with a planned mastectomy transitioning to breast conservation (114). A core biopsy of the breast is used to establish diagnosis and to obtain prognostic histologic features of the primary tumor. Multiple cores allow for staining for receptors and HER2/neu. A negative biopsy in the setting of a clinically suspicious or dominant breast mass should prompt additional work-up with open biopsy. If the patient could be a candidate for breast conservation with appropriate downstaging of tumor size, a microclip should be placed in the relevant breast tumor(s). This facilitates later identification of the cancer site in case of complete response to neoadjuvant therapy. Additionally, axillary evaluation establishes the nodal stage. For palpable disease, a needle biopsy can be performed, with either axillary US with needle biopsy or sentinel node biopsy being reserved for nonpalpable disease.

Nonetheless, clinical examination of the axilla remains unreliable, with reported false-negative examination in 21% to 42% of cases (110,115,116). Hence, other methods of accurately staging the axilla before initiation of treatment have been explored. US combined with physical examination has been shown to increase the reliability of axillary evaluation (117). Further, fine needle aspiration cytology of suspicious nodes, defined as size greater than 1 cm, loss of fatty hilum, cortical hypertrophy, and hypoechogenic parenchyma, has a reported sensitivity and specificity of 36% to 92%, and 69% to 100%, respectively (118–120). In a study of 103 cases of indeterminate or suspicious appearing lymph nodes from the University of Texas MD Anderson Cancer Center, only 11% node-positive patients were missed by US-guided cytology (120). All cases with 3 or more positive nodes, and 93% of cases where the size of the metastatic deposit was greater than 5 mm, could be identified by this technique. In this study, the overall sensitivity of ultrasound-guided fine needle aspiration (US-FNA) was 86%, specificity was 100%, PPV was 100%, and the NPV was 67%. Despite this, the false-negative rate of US-FNA remains 15% to 20% in the reported literature, and a major limitation of US remains the inability to detect metastases less than 5 mm in size. While the identification of node-positive disease by US-FNA can reduce the number of sentinel lymph node biopsy (SLNB) procedures by up to 15% and identify those patients who would not otherwise be candidates for neoadjuvant chemotherapy, sentinel node biopsy is still required in those patients who are node-negative based on US-FNA (119,121). Re-evaluation of the axilla after neoadjuvant therapy has also been reported in small studies to be predictive of axillary downstaging (117).

The timing of sentinel node biopsy in the US-FNA node-negative patient relative to chemotherapy remains controversial.

Small single-institution studies demonstrate the feasibility of lymphatic mapping subsequent to neoadjuvant chemotherapy, and the largest trial of 428 patients from the NSABP B-27 trial described a false-negative rate of 10.7% comparable to 9.8% in the NSABP B-32 trial of sentinel node biopsy in patients undergoing primary surgery (88). However, given the potential downstaging of the axilla, there remain concerns about establishing the extent of nodal involvement as patients with greater than 4 positive nodes will have alteration in radiation therapy field distribution. Chagpar et al. have attempted to develop a nomogram to assist in identifying those patients more likely to require extended field radiotherapy (122).

Even for patients with known node-positive disease the idea of delayed lymphatic mapping affords the opportunity for axillary downstaging. Preliminary studies had been promising, with a false-negative rate of 9.8% of sentinel node biopsy in patients with a known positive axillary node treated with neoadjuvant chemotherapy and subsequent lymphatic mapping (123). The prospective multicenter ACOSOG Z-1071 trial analyzing the success of lymphatic mapping in node-positive patients, proven by needle biopsy without excision, who have received neoadjuvant chemotherapy has completed accrual, and data are in analysis. All patients with LABC should undergo a baseline bone scan, and CT scans of the chest, abdomen, and pelvis since 30% of these patients would have metastatic disease (124). Patients are clinically assessed for response after 2 to 3 cycles, and radiological response can also be recorded at this time. If no response is present, a decision is made to continue with surgery if possible, or to change systemic therapy. Prior to surgical decisions being made, re-imaging of the breast should be performed as clinical examination alone is unreliable (125–128). Occasional patients will have residual microcalcifications or DCIS while the invasive cancer has a complete pathologic response (129). The contraindications for breast conservation after neoadjuvant chemotherapy are similar to those for primary BCT and include residual tumor >5 cm, skin edema or involvement, chest wall fixation, diffuse calcifications on postchemotherapy mammogram, multicentric disease, and contraindications to radiation therapy. As the risk of local recurrence after breast conservation in patients undergoing neoadjuvant therapy is slightly higher, the use of postmastectomy radiation in patients with larger cancers and persistently positive axillary nodes is recommended (109,130).

Immediate reconstruction in patients with LABC undergoing mastectomy has been shown to have a slightly higher rate of complications and result in a delay in treatment, as well as problems with cosmesis when postmastectomy radiation therapy is required. Given the multiple issues that are at play in the patient desiring immediate reconstruction, early consultations with both plastic surgery and radiation oncology should be performed, preferably before any surgery takes place.

Management of the Axilla

Although the clinical implications of axillary lymph nodal involvement has taken a varied course over the years, it still remains a major prognostic indicator of survival in breast cancer (131). Additionally, an axillary dissection remains of value in improving local control in patients with clinically positive axillae, though this has not translated into improved survival.

The largest prospective randomized trial evaluating the role of axillary lymphadenectomy was the NSABP-B04 trial (131). In this trial, 1,079 women underwent radical mastectomy including an axillary dissection, total mastectomy with axillary radiation, or total mastectomy alone. Of note, patients did not receive systemic therapy on study. The results showed an axillary recurrence rate of 5% in clinically node-negative patients treated with surgery or irradiation compared to 20% when the axilla was observed. However, there was no difference in the rate of

distant metastases or in survival in clinically node-negative breast cancer patients after 25 years. Most patients with axillary recurrence were salvaged by the performance of a delayed axillary dissection, whereas 1 patient had inoperable regional disease. This study thus demonstrated that leaving behind axillary nodes with metastatic disease had no significant impact on the overall outcome of the disease. A Danish randomized trial compared an extended radical mastectomy with nodal resection to total mastectomy with postoperative radiation, showing similar survival and suggesting that axillary radiation might be an acceptable alternative to surgical dissection of the axilla (132). In light of these data, the American College of Surgeons Oncology Group under Dr. Armando Giuliano designed the landmark Z-0011 trial opening in 1999 (133), the results of which have challenged the axillary management paradigm. In this revolutionary study, patients with T1–2 tumors with a clinically negative axilla undergoing BCT with radiation, and with 1 to 2 positive sentinel nodes identified at surgery, were randomized to axillary dissection, or no further surgery. Radiation to the axilla was disallowed. Patients were eligible regardless of age or receptor status. All received whole breast radiation, and 98% received adjuvant systemic therapy. The study failed to accrue well and closed with 931 patients. Yet with 6 years follow-up, the group reported an OS of 92%. There was no survival advantage from completion axillary dissection. The operative group had a 27% node-positive rate, and given the randomized nature of the study, it follows that the nondissected group also had a 27% rate of positive nodes left *in situ*. Yet there was no significant difference in local-regional recurrence (134). It is critical to realize in this study that all patients received whole breast radiation and the overwhelming majority received adjuvant systemic therapy.

A complete axillary dissection involves removal of the Level I to II nodal tissue from the axilla. This is defined as the space bounded by the pectoral muscles anteriorly, the latissimus dorsi muscle posteriorly, and axillary vein superiorly. The nerves to the latissimus dorsi and serratus anterior are preserved. If possible, the intercostobrachial nerve is also preserved to decrease the risk of arm paraesthesias. Level III nodes, which can be accessed only by dividing the pectoral tendon, are usually not removed. These are included in the radiation field, which is recommended if multiple nodes are involved. The risk of lymphedema with this procedure is quoted at 6% to 50% (135,136). Axillary reverse mapping (ARM) has been developed as a technique of identifying the lymphatic channels and nodes that drain the arm rather than the breast. In a small series of 23 patients, 86% of the ARM nodes were uninvolved, whereas 20/23 had metastatic lymph nodes in the axilla (137). Potentially, there may be an ability to avoid these structures in axillary dissection, but the success of the technique in avoiding lymphedema remains unvalidated.

Sentinel Node Biopsy

The concept of sentinel lymph node biopsy was designed to evaluate the stage of the disease in lieu of lymphadenectomy. It has revolutionized the surgical management of the axilla, and largely replaced axillary dissection in the node-negative axilla. In a recent meta-analysis involving 69 trials run between 1970 and 2003 and over 8,000 patients, the false negative rate averaged 7.3% across studies (ranging from 0% to 29%) (138).

While Dr. Donald Morton pioneered lymphatic mapping in the surgical management of melanoma (139), the simplicity and elegance of this technique was championed by Giuliano for breast cancer utilizing the blue-dye-only technique with lymphazurin dye to identify the sentinel nodes, while the radioisotopic technique followed 1-year later and is credited to Krag (88,140). Currently, a combination of these techniques has become most widely employed, although continued controversy persists on the different techniques of injection, whether they be

peritumoral, subareolar, or subdermal (141,142). Although all are likely successful in the majority of patients, the peritumoral technique may be important for posteriorly situated lesions. The subareolar technique may not drain to the internal mammary nodes (143). Methylene blue, diluted 1:4 in saline, is easily substituted for isosulfan blue, which has rare but real allergic reactions (144).

Following injection of isotope, the dissection begins with a separate axillary incision. Dissection is taken down to the clavicular fascia, which is opened. The axilla is interrogated with a hand-held receiving device, and further exploration for the “blue or hot” node is performed. The node is carefully dissected from the surrounding tissue, paying attention to close dissection, as the critical motor nerves have not been identified. Each node is subsequently removed and counted over 10 seconds; if more than 1 node comes out together, they should be separated. The node with the highest count becomes the benchmark, and all nodes with greater than 10% activity are considered sentinel nodes. If blue dye is used, any blue node or node with a blue stained lymphatic adjacent is a sentinel node. The sentinel nodes may be hot, blue, or hot and blue. Each technique used independently gives a 90% identification rate, and 95% when combined. Each agent’s benefits are inherently obvious: the visualization of the blue dye, and the audibility of the isotope. Before completion of the procedure, the axilla must be digitally evaluated for any palpable nodes, as false negativity is common with nodes replaced by tumor. Furthermore, care to try to identify low-lying nodes in the axillary tail of the breast is useful. An anatomical description by Clough divided the axilla into 4 zones, separated by the lateral thoracic vein and the second intercostal brachial nerve. In this scheme, in 242 Stage I/II breast cancer patients, the sentinel node was identified in medial to the vein 98.2% of the time, usually below the nerve (86.8%). The upper lateral zone, adjacent to the lymphatic drainage of the arm, never contained the sentinel node (145). While lymphatic mapping to the internal mammary chain has been performed, its impact on outcome remains unclear (146).

It has now been demonstrated that sentinel lymph node evaluation is feasible and accurately predicts the regional nodal status (139,140,147). The analysis of the few removed sentinel lymph nodes enabled pathologists to do multiple sections and a far more careful analysis of a few nodes, rather than a single section of the 10 to 20 nodes usually obtained from an axillary dissection. This detailed examination has sharply increased (by 20% to 30%) the proportion of “positive” nodes.

Intraoperative assessment of sentinel lymph nodes using touch imprints and routine IHC staining is used by some to enable an immediate therapeutic lymphadenectomy if the nodes were positive, thus sparing the patient from a second procedure. However, intraoperative assessment may have unacceptable rates of false-negative results, ranging from 36% to 71% (148). Not all “positive” sentinel lymph nodes require a subsequent therapeutic lymphadenectomy since studies have shown low risk of regional nodal recurrence after observation only for patients with a positive sentinel lymph node (149) and given the ACOSOG Z-11 trial. Nonetheless, patients undergoing mastectomy, neoadjuvant chemotherapy, or not receiving whole breast radiotherapy were not addressed in Z-11, and intraoperative nodal assessment continues to remain pertinent.

For this unaddressed cohort, we strive to ascertain which of the patients with a positive sentinel node need axillary node dissection. Nomograms predicting the extent of further nodal involvement have been developed and continue to assist us in the areas where Z-11 does not apply (150,151).

Current data suggest that with smaller tumor size in the era of mammographic screening, only 30% of breast cancers are node-positive at presentation. In approximately 50% to 60%, the only positive node is the sentinel node. Data from the NSABP B-04 and other trials, performed before the routine use

of systemic chemotherapy, demonstrated no survival benefit in removing the axillary lymph nodes for occult disease.

The use of axillary dissection and sentinel node biopsy comes at a cost to the patient. The incidence of lymphedema after axillary dissection and after axillary radiation is similar and higher when the two are combined. For sentinel node biopsy, the Z-10 trial found a 7% incidence of lymphedema defined as greater than 2-cm circumferential change. Overall, 50% to 70% patients have some complaint after axillary dissection, including restricted shoulder motion (17%), intercosto-brachial nerve numbness (78%), and pain (25%); though less frequent than in sentinel node biopsy patients, these problems are still possible (116). Though these problems are not life threatening, their effect on quality of life can be significant (152). The ARM technique has also been applied to sentinel node biopsy and may be useful in reducing lymphedema for this procedure as well (153).

Oncoplastic Surgery

Subsequent to the revolutionary advances taking surgeons from radical mastectomy to lumpectomy and axillary dissection, there remained a cohort of patients who required mastectomy to either resect their disease adequately, or who had significant risk of future breast carcinoma such that breast conservation was deemed inappropriate. For these patients continuing with the standard simple mastectomy, nodal evaluation lagged behind advances already achieved. Immediate reconstruction after mastectomy had been clearly documented to be safe from an oncological perspective and beneficial to a patient’s well-being for over 15 years (154). A more ideal technique of complete resection of the breast, with preservation of unaffected structures emerged and was primarily championed by Simmons et al. (155). Their landmark article compared recurrence patterns in women treated by skin-sparing mastectomy (SSM) versus non-SSM and demonstrated local recurrence rates of 3.90% and 3.25%, respectively, with an equivalent distant recurrence rate of 3.9% at 5 years.

SSM involves resection of the nipple areolar complex and nodal evaluation, when indicated, but with preservation of the entire overlying skin envelope. While initially reserved for early-stage breast cancer, Foster et al. have shown that SSM can be used in LABC stages IIB and III with comparable local recurrence (156). A recent analysis of recurrence patterns reveals that local recurrence is usually in the same quadrant as the disease and is more common with high-grade DCIS or grade 3 invasive tumors (157).

Given a retrospective analysis revealing that malignant involvement of the areola is uncommon (0.9%) (158), both the areola and nipple sparing mastectomy (NSM) have emerged as oncologically safe techniques for achieving a cosmetic mastectomy in appropriately selected patients (159,160). A recent meta-analysis of SSM and NSM versus non-SSM demonstrated equivalent local recurrence (6.2% vs. 4.0%) regardless of technique, with a follow-up of 37.5 to 101.0 months (161). In a pure NSM cohort of 658 patients, local recurrence was 2.4% at 3 year follow-up, and the complications of partial or full nipple necrosis and flap necrosis were 3.5% and 11.9%, respectively (162,163). Furthermore, the technique was extended to patients with more advanced disease, especially after neoadjuvant chemotherapy. The Milan group has used intraoperative radiotherapy (IORT) to reduce recurrence, but the risk of nipple necrosis is approximately 10% in most series (164). Intraoperative frozen section analysis of the subareolar ductal system to exclude occult disease is reported at 98.5%, but this is likely to be dependent on local expertise. The sensitivity of the preserved nipple areolar complex ranges widely in the literature.

While the reconstructed breast proved to appear more natural, the desire for improved breast conservation has remained

paramount, where we can provide not only the greatest assurance of nipple-areolar function, but to a lesser extent, minimize the sense of “violation” in the patient. Adopting techniques from breast reduction, breast surgeons have now expanded their armamentarium in achieving cosmetically desirable lumpectomy. Incorporation of breast reduction or mastopexy with lumpectomy has yielded successful results that translate to improved cosmetic outcome for patients with either macromastia or ptotic breasts. More recently, a clearer delineation of an array of techniques that utilize simple reshaping or local tissue transfer that diminishes skin retraction post lumpectomy has been developed (165). Clough has defined 3 factors, tumor size, location, and breast tissue density, that guide in the selection of appropriate oncoplastic surgical (OPS) techniques. His comprehensive quadrant-by-quadrant atlas approach to breast-conservation surgery separates techniques into two levels. Level 1 utilizes simple tissue undermining and approximation and potential nipple-areola recentralization, but without significant skin excision, whereas level II techniques permit greater tissue resection, and involve more complex procedures based on breast reduction procedures (163). Given that these techniques afford a greater volume of resection, in-breast tumor relapse remains low; the essential goal of oncoplastic surgery is greater attainment of clear margins, reduced re-excision and mastectomy, and ultimately, improved patient satisfaction and well-being.

CHEMOTHERAPY

Biologic Therapy

Biologic Therapies in HER2 Positive Breast Cancer

Approximately 20% of newly diagnosed invasive breast cancers overexpress human epidermal growth factor receptor 2 (HER2). This is associated in most, if not all, cases with the presence of additional copies of the gene that codes for the HER2 protein on chromosome 17. While the cause of this HER2 gene amplification, which is found only in the patient's breast cancer cells, is not understood, its biologic implications are clear—increased density of HER2 on the surface of the malignant cells leads to the formation of both homo- (HER2:HER2) and heterodimers with other members of the HER receptor family (HER1, HER3 and HER4), triggering activation of tyrosine kinases associated with the intracellular portions of the receptors, which in turn trigger a number of signaling pathways that enhance cancer cell growth and proliferation, resistance to apoptosis, and metastatic potential. The goal of HER2-directed therapy is to block this activation, which also has the effect of enhancing sensitivity to other antitumor treatments.

In 2007 a consensus panel of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) defined patients as having an HER2 positive (HER2+) breast cancer if either 1) at least 30% of their tumors cells exhibit uniform intense staining (3+) for HER2 by IHC stain; or 2) their tumor cells display either an average of more than 6 HER2 signals per cell or a ratio of HER2 to chromosome 17 (using a centromeric probe) (HER2/CEP17) signals by FISH of >2.0 (166). How to categorize, and thus how to treat, tumors with a subpopulation of cancer cells that display marked HER2 gene amplification but whose average FISH ratio is less than 2.0, and aneuploid tumors with numerous copies of chromosome 17 (and thus HER2) but a HER2/CEP17 ratio of less than 2.0, remains controversial.

Adjuvant Therapy for HER2+ Breast Cancer

Patients with HER2+ early-stage breast cancers are at increased risk for distant disease recurrence and death compared to patients

with HER2 negative (HER2-) cancers of identical size and stage. While adjuvant chemotherapy that incorporates both an anthracycline and a taxane, whether given concurrently or sequentially, clearly improves DFS and OS in this group of patients (167,168), they still remain at significant risk of relapse, especially if they have a larger primary tumor or axillary lymph node involvement at diagnosis. Once the addition of trastuzumab to taxane-based chemotherapy was demonstrated to be both effective and well tolerated in patients with HER2+ metastatic breast cancer (see below), studies were initiated to study its benefit in the adjuvant setting. In 2005, the initial results from 3 clinical trials—a joint analysis of two similar though not identical U.S. studies and a European study—were presented and published, each demonstrating substantial improvements in DFS and OS with the addition of trastuzumab during or after standard adjuvant chemotherapy. Results from these studies were recently updated (169,170).

In both the North Central Cancer Treatment Group (NCCTG) 9831 study and the NSABP B-31 study, patients received 4 cycles of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² (AC) every 3 weeks followed by paclitaxel, administered at 80 mg/m² weekly for 12 weeks (NCCTG) or either 80 mg/m² weekly for 12 weeks or 175 mg/m² every 3 weeks for 4 cycles (NSABP). Patients were randomized to receive trastuzumab 2 mg/kg weekly for 52 weeks or not; all patients on the NSABP study assigned to trastuzumab started it concurrent with the paclitaxel, while a third of the patients on the NCCTG study started trastuzumab concurrent with paclitaxel and another third did not start it until after completing the paclitaxel. The comparison of concurrent vs. sequential trastuzumab is discussed below; the following focuses solely on the patients who received concurrent chemotherapy and trastuzumab. The two arms of the studies included 4,045 patients, almost all of whom had node-positive HER2+ cancers. At last report, patients assigned to trastuzumab had a 48% improvement in DFS and a 39% improvement in OS; this translated into an 8% absolute improvement in DFS and a 7.4% absolute improvement in OS at 4 years. Patients in all subgroups (defined by age, tumor size, tumor grade, hormone receptor (HR) status, and extent of nodal involvement) benefited from the addition of trastuzumab. The addition of trastuzumab was associated with an increase in serious cardiac events (symptomatic congestive heart failure or death attributed to cardiac causes) from less than 1% for the control arms to 3% to 4% in the concurrent trastuzumab arms; risk factors for cardiac events included age ≥60 years of age, pre-existing hypertension, or a low normal left ventricular ejection fraction at baseline (169).

The Herceptin Adjuvant (HERA) trial randomized 5,090 women with HER2+ cancers who had completed adjuvant chemotherapy of their physician's choice (with <25% of patients receiving both an anthracycline and a taxane) to observation or the addition of 1 or 2 years of adjuvant trastuzumab. Thus far, only results for the 1-year arm have been reported. Compared to controls, patients assigned to a year of trastuzumab had a 24% relative (6.4% absolute) improvement in DFS at 4 years. By intention-to-treat analysis, patients assigned to trastuzumab had a nonsignificant 15% relative (1.6% absolute) improvement in OS, but results are confounded by the fact that 52% of patients on the observation arm crossed over to receive adjuvant trastuzumab at a median of 22.8 months from their original randomization. While patients assigned to trastuzumab had higher rates of grade 3 to 4 adverse events, the overall incidence of serious adverse events was low, and less than 1% of patients developed symptomatic congestive heart failure (170).

Given concerns about the incidence of cardiotoxicity seen in patients with HER2+ metastatic breast cancer who received both an anthracycline and trastuzumab, and the demonstrated synergy between trastuzumab and a variety of chemotherapeutic agents *in vitro*, the Breast Cancer International Research

Group (BCIRG) 006 trial was designed to test the efficacy and toxicity of a non-anthracycline-based chemotherapy regimen plus trastuzumab against a standard anthracycline-based chemotherapy regimen with or without trastuzumab (171). 3,222 women with node-positive (72%) or node-negative HER2+ breast cancer were randomized to 4 cycles of AC followed by 4 cycles of docetaxel 100 mg/m² every 3 weeks, with or without trastuzumab 6 mg/kg every 3 weeks started concurrent with the switch to docetaxel (AC-T and AC-TH), or carboplatin AUC 6, docetaxel 75 mg/m² and trastuzumab 6 mg/kg every 3 weeks for 6 cycles (TCH). Compared to AC-T, both trastuzumab-containing regimens demonstrated significant improvements in DFS—36% relative/9% absolute for AC-TH, 25%/6% for TCH—and OS—37%/5% for AC-TH, 23%/4% for TCH—at 5 years. The differences in DFS and OS between AC-TH and TCH are not statistically significant, but the study was not powered to compare these two arms. Of note, TCH was associated with a lower rate of congestive heart failure (0.4%) than either AC-TH (2%) or AC-T (0.7%), and a lower likelihood of a sustained drop in left ventricular ejection fraction (LVEF) (9.4% vs. 18.6% for AC-TH and 11.2% for AC-T). The addition of carboplatin in the TCH arm increased the incidence of anemia and thrombocytopenia, while the lower dose of docetaxel reduced the incidence of myalgias and arthralgias, and sensory and motor neuropathy. In addition to reducing cardiac toxicity, dropping the anthracycline reduced vomiting and mucositis, and appeared to markedly reduce if not eliminate the small but real risk (0.33% in patients on AC-T or AC-TH) of developing a treatment-related leukemia.

Concurrent trastuzumab with taxane-based chemotherapy appears to be more effective than sequential treatment. In addition to the greater improvements in DFS and OS reported by the NCCTG and NSABP trials compared to HERA, a recent analysis of patients on the NCCTG study assigned to receive trastuzumab after completion of chemotherapy (172) demonstrated that while these patients still had significant improvements in DFS and OS compared to patients who did not receive trastuzumab, there was a clear trend favoring concurrent over sequential treatment (a 23% relative improvement in DFS and 22% in OS), though this did not achieve statistical significance.

As exciting as the results from the adjuvant trastuzumab trials have been, the 4 trials reviewed above all administered at least 1 year of trastuzumab (barring toxicity)—the only duration of treatment question being addressed is whether 2 years of trastuzumab is more effective than 1 (by the HERA trial). Whether this duration of treatment, and the associated costs, inconvenience, and toxicities, are necessary to achieve benefit from adjuvant trastuzumab is not clear. The Finland Herceptin (FinHer) trial randomized 232 HER2+ patients to chemotherapy (3 cycles of docetaxel 80 mg/m² or vinorelbine 25 mg/m² days 1 and 8 every 21 days) with or without 9 weeks of trastuzumab, followed by 3 cycles of FEC (173). Patients assigned to receive trastuzumab had nonsignificant trends toward improved DFS (35% relative improvement) and OS (45% relative improvement) at 5 years, and no evidence of increased cardiac toxicity. Shorter durations of adjuvant trastuzumab are currently being studied; the identification of an equally effective but briefer adjuvant trastuzumab regimen would be of great benefit in terms of optimal use of medical resources.

For high-risk HER2+ patients with no contraindication to administration of an anthracycline (no characteristics suggesting an increased risk of significant cardiotoxicity), we still favor AC followed by weekly paclitaxel with initiation of weekly trastuzumab concurrent with the paclitaxel, followed by trastuzumab 6 mg/kg every 3 weeks to complete a year of trastuzumab. In patients with any contraindication to treatment with an anthracycline, those who, after discussing treatment alternatives, opt not to receive an anthracycline, and patients with relatively low-risk (such as T1N0) cancers, we are comfortable administering the TCH regimen.

Patients who are going to receive an anthracycline-based chemotherapy regimen followed by trastuzumab should have cardiac function evaluated (with an echocardiogram or gated cardiac ejection fraction scan) prior to starting chemotherapy and prior to starting trastuzumab, after which cardiac monitoring should be individualized based on patient age, baseline ejection fraction, and risk factors for developing cardiac dysfunction. Guidelines for holding or discontinuing trastuzumab in patients with symptoms of cardiac dysfunction or a falling LVEF should be followed.

Current areas of interest include determining whether substitution of or addition of lapatinib (an HER2 tyrosine kinase inhibitor discussed in the section on treatment of HER2+ metastatic disease) to trastuzumab (concurrent or sequential) will further improve DFS and OS; this is being addressed by the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial (NCT00490139), which has completed accrual of 8,381 patients. There is also interest in trying to identify effective but briefer and/or less toxic chemotherapy regimens to administer with adjuvant trastuzumab. At the San Antonio Breast Cancer Symposium in 2011, early results were presented for a phase II adjuvant trial of 486 patients with lower-risk HER2+ disease (79% node-negative, 68% $T \leq 2$ cm) treated with 4 cycles of docetaxel and cyclophosphamide every 3 weeks and a year of trastuzumab. At 3 years, DFS was 95%, and OS was 99%. A phase II trial of weekly paclitaxel and trastuzumab for 12 weeks followed by single-agent trastuzumab has completed accrual of 400 patients with $T \leq 3.0$ cm, node-negative HER2+ cancers.

The role of chemotherapy and trastuzumab in patients with small (T1a or T1b), node-negative HER2+ cancers is also controversial. While some retrospective analyses have reported higher rates of overall and distant disease recurrence for patients with small HER2+ cancers compared to small HER2- cancers (174), whether all such patients warrant systemic adjuvant therapy is unclear. Our inclination is to treat patients with T1bN0 cancers, especially if they are HR-negative (HR-), unless the patient has a contraindication to receiving chemotherapy. Whether to treat any T1aN0 cancers, or T1bN0 HR positive (HR+) HER2+ cancers, is less clear. Whether patients with early-stage, HR+, HER2+ cancers, who have a better prognosis than patients with HR-, HER2+ cancers, might derive sufficient benefit from a combination of endocrine and HER2-targeted therapy to eliminate the need for chemotherapy has not been studied.

Neoadjuvant Therapy in HER2+ Disease

Given the rapid growth kinetics of HER2+ breast cancers, it is not surprising a significant percentage of patients with these cancers present with large tumors or locally advanced disease, making them good candidates for neoadjuvant therapy. While the percentage of patients with HER2+ cancers who achieve a pCR with neoadjuvant chemotherapy alone, especially those with HR-/HER2+ disease, is relatively high, blocking HER2 signaling clearly enhances the chemosensitivity of HER2+ breast cancers. Two prospective randomized studies have demonstrated significant improvements in pCR rates with the addition of trastuzumab (175,176), and a recent retrospective analysis confirmed improvement of DFS in HER2+ patients who receive trastuzumab as part of their neoadjuvant regimen.

A pooled analysis of the 2 randomized studies (177) reported that the addition of trastuzumab to the control chemotherapy regimen doubled the pCR rate, and improved both DFS and OS by 33% (though the OS increase did not reach statistical significance); treatment with trastuzumab (in both studies given concurrent with an anthracycline) was associated with a non-significant increased risk of cardiac dysfunction. In the larger of the two studies, the NOAH trial, 235 women were treated with

doxorubicin and paclitaxel followed by cyclophosphamide, methotrexate, and 5-fluorouracil plus or minus trastuzumab for 1 year. Compared to chemotherapy alone, the addition of trastuzumab increased the pCR rate from 23% to 43% and increased event-free survival at 3 years from 56% to 71%, but was associated with a 2% rate of symptomatic congestive heart failure.

These studies support the use of trastuzumab plus chemotherapy in the neoadjuvant setting for HER2+ breast cancer, but given concerns about the risk of cardiac dysfunction associated with concomitant administration of an anthracycline and trastuzumab, combining these agents should be avoided until further data on the safety of that approach become available. One standard neoadjuvant regimen for a HER2+ patient includes 4 cycles of doxorubicin and cyclophosphamide administered every 2 or 3 weeks followed by 12 weeks of weekly paclitaxel (80 mg/m²) plus trastuzumab (4 mg/kg week 1 then 2 mg/kg weekly) as neoadjuvant therapy, then single-agent trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks) after surgery to complete a full year of the biologic treatment. This is similar to the most effective trastuzumab-containing regimen from the NCCTG adjuvant trial (169).

Other appropriate neoadjuvant regimens for patients with HER2+ cancers include those used as adjuvant treatment in early-stage HER2+ breast cancer, such as AC followed by paclitaxel or docetaxel every 3 weeks, with initiation of the trastuzumab concurrent with the taxane, or a non-anthracycline-containing regimen such as docetaxel, carboplatin and trastuzumab (TCH) every 3 weeks for 6 cycles or even, in lower-risk HER2+ patients, docetaxel, cyclophosphamide, and trastuzumab every 3 weeks for 4 to 6 cycles (based on I1). A phase II study of neoadjuvant dose-dense TCH (administered every 2 weeks for 6 cycles) in 48 HER2+ patients reported a pathologic complete response rate of 36%.

More recently, there has been interest in administration of dual HER2-targeted treatments together with neoadjuvant chemotherapy to overcome potential trastuzumab resistance. The NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimization (Neo-ALTTO) trial randomized 453 women with stage II-III HER2+ breast cancers to lapatinib 1,500 mg daily, trastuzumab, or the combination of trastuzumab and lapatinib 1,000 mg daily (178). Patients received 6 weeks of HER2-targeted therapy alone, followed by 12 weeks of weekly paclitaxel (80 mg/m²) along with their assigned HER2-targeted treatment, then underwent surgery. Patients were assessed for response after the initial 6 weeks of targeted therapy as well as prior to surgery using physical exam, mammogram, and US or breast MRI. Patients assigned to the trastuzumab/lapatinib combination had a significant higher clinical response rate at the end of biologic therapy alone (67 vs. 30 and 52% with single-agent trastuzumab or lapatinib, respectively) and at the time of surgery (80 vs. 71 and 74%, respectively), a significantly higher pCR rate (51 vs. 30 and 25%, respectively), higher pCR rates in both hormone receptor positive and hormone receptor negative patients, but similar rates of BCS (41 vs. 39 and 43%, respectively). There were more serious (grade 3/4) adverse events in the groups treated with lapatinib than in the group treated with trastuzumab alone. These consisted of diarrhea, elevated transaminases, neutropenia (only during administration of paclitaxel), and rash. However, no significant cardiac adverse events were reported in any of the 3 arms.

Pertuzumab is a humanized monoclonal antibody that blocks the dimerization domain of HER2, preventing the formation of HER2 heterodimers with HER3 as well as other members of the HER receptor family. The formation of HER2:HER3 heterodimers is a proposed mechanism by which HER2+ breast cancer cells may bypass inhibition by trastuzumab. Since pertuzumab binds to a different region of HER2 than trastuzumab, dual HER2-targeting with the trastuzumab and pertuzumab

combination is being evaluated in the neoadjuvant as well as the metastatic setting (see below). The NeoSPHERE trial was an open-label randomized phase II trial that enrolled 417 women with operable, locally advanced, or inflammatory HER2+ breast cancer and randomly assigned them to 12 weeks of treatment using 1 of 4 regimens: docetaxel (100 mg/m² every 3 weeks for 4 cycles) plus trastuzumab (group A), docetaxel plus trastuzumab and pertuzumab (group B), pertuzumab plus trastuzumab alone (group C), or docetaxel plus pertuzumab (group D) (179). After surgery, patients on the docetaxel arms received 3 cycles of FEC then completed a year of trastuzumab, while patients in group C received both docetaxel and FEC followed by trastuzumab. pCR rates were 29%, 46%, 17%, and 24% in groups A, B, C, and D, respectively. Compared to women with HR+ disease, the pCR rates were generally higher in women with HR-tumors. Serious (grade 3/4) adverse events in patients treated with docetaxel (groups A, B, D) included neutropenia, febrile neutropenia, and diarrhea. The addition of pertuzumab to the docetaxel plus trastuzumab combination did not appear to increase toxicity, including any increase in the low incidence of cardiac adverse events. Few adverse events occurred in women receiving combined HER2 treatment without docetaxel (group C). These results are fascinating not only because of the higher pCR rate seen on the chemotherapy plus trastuzumab and pertuzumab arm, but also because of the frequency of pCRs associated with dual HER2-targeted therapy alone, raising the intriguing possibility that there may be a subset of HER2+ patients who can be effectively treated without the toxic effects of chemotherapy.

Treatment of HER2+ Metastatic Breast Cancer

The central role of HER2 activation in the survival and growth of HER2+ breast cancers is illustrated by the single-agent antitumor activity of trastuzumab, lapatinib, and other HER2-targeted therapies. However, they have an even greater impact when given together with cytotoxic chemotherapy, as in the pivotal phase III study that compared standard first-line chemotherapy with either doxorubicin and cyclophosphamide (AC), or single-agent paclitaxel (in patients not eligible to receive an anthracycline), alone or with the addition of trastuzumab (60). Addition of the targeted therapy not only improved response rates (RR) and time to progression (TTP), but prolonged OS (25 vs. 20 months) despite a high percentage of patients on the control arm crossing over to receive trastuzumab after disease progression. That study was also the first to demonstrate the additive or synergistic cardiotoxicity of anthracyclines and trastuzumab, as a result of which the combination of paclitaxel and trastuzumab became the initial standard regimen. Since then, trastuzumab has been shown to improve RR, TTP, and OS with a variety of different chemotherapeutic agents. Only one relatively small study has compared concurrent chemotherapy (docetaxel) plus trastuzumab to sequential single-agent trastuzumab followed by docetaxel (180), and while progression-free survival (PFS) was similar across the two arms, patients on concurrent therapy had higher RR and a trend toward improved OS (30.5 vs. 19.7 months).

The optimal first-line chemotherapy plus trastuzumab combination is not known, as few have been tested head-to-head. While taxane (usually weekly paclitaxel at 80 mg/m² or q3week docetaxel at 75 to 100 mg/m²)-based regimens remain common, some doctors and patients will opt for regimens not usually associated with hair loss, such as vinorelbine-, gemcitabine-, capecitabine- or liposomal doxorubicin-trastuzumab. Combinations of chemotherapeutic agents given with trastuzumab may (paclitaxel and carboplatin vs. single-agent paclitaxel) or may not (docetaxel and carboplatin vs. single-agent docetaxel) produce higher RR and improved TTP, but have not been shown to improve OS (181,182).

When a patient has achieved maximal benefit from a chemotherapy-trastuzumab combination or starts to develop cumulative toxicities, she is often switched to single-agent trastuzumab “maintenance” therapy, a logical strategy given the level of activity of single-agent trastuzumab but has not been tested in a randomized trial. What is clear is that HER2+ patients progressing on treatment retain sensitivity to HER2-targeted therapies. Patients progressing on trastuzumab who were randomized to capecitabine with continuation of trastuzumab had superior TTP (8.2 vs. 5.6 months) and OS (25.5 vs. 20.4 months) to patients assigned to single-agent capecitabine (183). Even before these results became available, it had been routine practice in patients with HER2+ metastatic breast cancer who were progressing on one chemotherapy-trastuzumab combination to change the cytotoxic agent but continue trastuzumab.

Lapatinib is a small molecule oral tyrosine kinase inhibitor that blocks activation of pathways triggered by either the epidermal growth factor receptor (EGFR, also called HER1) and HER2. Its most common toxicities, including diarrhea and an acneiform rash, appear to be caused by blockade of EGFR-stimulated pathways, as they are similar to those seen with EGFR-targeted monoclonal antibodies. It has modest single-agent activity in patients with HER2+ metastatic breast cancer who have progressed on trastuzumab, but, in patients previously treated with an anthracycline, taxane, and trastuzumab, the combination of capecitabine and lapatinib bested single-agent capecitabine in terms of TTP (6.2 vs. 4.3 months) and OS (75.0 vs. 56.4 weeks) (184).

Interest in lapatinib is stimulated in part by its ability to counteract some mechanisms of resistance to trastuzumab and to penetrate into areas, like the central nervous system, that trastuzumab cannot reach.

The potential merit of combined HER2 pathway blockade by agents with differing mechanisms of action is illustrated by the following studies: patients with HER2+ metastatic breast cancer who had progressed on one or more trastuzumab-containing regimens were assigned to treatment with single-agent lapatinib vs. lapatinib and trastuzumab (185); patients on the combination arm had a superior clinical benefit rate (24.7 vs. 12%), improved TTP (12 vs. 8 weeks) and a nonsignificant improvement in OS (52 vs. 39 weeks), which was likely confounded by the 49% of patients randomized to single-agent lapatinib who crossed over to the combination arm after early disease progression. In the first-line metastatic setting, 808 HER2+ patients received docetaxel 75 mg/m² and trastuzumab, and were randomized to the HER-dimerization blocker pertuzumab or placebo (186). Patients assigned to the dual-targeted agents had improved RR (80 vs. 69%; PFS, 19 vs. 12 months) and a trend toward improved OS. The addition of pertuzumab was associated with higher rates of diarrhea, mucositis, rash, and febrile neutropenia (14 vs. 8%), but no increase in cardiac toxicity.

In approximately half of the patients with HER2+ breast cancer, the tumor cells also express hormone receptors. Data from the combined analysis of the NCCTG N9831 and NSABP B-31 adjuvant trials suggest that patients with early-stage HER2+ cancers whose tumors co-express hormone receptors (HR+) have an improved prognosis whether they get trastuzumab with their adjuvant chemotherapy (4 years DFS of 89.4 vs. 81.6% for HR negative [HR-] or not (77.2 vs. 69.4%), with no decrement in the benefit from the targeted agent (169). While patients with HR+/HER2+ cancers are less likely to achieve a pathologic complete response with neoadjuvant chemotherapy plus trastuzumab, their overall prognosis is better than for patients with HR-/HER2+ cancers. On average, patients with advanced stage HR+/HER2+ cancers live longer than HR-/HER2+ patients with HER2+/HR- cancers. This presumably reflects differences in tumor biology, such as proliferative rate. While results from individual studies vary, a meta-analysis of 12 studies involving 2,379 patients with HR+ MBC treated with various endocrine

therapies demonstrated that PFS for HR+/HER2+ patients was 42% shorter compared to HR-/HER2- patients (187). The addition of an HER2-targeted agent at least partially reverses this disadvantage. The TAnDEM trial randomized 207 postmenopausal patients with HR+/HER2+ metastatic breast cancer to anastrozole with or without trastuzumab (188). Patients treated with the combination had improvement in PFS (4.8 vs. 2.4 months), as well as improved response (20.3% vs. 6.8%), and clinical benefit (42.7% vs. 27.9%) rates; the absence of a significant improvement in OS (28.5 vs. 23.5 months) may have been caused by the fact that 70% of patients assigned to anastrozole alone received trastuzumab at some point in their subsequent treatment. A double-blind study of letrozole with either lapatinib 1,500 mg daily or placebo in HR+ patients with metastatic breast cancer included 219 postmenopausal patients who were considered HER2+ (189). In these patients, the addition of lapatinib improved PFS from 3.2 to 8.0 months, RR from 15% to 28%, and clinical benefit rate from 29% to 48%. HR+/HER2- patients did not benefit from the addition of lapatinib. Side effects were those that would be expected with this dose of lapatinib. These results suggest that in older patients with less extensive or minimally symptomatic metastatic HR+/HER2+ cancer, a trial of endocrine therapy plus a HER2-targeted therapy (with close monitoring for disease progression) could be considered.

Other Biologic Therapies

Bevacizumab and Other Angiogenesis Inhibitors

Bevacizumab is a partially humanized monoclonal antibody, which was designed to bind vascular endothelial growth factor (VEGF) and inhibit tumor-stimulated neoangiogenesis. It is approved as a single agent or in combination with chemotherapy to treat a variety of advanced solid tumors. In patients with advanced breast cancer, it has modest activity as a single agent. However, when given in combination with weekly paclitaxel (90 mg/m² days 1, 8, and 15 mg/m² every 28 days) on the ECOG 2100 study, the addition of bevacizumab improved RR (37% vs. 21%) and PFS (11.8 vs. 5.9 months) compared to single agent paclitaxel (190), for which the drug was granted preliminary FDA approval even though it did not improve OS (26.7 vs. 25.2 months). In a number of several subsequent randomized, double-blinded studies in the first- or second-line metastatic setting (AVADO, RIBBON-1, RIBBON-2), the addition of bevacizumab to a variety of chemotherapeutic agents improved RR and PFS, but again failed to prolong OS. Treatment with bevacizumab is associated with a 10% to 20% incidence of hypertension requiring treatment, proteinuria, an increase in thromboembolic events, and more frequent hematologic and nonhematologic toxicities related to the concurrent chemotherapy regimen. In other patient populations treated with bevacizumab, an increase in stroke, myocardial infarction, impaired cardiac function, wound dehiscence, and bowel perforation had been reported but were not seen in the advanced breast cancer population. Weighing the benefits of delayed disease progression in the absence of a survival advantage against the risks associated with the drug, in November 2011 the FDA revoked its provisional approval as part of first-line therapy in metastatic breast cancer. However, since the drug is approved for several other indications, it remains an available option for patients with advanced breast cancer.

Results of two studies in the neoadjuvant setting suggest that bevacizumab can improve the pCR rate in selected patients, though which group of patients may benefit is less clear. In the GeparQuinto study (191), the addition of bevacizumab to neoadjuvant chemotherapy consisting of 4 cycles of epirubicin and cyclophosphamide followed by four cycles of docetaxel in 1,948 patients with HER2- breast cancer increased the pCR rate from 27.9% to 39.3% in patients with triple-negative cancers (a 67% improvement), but had no effect on the pCR rate in patients

with HR+ cancers (7.8 and 7.7%). In contrast, in the NSABP B-40 study (192), the addition of bevacizumab to 4 cycles of docetaxel-based therapy followed by 4 cycles of AC in 1,206 HER2- cancers improved the pCR in HR+ patients from 15.1% to 23.2% (a 54% increment) while having a minimal impact in the triple-negative cohort (47.1% to 51.5%). What impact, if any, these differences will have on long-term outcomes such as DFS and OS is not known.

A number of completed (but not reported) and ongoing large, randomized studies of bevacizumab in the adjuvant and neoadjuvant settings should shed further light on whether this agent will have a role in the management of early-stage breast cancer in the future.

A number of small molecule tyrosine kinase inhibitors that target the VEGF receptor, including sunitinib, sorafenib, axitinib, and pazopanib, have been studied in patients with advanced breast cancer; thus far, none of these agents have demonstrated substantial benefits in this population. Aflibercept, also referred to as VEGF-trap, functions as a soluble decoy receptor, binding circulating VEGFs and preventing them from binding to (and activating) their cellular receptors.

Other Biologic Agents of Interest

The epidermal growth factor receptor (EGFR) is overexpressed in a subset of aggressive, poorly responsive breast cancers, including some triple-negative cancers. Agents that block this receptor, including monoclonal antibodies that block its extracellular ligand-binding domain like cetuximab, and small molecules that block its intracellular tyrosine kinase domain like gefitinib and erlotinib, have been tested in advanced breast cancer but exhibit little antitumor activity. Inhibitors of poly (ADP-ribose) Polymerase-1 (PARP-1) interfere with base excision repair, an important mechanism of DNA repair in cells with defects in homologous recombination, such as those with mutations in or inactivation of the breast cancer associated *BRCA1* and *BRCA2* genes, and some triple-negative cancers. As single agents, some PARP inhibitors have demonstrated activity against breast cancers in patients with *BRCA* mutations, but their usefulness in patients with sporadic triple-negative cancers, either alone or in combination with DNA-damaging chemotherapy, has yet to be demonstrated.

As our understanding improves of the complex pathways that influence the behavior of normal cells and of how aberrations of those pathways give rise to the hallmarks of malignancy, we may be able to target those abnormalities to the benefit of our patients. For example, everolimus is an oral mTOR (mammalian target of rapamycin) inhibitor that blocks the phosphoinositide 3-kinase (PI3k)-Akt signal transduction pathway. It is FDA approved as a single agent to treat advanced renal cell carcinoma and pancreatic neuroendocrine tumors in addition to its role as an immunosuppressive agent following solid organ transplants. The phase III Breast cancer trials of Oral everolimus-2 (BOLERO-2) study randomized 724 postmenopausal patients with HR+ breast cancers who had progressed on a nonsteroidal aromatase inhibitor (166) (anastrozole or letrozole) to the steroidal AI exemestane with everolimus 10 mg/d or placebo. Patients assigned to take everolimus had higher RR and clinical benefit rates, and a significant improvement in median PFS (11.0 vs. 4.1 months). Further study of this and other inhibitors of the PI3k-Akt pathway would appear to be warranted.

Bisphosphonates as Adjuvant Therapy

Bisphosphonates are potent inhibitors of osteoclast activation and have been shown to reduce bone mineral loss in women with natural and treatment-induced menopause, and to reduce the frequency of fractures and bone pain in breast cancer patients with bone metastases. Pre-clinical studies have suggested that bisphosphonates may also possess antitumor activity, including

antiangiogenic, antiproliferative, and proapoptotic effects. Bisphosphonate-induced osteoclast inhibition might make the bone microenvironment less supportive of tumor cell proliferation, and epidemiologic data suggest that bisphosphonates used in the management of osteopenia and osteoporosis may decrease the risk of developing breast cancer.

Data on the value of bisphosphonates as adjuvant therapy are conflicting. In the NSABP B-24 study of 3,323 women with early-stage breast cancer, all of whom received adjuvant chemotherapy ± endocrine therapy, 3 years of clodronate (1,600 mg/d) was compared to placebo and demonstrated trends favoring the oral bisphosphonate for improved recurrence-free survival and OS, but no statistically significant differences. Combined analysis of two studies (Z-FAST and Zo-FAST) that compared immediate versus delayed (treatment deferred until a drop in bone density) administration of the potent IV bisphosphonate zoledronic acid 4 mg every 6 months for 5 years in patients taking adjuvant letrozole suggested a cancer recurrence benefit for the immediate treatment group (193). The strongest evidence favoring adjuvant bisphosphonates comes from the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 study. A total of 1,803 premenopausal women with HR+ breast cancers were treated with ovarian suppression and either tamoxifen or anastrozole (no patients received adjuvant chemotherapy), and were randomized to receive zoledronic acid 4 mg every 6 months for 3 years or not. Updated results from this study demonstrate that those patients who received zoledronic acid had a 28% improvement in DFS and a 40% improvement in OS, with benefits seen only in older (>40 years of age) patients. In contrast, a larger study, the Adjuvant Treatment With ZOL in Stage II/III Breast Cancer (AZURE, BIG 01/04), randomized 3,360 patients, almost all of whom received adjuvant chemotherapy, to a longer, more intensive zoledronic acid regimen or not (194). At 5 years, there were no overall differences in DFS or OS, though in the subset of women who were at least 5 years postmenopausal at study entry, zoledronic acid did improve DFS and OS.

Chemotherapy for Breast Cancer

Cytotoxic chemotherapy is commonly given to patients with early- and advanced-stage breast cancer whose disease is either hormone insensitive (ER and PR negative), has developed resistance to endocrine therapy, has high-risk features, including low expression of ER and PR, HER2 gene amplification, high grade or a high proliferative rate, evidence of rapid tumor growth, or, in patients with metastatic disease, has evidence of extensive involvement of one or more vital organs. Concepts that often arise in a discussion of chemotherapy include:

Dose Intensity

When studied in the laboratory, for many chemotherapeutic agents, higher drug concentrations result in increased killing of cancer cells, displaying what is referred to as a dose-response curve. When treating patients with breast cancer, it is less clear that more is always better, and with increased dose, the toxic effects of the drug almost always increase. For example, in the adjuvant setting, the Cancer and Leukemia Group B (CALGB) 8541 study demonstrated that administering what are now standard doses of cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) improved DFS and OS, especially in patients with more aggressive cancers, compared to lower doses of the same drugs (195,196), while a subsequent study, CALGB 9344, failed to show further benefit from raising the doxorubicin dose from 60 mg/m² to its highest tolerated level (90 mg/m²) (197). The ultimate test of dose intensity involves administration of such high doses of chemotherapy that the patient requires autologous hematopoietic stem cell support for recovery of blood counts, sometimes

referred to as a bone marrow transplant. While initial studies suggested that such an approach might be better than standard dose chemotherapy, subsequent larger, randomized trials clearly demonstrated that this treatment, whether administered as adjuvant therapy for high-risk patients or for metastatic disease, is no more effective than standard dose therapy and associated with a much higher rate of serious and life-threatening side effects. (198)

Dose Density

In contrast to administering higher individual doses of one or more chemotherapeutic agents, this involves administering similar or lower doses of one or more agents more frequently. This often allows administration of a higher overall dose of a drug with less toxicity, and also may increase the drug's cytotoxic effects by increasing the likelihood of catching a higher proportion of cancer cells in the most vulnerable phases of their cell cycle. Examples of this include CALGB 9840, which demonstrated the superiority of weekly paclitaxel over every 3 week (q3week) paclitaxel in patients with metastatic breast cancer (199); CALGB 9741, which demonstrated improvements in DFS and OS in patients with node-positive breast cancer who received the same total number of cycles of doxorubicin and cyclophosphamide (AC) followed by paclitaxel q2weeks (with granulocyte-colony stimulating factor [G-CSF] support) as opposed to the standard schedule (q3weeks) (200); and ECOG 1199, which demonstrated superior DFS and OS in node-positive patients who received weekly paclitaxel compared to q3week paclitaxel after 4 cycles of AC (201). This strategy also has its limitations, as illustrated by initial results from the Southwest Oncology Group (SWOG) 0221 adjuvant study in which a regimen of weekly doxorubicin and daily oral cyclophosphamide was not superior to q2week AC. Another example of dose density is what is referred to as metronomic chemotherapy in which patients with metastatic disease receive low daily or twice weekly doses of (usually oral) chemotherapy (202); this approach has demonstrated some efficacy with relatively little toxicity in patients who had progressed after a number of standard dose chemotherapy regimens, though it has not yet been directly compared to other forms of salvage chemotherapy.

Non-Cross-Resistant Drug Combinations

To increase the effectiveness of treatment, in choosing which chemotherapeutic agents to administer, either concurrently or sequentially, it is best to select agents with different mechanisms of action, different mechanisms of drug resistance, and, when possible, nonoverlapping toxicities. Switching to a non-cross-resistant drug or regimen may improve response, even when the patient is responding to the initial regimen. An example of this is the Aberdeen neoadjuvant trial, in which patients whose tumors were responding after 4 cycles of a doxorubicin-based regimen were randomized to continue the same regimen for 4 additional cycles or were switched to 4 cycles of docetaxel (203). At the completion of treatment, patients switched to docetaxel had higher rates of clinical and pathologic complete response, and subsequently improved DFS and OS. In the adjuvant setting, patients receiving 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) who were randomized to switch to either weekly paclitaxel or q3week docetaxel had improved DFS compared to patients who continued on FEC (204,205).

Combination versus Sequential Single-Agent Chemotherapy

An ongoing controversy is whether breast cancer patients, especially those with metastatic disease, do better with combinations of chemotherapeutic agents or administration of individual

agents, switching to another agent upon disease progression. This is discussed in greater detail later. In general, combination chemotherapy results in higher response rates and a modest increase in time to disease progression (TTP), but has little impact on OS. Thus, combinations may be appropriate in situations where rapid response is vital, such as in patients with diffuse symptomatic disease or extensive involvement of vital organs such as the liver or lungs (referred to as visceral crisis), whereas single agents may be more appropriate in patients with less extensive or symptomatic disease, and in older or frail patients less likely to tolerate a combination. The question of sequential single agents vs. combinations has been studied less in the adjuvant setting, but in the CALGB 9741 study mentioned above, patients were also randomized to q2week sequential single-agent doxorubicin, paclitaxel, and cyclophosphamide, and these patients did as well as patients randomized to q2week AC followed by paclitaxel (201).

Adjuvant Chemotherapy

When discussing adjuvant chemotherapy, the first question to address is who should receive it. Almost all patients with either triple-negative (TNBC, defined as ER and PR expressed on less than 1% of tumor cells by IHC stain and HER2- by IHC 0-1+ or FISH <2.0 if IHC 2+) or HER2+ cancers, unless contraindicated by age and major comorbid medical problems, should receive adjuvant chemotherapy, together with trastuzumab in HER2+ patients (see discussion of treatment of HER2+ cancers in the section on biologic therapies). Whether adjuvant treatment is necessary in patients with TNBC or HER2+ tumors <1.0 cm and negative lymph nodes is unclear; while retrospective analyses clearly demonstrate that such patients have a higher risk of recurrence than patients with small HR+/HER2- cancers, they still have a relatively good prognosis (174,206). Many (but far from all) oncologists recommend adjuvant treatment to patients with TNBC and HER2+ tumors 0.6 to 1.0 cm (T1b) and discuss adjuvant treatment with patients whose tumors are <0.5 cm (T1a) if they are both HER2+ and HR-.

If the oncologist is uncertain if he or she is accurately estimating a patient's risk of recurrence and potential benefit from adjuvant chemotherapy, an available resource to assist in this process is the free online service *Adjuvant!* (www.adjuvantonline.com). The *Adjuvant!* program compares a patient's baseline tumor characteristics with those from two large databases to approximate her risk of distant disease recurrence, then applies results from major clinical trials and actuarial projections based on the patient's age and overall health status to estimate the reduction in disease recurrence that would be expected from administration of adjuvant endocrine therapy (in ER+ patients) and/or chemotherapy measured against the patient's risk of dying of other causes over the next 10 years. While far from perfect—among other limitations, its estimates separate prognostic variables, such as tumor size and number of lymph nodes involved, which are known to be continuous, into discrete categories; it does not currently take lymphovascular invasion (LVI), the size of nodal metastases, or HER2 status into account; and it assumes that all patients receive the same relative risk reduction from a given chemotherapy regimen independent of tumor characteristics—*Adjuvant!* can be used to corroborate the oncologist's assessment and to communicate the concepts of risk and risk reduction to patients and their family members.

In patients with lower risk ER+/HER2- cancers—smaller primary tumors with no or minimal axillary lymph node involvement—the value of adding adjuvant chemotherapy after taking into account the substantial risk reduction expected from adjuvant endocrine therapy is often modest. The NSABP B-20 trial demonstrated improvements in DFS and OS with adjuvant CMF in patients with ER+, node-negative cancers, but with a

high number of patients needed to treat to benefit one (207). Given this, efforts have been made to develop a test that could differentiate patients likely to do well with adjuvant endocrine therapy alone from those who would be expected to receive greater relative benefit from the addition of chemotherapy. Two such tests, both of which use gene expression arrays—using the level of expression of messenger RNA (mRNA) for a variety of genes to characterize the cancer and predict its biologic behavior—are licensed in the U.S.

Oncotype DX® is a pCR-based array that measures gene expression by mRNA for a total of 16 cancer-related genes, some of which reflect its level of estrogen stimulation (and thus likely sensitivity to endocrine therapies) and some of which correlate with cell proliferation and metastasis (associated with relative insensitivity to endocrine therapies and potential greater benefit from chemotherapy), relative to 5 “housekeeping” genes. Paik et al. have demonstrated that the recurrence score (RS) derived from the levels of expression of these genes is both prognostic for risk of recurrence in untreated patients and predictive of degree of risk reduction achieved with endocrine therapy (specifically tamoxifen) and CMF chemotherapy (R, S). The assay is performed on paraffin-embedded tissue, thus it can be sent any time after the surgical procedure. The assay is most useful when a patient’s RS is in the low end of the range (≤ 10), indicating a low-grade, very hormone-responsive cancer for which adjuvant endocrine therapy should prove very effective and chemotherapy would offer little benefit, or in the upper end of the range (>25), indicating a more aggressive cancer for which endocrine therapy alone has relatively little effect and in which adjuvant chemotherapy is more likely to be beneficial. A large clinical trial—TAILORx (ECOG-PACCT-1, NCT00310180), in which patients with a low RS are assigned to endocrine therapy only, high RS patients are assigned to receive chemotherapy followed by endocrine therapy, and patients in the middle (of the range 11–25) are randomized to receive chemotherapy or not—designed to confirm the prognostic and predictive value of the test in ER+, node-negative patients, has completed enrollment. More limited data support its use in patients with a limited number (1–3) of involved axillary nodes (208); this is being tested in an ongoing trial, RxPONDER (SWOG 1007, NCT01272037), on which patients with low-intermediate RS (0–25) are randomized to chemotherapy followed by endocrine therapy vs. endocrine therapy only. Studies have demonstrated that RS is also predictive of benefit with an aromatase inhibitor (anastrozole) (209). A study that compared predicted results obtained for the same tumors from the *Adjuvant!* database with analysis by Oncotype Dx concluded that the gene expression assay provided additional prognostic and predictive information (210). An attempt to improve the biologic Oncotype assay by incorporating the cancer’s clinical and pathologic features demonstrated that while the revised RS did improve its prognostic accuracy and reduce the number of patients with intermediate scores, this did not improve its ability to predict benefit from adjuvant chemotherapy (211).

MammaPrint® is a microarray-based gene expression assay that measures mRNA levels for 70 genes that reflect tumor proliferation, invasion, and angiogenesis. The score derived from this assay has been shown to be prognostic of risk of recurrence in patients with ER+, node-negative cancers (212,213), but it has not yet demonstrated the ability to predict benefit from the addition of adjuvant chemotherapy to endocrine therapy. Also, because of the methodology of the assay, it requires fresh tissue, which may limit its usefulness. This assay is also being studied in a prospective clinical trial called MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy, NCT00433589), which is designed to determine if ER+ patients with 0 to 3 involved lymph nodes considered higher risk by clinical features but low risk by MammaPrint can be spared chemotherapy.

In addition to these commercially available assays, evaluation of a large number of breast cancers by broader gene expression analyses demonstrates that their patterns of expression can be divided into a limited number of what are called intrinsic subtypes, though there remains a good deal of heterogeneity of gene expression within these designations (214). Luminal A and luminal B tumors tend to be ER+ and are expected to benefit from endocrine therapies, though the somewhat more aggressive luminal B tumors also display sensitivity to chemotherapy. The basal-like (the majority of TNBC) and HER2 (largely ER-/HER2+ tumors) subtypes are more aggressive and require cytotoxic therapy. Analysis by gene expression array demonstrates that a significant fraction of patients may be mischaracterized by IHC results alone. However, assays based on this more in-depth analysis of gene expression are not yet approved for routine clinical use.

Recent Meta-Analyses of Adjuvant Chemotherapy

The EBCTCG recently updated their ongoing meta-analyses of the role of adjuvant chemotherapy in early-stage breast cancer, and for the first time added an analysis of the benefits of the addition of a taxane (paclitaxel or docetaxel), concurrently or sequentially, to anthracycline-based adjuvant chemotherapy (215). Overall, in older trials, which included a no-chemotherapy arm, administration of anthracycline-based adjuvant chemotherapy reduced breast cancer recurrences by 27%, resulting in an absolute improvement in the 10-year recurrence rate of 8.0% (39.4% vs. 47.4%), a 6.5% reduction in breast cancer-related mortality and a 5.0% improvement in overall mortality. Chemotherapy regimens which included 6 cycles of cyclophosphamide with standard doses of either doxorubicin or epirubicin and 5-fluorouracil (CAF or CEF) resulted in larger relative improvements in OS (36%) than regimens in which patients receive just 4 cycles of standard-dose doxorubicin or epirubicin with cyclophosphamide (AC or EC) (22%). Compared to no-chemotherapy controls, administration of CMF was associated with a 30% relative reduction in breast cancer recurrence (29.6% vs. 39.8%), which resulted in a 6.2% improvement in breast cancer mortality and a 4.7% improvement in overall mortality. All of these results were highly statistically significant due to the large numbers of women involved (8,575 women in the anthracycline-based trials, 5,253 in the CMF trials). The difference in the outcomes for the control groups likely reflects different patient populations, with only 18% of patients treated on the anthracycline-based trials having node-negative cancers compared to 66% on the CMF trials. Benefits from chemotherapy were essentially equivalent across multiple patient subgroups, including age, node status, HR status, and tumor grade, and administration of adjuvant endocrine therapy (tamoxifen) did not reduce the benefit of receiving adjuvant chemotherapy.

A number of studies have compared anthracycline-based regimens with standard or near-standard CMF. Studies on which patients (9,527 women, of whom 53% were node-positive) received higher cumulative doses of anthracycline (such as 6 cycles of CAF or CEF) demonstrated superiority of anthracycline-based therapy, with a relative 11% reduction in breast cancer recurrences, corresponding to a 2.6% absolute benefit, a 20% reduction in breast cancer mortality (4.1% absolute), and a 16% reduction in overall mortality (3.9% absolute). In contrast, studies which compared briefer anthracycline-based regimens, such as 4 cycles of AC or EC, to CMF (5,122 women, of whom 61% were node-positive), failed to show improvement in outcomes.

In regards the benefits of adding a taxane to anthracycline-based adjuvant chemotherapy, the recent meta-analysis identified an overall relative reduction in breast cancer recurrence of 14%, breast cancer mortality of 13%, and overall mortality of 11%. Studies in which the taxane was added to an anthracycline regimen of standard duration demonstrated the greatest

benefit for the new class of agents, including a 16% reduction in recurrences (4.6% absolute), 14% improvement in breast cancer mortality (2.8% absolute), and 14% improvement in overall mortality (3.2% absolute), while studies in which patients on the nontaxane arm continued on their anthracycline-based regimen to match the duration of treatment of patients assigned to receive the taxane failed to show significant improvements in outcomes. The aggregate results were consistent across age groups, nodal status, and HR status, the latter despite analyses of 2 large studies that suggested a lack of benefit to the addition of a taxane in patients with ER+/HER2-cancers (167,168). Assessing these results is confounded by shorter follow-up than for the chemotherapy/no chemotherapy and anthracycline/CMF comparisons discussed above, and a fair amount of heterogeneity in the control and experimental treatment regimens, including whether the taxane was administered sequentially or concurrently with the anthracycline. In the majority of studies included in this meta-analysis, the taxane (whether paclitaxel or docetaxel) was administered q3weeks, thus potentially underestimating the benefits of dose-dense q2week or weekly paclitaxel. While the results might suggest that patients would do as well with 6 cycles of CAF or CEF q3weeks as with briefer exposure to an anthracycline followed by a taxane, studies that most directly compared these approaches, including the PACS 01 and the German AM02 trials of 6 cycles of FEC vs. 3 cycles of FEC or EC followed by 3 cycles of docetaxel, demonstrated improvement in DFS and OS with the sequential regimen, as well as fewer cardiac and hematologic adverse events (204,205).

A meta-analysis of 10 trials that compared standard versus dose-dense adjuvant chemotherapy reported that dose-dense treatment was associated with relative improvements in DFS (17% to 19%) and OS (15% to 16%), whether the dose-dense regimen used similar or modified chemotherapy doses compared to the control regimen. However, this difference was seen only in patients with ER-negative cancers (in whom the DFS benefit was 29%), not in patients with ER+ cancers (8% benefit, which did not reach statistical significance).

While useful to detect treatment effects that might not be apparent or statistically significant in an individual study, a meta-analysis is limited by its tendency to lump sometimes substantially different patient groups and treatments together; for example, are the node-positive patients of 20 years ago the same as the node-positive patients of 2012, with widespread use of sentinel node sampling, and is lower-dose weekly paclitaxel the same treatment as higher-dose q3week paclitaxel? The meta-analyses are likely more useful to help to estimate the magnitude of a treatment effect than for current treatment recommendations.

Recent Trials of Adjuvant Chemotherapy

Updated results from the U.S. Oncology Trial 9735, which compared 4 cycles of AC to 4 cycles of docetaxel and cyclophosphamide (TC) q3weeks in 1,016 patients, of whom half were node-positive and 71% ER+, at a median of 7 years follow-up, continue to demonstrate superiority of the TC regimen, with a 26% improvement in DFS, which translated into a 6% absolute increase, and a 31% rise in OS (5% absolute) (216). The DFS benefit was apparently independent of age, nodal status, and HR status (though not statistically significant in the subgroups). Short-term toxicities were comparable across the 2 arms of the study, but 4 patients on the AC arm have died of possible late complications of treatment, one with congestive heart failure, and 3 with leukemia or myelodysplasia. Though of relatively modest size, this study has had a major impact on the treatment of patients with low- to intermediate-risk disease in the U.S., presumably due to the appeal of avoiding exposure to an anthracycline without (apparently) sacrificing efficacy.

CALGB 49907 compared standard chemotherapy (4 cycles of AC or 6 cycles of CMF, physician's choice) to single-agent oral capecitabine (daily for 14 days every 3 weeks for 6 cycles) in good performance status patients age 65 or older with stage I (tumors at least 1 cm in diameter) or II disease (217). While accrual to the study was slower than anticipated, 633 patients were enrolled over slightly more than 5 years. Of the patients enrolled, 70% were over the age of 70, 70% were node-positive, and 68% were HR+. Patients assigned to capecitabine were twice as likely to relapse as patients assigned to standard chemotherapy, and also twice as likely to die due to breast cancer. The standard chemotherapy was generally well tolerated, but the investigators noted that patients treated with CMF were less likely to complete their planned treatment, most often due to nonhematologic (mostly gastrointestinal) toxicities. Results of this study support administration of standard adjuvant chemotherapy, in contrast to a lessintensive regimen, in older women deemed to be at significant risk for disease recurrence who have no obvious contraindications to such treatment.

Based on the superiority to adjuvant docetaxel, doxorubicin and cyclophosphamide (TAC) over CAF in the BCIRG 001 trial (218), a number of studies have examined concurrent anthracycline and taxane regimens. ECOG 2197 compared 4 cycles of q3week AC with 4 cycles of q3week doxorubicin and docetaxel (AT) in 2,882 patients, of whom two-thirds were node-negative and 68% HR+ (219). There were no significant differences in DFS or OS for the overall study population, though a trend favored AT in patients with HR- tumors. The AT regimen was associated with a significantly higher rate (26% vs. 10%) of febrile neutropenia.

Two studies tested the TAC regimen against sequential AC followed by docetaxel (AC-T) in node-positive patients, with differing results. The NSABP B-30 study pitted 4 cycles of q3week AC followed by 4 cycles of docetaxel against 4 cycles of q3week TAC or 4 cycles of AT in 5,351 patients, of whom 75% were ER+, and just under half were premenopausal. At a median follow-up of 6 years, the sequential AC-T demonstrated superiority to the 2 briefer regimens in terms of DFS (74% vs. 69% for TAC and AT) and OS (83% vs. 79% for TAC and AT), an advantage that held up in all of the subgroups examined. In contrast, the BCIRG 005 trial demonstrated equivalent DFS and OS in 3,298 women randomized to either the same AC-T regimen or 6 cycles of TAC. The NSABP reported a higher incidence of febrile neutropenia with the sequential AC-T regimen (22% vs. 16% for TAC), while in the BCIRG study it was more common with TAC (17% vs. 8%); on neither study did patients routinely receive G-CSF support. The higher dose of docetaxel administered in the sequential arm of the BCIRG study (100 vs. 75 mg/m² with TAC) was associated with more sensory neuropathy, myalgias, and onycholysis. Of interest, premenopausal patients on the NSABP B-30 study who developed persistent amenorrhea following adjuvant chemotherapy had a 24% improvement in DFS independent of which chemotherapy regimen they received.

Results of these studies, together with CALGB 9741 and ECOG 1199 (200,201), which demonstrated superiority of either q2week or weekly paclitaxel or q3week docetaxel over the q3week paclitaxel control regimen after 4 cycles of q3week AC, and the CALGB 9344 and NSABP B-28 (197,220) studies, which first demonstrated the advantage of adding a taxane to anthracycline-based adjuvant chemotherapy in node-positive patients, suggest that current standard adjuvant chemotherapy regimen for higher risk HER2- breast cancer (see the discussion of adjuvant chemotherapy for HER2+ breast cancer in the section on biologic therapies) should be either: (1) 4 cycles of AC (or EC), preferably administered every 2 weeks (especially in ER-negative patients) with G-CSF, followed by either lower dose (80 mg/m²) weekly paclitaxel for 12 weeks, higher dose (175 mg/m²) paclitaxel every 2 weeks (also with G-CSF) or docetaxel 100 mg/m² every 3 weeks for 4 cycles; or (2) 6 cycles of TAC every 3

weeks (with G-CSF support). Given data questioning the value of incorporating an anthracycline in adjuvant chemotherapy for HER2+ patients, an ongoing study compares 6 cycles of TAC with 6 cycles of the TC regimen; until the results of that study are available, such an approach is appropriate only in patients in whom there is a clear contraindication to administration of an anthracycline (such as pre-existing impaired cardiac function).

A number of trials have investigated the addition of other chemotherapeutic agents to this anthracycline-taxane “backbone”. NSABP B-38, which has completed accrual of 4,894 node-positive patients but with no results yet reported, compares 6 cycles of TAC with 4 cycles of q2week AC followed by 4 cycles of q2week paclitaxel or 4 cycles of q2week AC followed by 4 cycles of paclitaxel and gemcitabine. The FinXX study compared the sequence of 3 cycles of docetaxel (80 mg/m²) followed by 3 cycles of CEF (T-CEF) with 3 cycles of docetaxel (60 mg/m²) and capecitabine followed by 3 cycles of CEX (in which 5-fluorouracil was replaced by capecitabine) (XT-CEX) in 1,500 women, of whom 90% were node-positive and 77% ER+. Treatment with the XT-CEX regimen was associated with modest improvements in DFS (absolute 2.5% at 5 years) and OS (2.9% at 5 years); these differences were not statistically significant, and the experimental regimen was associated with a much higher rate of early treatment discontinuation (25% vs. 4%), as well as more mucositis, diarrhea, and hand-foot dermatitis, though a lower rate of febrile neutropenia (6% vs. 12%). Exploratory analyses suggested that the experimental regimen was superior to the control regimen in patients with TNBC, in whom the recurrence rate was halved, and in patients with 4 or more positive axillary nodes. The U.S. Oncology 01062 trial treated 2,611 women, of whom 70% were node-positive and 62% HR+, with 4 cycles of q3week AC followed by either 4 cycles of docetaxel (100 mg/m²) (AC-T) or docetaxel (75 mg/m²) and capecitabine (825 mg/m² BID) (AC-TX). After a median follow-up of 5 years, the AC-TX regimen did not demonstrate statistically significant improvement in DFS (89% vs. 87% for AC-T), but did improve OS (94% vs. 92%). As in the FinXX study, patients with TNBC appeared to receive more benefit from the addition of capecitabine, as did patients whose tumors exhibited a relatively high proliferative rate (Ki67 > 10%). As expected, patients assigned to receive capecitabine experienced more mucositis, diarrhea, and hand-foot dermatitis, and required more frequent dose modifications and treatment discontinuation, but had fewer instances of febrile neutropenia. While intriguing, especially in high-risk TNBC, results from these 2 studies are not felt to be sufficient to alter the standard treatment recommendations above.

Neoadjuvant Chemotherapy

Preoperative or neoadjuvant chemotherapy (NACT) is the standard treatment for women with locally advanced, unresectable breast cancers and for women with large breast tumors who would require a mastectomy but desire an attempt at breast conservation, unless the patient is too old or frail to tolerate chemotherapy. In LABC, NACT often renders the patient resectable, and sometimes even a candidate for BCS, as well as eradicating occult metastatic disease and improving DFS and OS. In patients with resectable breast cancer, a meta-analysis of studies that compared preoperative with identical postoperative chemotherapy demonstrated equivalent DFS and OS and a significant increase in the percentage of patients able to undergo BCS, though the latter was accompanied by a slightly higher risk of locoregional recurrence (221). Updated results from one of the largest of the studies included in this analysis, the NSABP B-18 study, demonstrated DFS trends favoring preoperative chemotherapy in patients under the age of 50 and in patients who were still alive and free of disease at 5 years (222). While intriguing, these results should be considered more as hypothesis generating than for treatment guidance.

Evaluating Response To NACT

It is clear that patients with chemo-responsive disease, as indicated by achievement of a pCR—varying definitions of this endpoint are discussed below—have significantly improved outcomes compared to patients with residual invasive disease in the breast and/or axillary nodes; in the meta-analysis, pCR was associated with 52% improvements in both DFS and OS.

The optimal method to assess response to NACT is controversial. In patients with visible or palpable disease, response (or lack thereof) can often be assessed on physical examination. Sequential imaging studies by US or MRI will usually indicate whether a patient is responding or not, though occasionally clinically “stable” tumors will prove to be largely or totally replaced with fibrous tissue, but are relatively insensitive for assessing the breast and axilla for microscopic disease following resolution of any visible tumor mass or abnormal nodes (223). In clinical trials, a significant proportion of patients with clinical complete responses will prove to have residual invasive disease in the breast and/or axilla at surgery. Pilot studies evaluating the utility of positron emission tomography (PET) to assess treatment response suggest that persistence of tumor FDG avidity during NACT is associated with a low likelihood of pCR, as well as higher disease recurrence and mortality rates (224).

The initial NSABP studies (B-18 and B-27) defined pCR as the absence of invasive disease in the breast, irrespective of the presence of any residual disease in the axillary nodes (222). A retrospective analysis of patients treated at the University of Texas MD Anderson Cancer Center (MDACC) demonstrated that the presence of residual DCIS in the breast, in the absence of residual invasive disease, did not impact outcomes (DFS and OS) (129). In contrast, persistent disease in the axillary nodes is associated with higher recurrence rates, while conversion from node-positive to node-negative with NACT indicates a good prognosis (225,226). In B-27, the NSABP noted that the presence of residual disease in the axillary nodes at surgery was predictive of recurrence independent of the presence or absence of residual invasive disease in the breast (227). Based on these findings, most U.S. studies use the absence of invasive disease in the breast and axilla (ypT0/isN0) as their definition of pCR.

A recent retrospective analysis of several NACT studies performed by German investigators questions the validity of this definition (228). Correlating tumor response at surgery to long-term outcome in 6,377 patients treated on 7 prospective trials with a median post-op follow-up of 46 months, the absence of either invasive or *in situ* disease in the breast and negative lymph nodes (ypT0N0), which was achieved in 15.0% of patients, was associated with the greatest improvement in DFS (55%) compared to patients who did not achieve this level of response. Classifying patients with residual *in situ* disease, involved lymph nodes and/or residual invasive disease less than 1 mm in diameter (ypT1mic) as pCRs reduced the DFS advantage, and patients in those categories did not appear to have improved DFS or OS compared to patients with more extensive residual disease. Also of interest, the correlation between achieving pCR (ypT0N0) with NACT and prognosis (DFS and OS) was apparent only in patients with more aggressive cancers, including TNBC, ER-/HER2+ and atypical ER+ (luminal B) cancers, but not in typical ER+ (luminal A) and ER+/HER2+ cancers. Patients with less-aggressive cancers were less likely to obtain a pCR, but had similar outcomes whether or not they achieved one, while patients with more-aggressive cancers were both more likely to achieve a pCR and to recur early if they did not. In TNBC, this observation has been referred to the “triple-negative paradox” (229).

The German data present response to NACT as a black/white contrast—a patient either achieves a pCR or is counted as a treatment failure. Other analyses suggest that extent of residual disease after NACT remains prognostic in the absence of a pCR. European investigators have used a number of scoring systems,

the best known of which is the Miller/Payne grading system, to assess post-NACT pathologic specimens for both residual disease and chemotherapy response, the results of which have been shown to correlate with DFS and OS (230). Symmans et al. at MDACC also assessed pathologic findings after anthracycline- and taxane-based NACT and found that the size and cellularity of residual invasive disease in the breast and number and size of metastatic deposits in the axillary nodes were predictive of distant recurrence (231). These variables are incorporated into a formula called the patient's Residual Cancer Burden (RCB). Of interest, patients with minimal residual disease (RCB-I) appear to be at no greater risk of distant disease recurrence than patients with a pCR (RCB-0), while patients with more extensive residual disease (RCB-II and -III) are at much greater risk of recurrence, especially if their tumor is HR-. RCB analyses have been incorporated into a number of NACT studies, both to stratify non-pCR responses and to validate this methodology.

NACT Regimens

A general principle regarding NACT regimens is that chemotherapeutic agents that have proven effectiveness in the adjuvant setting should have similar efficacy against disease in the breast and axillary nodes as well as occult metastatic disease in the neoadjuvant setting. Thus, there is no reason to use different regimens based on when the chemotherapy is given with respect to surgery. The choice of specific chemotherapy drugs and regimens should be based on our understanding of therapy response as related to tumor biology and patient subsets such as ER+/HER2-, HER2+, and TNBC.

Given the high-risk factors present in most patients who are offered NACT—tumor size, clinically apparent axillary lymph node involvement, more aggressive subtypes such as HER2+ or TNBC, and in some cases evidence of extensive disease in the breast and/or regional lymph nodes—in most patients, sequential administration of both an anthracycline and a taxane is indicated and is associated with higher pCR rates than AC alone or concurrent AT (232). For example, in the NSABP B-27 trial, 2,411 patients received 4 cycles of q3week AC and were randomized to receive either no further chemotherapy, 4 cycles of neoadjuvant q3week docetaxel (100 mg/m²) or surgery followed by 4 cycles of docetaxel. The addition of neoadjuvant docetaxel doubled the pCR rate from 13% to 26%, and while this did not translate into improvements in DFS and OS, the subset of patients who had a partial clinical response to the 4 cycles of AC did have improved outcomes with the addition of neoadjuvant docetaxel. In the Aberdeen study, switching patients who were responding after 4 cycles of an anthracycline-based regimen to docetaxel improved not only the pCR rate (to 34%, compared to 16% in patients who continued the anthracycline-based regimen) and the BCS rate (67% vs. 48%), but also OS at 3 years.

pCR rates for sequential therapy with an anthracycline and a taxane depend on the tumor type, ranging from as low as 5% for low-grade ER+/HER2- (luminal A) cancers to 34% for basal-like TNBC to 55% for HER2+ (with concurrent trastuzumab). Though the use of dose-dense NACT is based largely on data from the adjuvant setting, there are a few studies that demonstrate higher pCR rates with dose-dense chemotherapy in the preoperative setting (233,234). Thus far, the addition of other chemotherapeutic agents to this regimen—such as capecitabine with the docetaxel in the GeparQuattro trial (235), or either capecitabine or gemcitabine with the docetaxel in the NSABP B-40 trial (192)—has failed to improve pCR rates.

Based on similarities in clinical and pathologic features, and gene expression patterns between cancers that develop in women who carry *BRCA1* mutations and sporadic TNBC, and data demonstrating suggesting high pCR rates in patients with *BRCA*-related cancers treated with platinum analogs (236),

there is interest in studying the addition of this class of agents to standard NACT in TNBC.

What to do for patients who are not responding to NACT is unknown. In the Aberdeen trial, patients not responding after 4 cycles of the anthracycline-based regimen were switched to docetaxel, and while 55% had a clinical response to the taxane, their pCR rate was only 2%, and their 3-year survival was markedly inferior to the responsive patients. In the GeparTrio trial, patients who did not respond with at least a 50% reduction in tumor size after 2 cycles of TAC were randomly assigned to either 4 more cycles of TAC or 4 cycles of vinorelbine and capecitabine (NX) every 21 days. While both groups of patients had similar clinical response (51%) and pCR (5% to 6%) rates, a recent update of the trial reported that patients switched to NX demonstrated significant (41%) improvement in DFS compared to patients who continued on TAC (GGG). Meanwhile, patients responding after 2 cycles of TAC were randomized to 4 or 6 more cycles of the same regimen, and while the longer treatment duration had only a modest impact on the pCR rate (24% vs. 21%), it did result in significant improvement in DFS.

Treatment for patients who go to surgery after NACT and are found to have significant residual disease is based on their tumor type. Patients with ER+ tumors typically receive adjuvant endocrine therapy, while patients with HER2+ cancers receive trastuzumab. There is no evidence that administration of additional chemotherapy, sometimes referred to “adjuvant after neoadjuvant”, in a patient who has received both an anthracycline and a taxane in the preoperative setting, will reduce recurrences in patients with residual TNBC, though the GeparTrio data cited above offer a glimmer of hope. There is also interest in testing novel targeted (biologic) agents in these patients.

Chemotherapy for Metastatic Breast Cancer

As noted previously, chemotherapy is appropriate treatment for patients with metastatic breast cancer (MBC) that is hormone-insensitive (ER- and PR-) or refractory (having progressed on one or more endocrine therapies), displays aggressive biology (rapid disease progression or early recurrence following adjuvant or neoadjuvant therapy), or is associated with significant symptoms or evidence of extensive or rapidly progressive involvement of vital organs (most often the liver or lungs), which is referred to as visceral crisis. Choice of chemotherapeutic agent or combination of agents depends upon the extent and biology of the patient's disease, her age, performance status and comorbid medical conditions, timing and extent of prior treatment, and her doctor's willingness to accept the risks of various toxicities as a tradeoff for antitumor efficacy, with the understanding that her condition is not curable and that differences in survival with various approaches are modest at best.

Combinations versus Sequential Single-Agent Chemotherapy

A meta-analysis published in 2005 reported significant, though relatively modest, improvements in overall response rate (ORR), PFS, and OS with administration of combination chemotherapy compared to single-agent chemotherapy in MBC, at the cost of increased hematologic and gastrointestinal toxicities (237). However, the studies included in that analysis predated approval of many of the active classes of single agents currently available. The general consensus among oncologists is that combination chemotherapy regimens often produce higher ORR and modest increases in PFS compared with single-agent chemotherapy, but without meaningful improvements in OS (this generalization

is not intended to cover the addition of HER2-targeted agents in patients with HER2+ cancers, which have clearly shown significant improvements in OS; these are covered in the section on biologic therapies). A few more recent randomized studies comparing novel chemotherapy combinations to a single agent have demonstrated improvement in OS as well as ORR and PFS, but have been faulted for the absence of crossover of patients assigned to the single agent and/or inadequate documentation as to subsequent treatment received. On the other hand, patients who require rapid disease response due to symptoms or life-threatening visceral involvement are more likely to respond to a combination regimen.

Combination Regimens

Combination regimens worth considering in the appropriate clinical setting include doxorubicin (or epirubicin) and cyclophosphamide; Anthracyclines have the best single-agent activity in chemotherapy-naïve patients with MBC, and older studies demonstrated that the addition of cyclophosphamide increased that activity, at the cost of greater (primarily hematologic) toxicity. Patients who received an anthracycline in the adjuvant setting are generally not considered candidates to receive the same or a similar agent for metastatic disease unless at least 12 months elapsed from completion of their prior anthracycline-based treatment to disease recurrence; even then, administration of a standard anthracycline will be limited by the increasing risk of cardiotoxicity when the cumulative doxorubicin dose crosses 450 mg/m². The addition of the cardioprotectant dexrazoxane in a 10:1 ratio to the dose of doxorubicin being administered, after response to the anthracycline-based regimen is documented, may allow more prolonged treatment with the regimen, with cardiac monitoring recommended every 2 cycles once the cumulative dose exceeds 450 mg/m². Another alternative is substitution of pegylated liposome-encapsulated doxorubicin (PLD), which is associated with less cardiotoxicity than the standard form of the drug. A multicenter study of PLD 35 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks as first-line chemotherapy in patients with MBC who had received an anthracycline-containing regimen in the adjuvant setting greater than 12 months earlier demonstrated an ORR of 38%, with another 33% of patients achieving stable disease (SD) for at least 6 months, a median TTP of 12.2 months and median OS of 16.5 months.

Anthracycline and taxane combinations: Given the activity of taxanes in untreated and anthracycline-pretreated MBC, several studies have compared anthracycline-taxane combinations (doxorubicin or epirubicin with paclitaxel or docetaxel, AT or ET) with nontaxane combinations like AC or CAF. A meta-analysis of these studies demonstrated that the taxane-based combinations were associated with a higher ORR (57% vs. 46%) and a modest improvement in PFS, but no significant improvement in survival. The taxane-based combinations were associated with higher rates of febrile neutropenia, and concurrent paclitaxel and doxorubicin have also been linked to increased cardiotoxicity.

Taxanes and other agents. The addition of capecitabine (1,250 mg/m²) to docetaxel (100 mg/m² as a single agent; 75 mg/m² when combined with capecitabine) in patients with anthracycline-refractory MBC improved the ORR (from 30% to 42%), median TTP (from 4.2 to 6.1 months) and median OS (from 11.5 to 14.2 months), at the cost of increased mucositis, diarrhea, and hand-foot dermatitis (238). This study has been criticized for the low percentage of patients assigned to single-agent docetaxel who received any subsequent chemotherapy, including capecitabine. Subsequent single-arm studies have suggested better tolerance with lower doses of capecitabine or substitution of weekly paclitaxel for the q3week docetaxel (239).

The addition of gemcitabine 1,250 mg/m² on days 1 and 8 to paclitaxel 175 mg/m² on day 1 every 3 weeks also improved ORR (26% to 41%), median TTP (4 to 6 months), and median

OS (15.8 to 18.5 months), at the cost of an increase in neutropenia, rare cases of febrile neutropenia, and fatigue (240). Again, assessment of this study was hampered by the failure to administer gemcitabine to a significant fraction of patients who progressed on single-agent paclitaxel. In a subsequent randomized study, the combination of gemcitabine and docetaxel failed to demonstrate superiority to the sequence of docetaxel followed by gemcitabine (241).

The addition of the VEGF-targeted agent bevacizumab to weekly paclitaxel and other chemotherapeutic agents, including docetaxel, is addressed in the biologic therapies section.

Other combinations. The combination of the epothilone ixabepilone 40 mg/m² q3weeks and capecitabine was compared to single-agent capecitabine in patients with MBC considered refractory to anthracyclines and taxanes (242). The addition of ixabepilone increased the ORR from 14% to 35%, with the largest impact on patients with TNBC (11% to 35%) and patients who had relapsed within 12 months of receiving both an anthracycline and a taxane in the adjuvant setting (17% to 68%), and median PFS from 4.1 to 5.7 months, but did not improve median OS, and was associated with increased hematologic (especially neutropenia) and nonhematologic (neuropathy, nausea/vomiting, myalgias and alopecia) toxicities.

The platinum analogs, cisplatin and carboplatin, have been studied in combination with a variety of agents, including the taxanes and gemcitabine. This class of agents may have greater activity in patients with TNBC, but whether they can prolong survival in these patients compared to single agents or other combinations is unclear.

Metronomic chemotherapy, most often consisting of daily low-dose oral cyclophosphamide and twice-weekly low-dose methotrexate, is generally well tolerated, but has had varying results in patients with advanced breast cancer. One recent study in 41 patients, of whom 16 had had no prior chemotherapy for MBC, demonstrated an ORR of 17% and median TTP of only 10 weeks (202).

Single-Agent Chemotherapy

A large number of cytotoxic agents have demonstrated some degree of antitumor efficacy in BC. There is no evidence that order of administration influences survival, though ORR predictably falls with successive lines of treatment. Relatively few have been compared head-to-head, and, despite ongoing efforts to develop such testing, there is no reliable chemosensitivity assay to help guide treatment selection. Thus, decisions as to which agents to try and in which order are often based more on patient preferences regarding route and schedule of administration and relative toxicities than on likelihood of response. Cost factors may also play a role.

Among the Active Classes of Agents

Anthracyclines remain the most effective class of agents, with ORR of 35% to 50% in patients who are chemotherapy naïve or at least 12 months out from anthracycline-based adjuvant chemotherapy. As with most classes of agents, they are clearly less effective when administered as second- or subsequent-line therapy. As discussed above, cumulative doses of doxorubicin exceeding 450 mg/m² are associated with increasing risk of cardiomyopathy, a concern that can be addressed by adding dexrazoxane or substituting PLD. In a phase III study, PLD 50 mg/m² q4weeks demonstrated equivalent PFS and OS compared to standard doxorubicin 60 mg/m², with less cardiotoxicity, alopecia, nausea, vomiting and neutropenia, but greater mucositis and hand-foot dermatitis.

Taxanes, including paclitaxel, docetaxel, and nanoparticle albumin-bound paclitaxel (nab-paclitaxel), show significant activity against both chemotherapy naïve and

anthracycline-pretreated MBC. In a meta-analysis of studies comparing single-agent taxanes to anthracyclines, the ORR was slightly higher for the anthracyclines (38% vs. 33%), but PFS and OS were equivalent (243). However, in these older studies, paclitaxel was administered q3weeks, while a meta-analysis of studies comparing weekly to q3week paclitaxel demonstrated a survival benefit for the weekly schedule (244). While the frequency and severity of neuropathy may be worse with the weekly schedule (199), this toxicity can be reduced by giving the patient every fourth week off, thus administering the drug at 80 to 100 mg/m² on days 1, 8, and 15 every 28 days. In contrast, weekly docetaxel appears to be no more effective and potentially more toxic than q3week docetaxel. A trial that compared q3week paclitaxel (175 mg/m²) to docetaxel (100 mg/m²) demonstrated slight improvements in median PFS and OS for docetaxel, along with significantly more severe hematologic and nonhematologic toxicities (245). Docetaxel has not been directly compared to weekly paclitaxel in MBC. Of interest, the 2 drugs do not appear to be completely cross-resistant, suggesting that a trial of the alternate taxane, preferably administered on a different schedule, can be considered in patients who relapse at least 12 months after completing a taxane-based adjuvant regimen (246).

The advantage of administering nab-paclitaxel is the elimination of polyethoxylated castor oil (Cremaphor), which is required to maintain standard paclitaxel in solution and appears to be responsible for most of the hypersensitivity reactions seen with “solvent-based” paclitaxel, thus permitting the elimination of corticosteroids and antihistamines from the premedication regimen. In theory, albumin binding might also facilitate penetration of the drug through the endothelial layer into cancer tumors. A phase III study comparing nab-paclitaxel 260 mg/m² with paclitaxel 175 mg/m² q3weeks demonstrated a higher ORR (33% vs. 19%), prolonged TTP (23 vs. 16.9 weeks) and a trend favoring prolonged OS for the nab-paclitaxel, with a lower incidence of grade 4 neutropenia despite the higher dose (247). No study has yet reported a comparison between nab-paclitaxel and a weekly standard paclitaxel regimen.

Antimetabolites: The oral 5-fluorouracil pro-drug capecitabine, more often administered at doses ranging from 1,500 mg BID to 1,000 mg/m² BID than at the approved dose of 1,250 mg/m² BID for 14 days q3weeks (248), yields an ORR of approximately 30% as first-line chemotherapy, and is also active as salvage therapy, though likely less so in patients with more-aggressive tumors such as TNBC. While it can cause diarrhea and hand-foot dermatitis, it seldom causes alopecia or myelosuppression. Alternative schedules, such as alternating one week on and one week off treatment, are being investigated to reduce toxicity while retaining antitumor efficacy.

The nucleoside analog gemcitabine, typically administered at 1,000 to 1,250 mg/m² IV days 1 and 8 q3weeks, is an active agent in first-line MBC (249) and is also generally well tolerated, with mild nausea and infrequent alopecia, though it can cause myelosuppression, especially thrombocytopenia, in previously treated patients, as well as fatigue, rashes, and rare serious hepatic and pulmonary toxicities.

Tubulin-targeted agents: The antimicrotubule agent vinorelbine, typically administered at 25 mg/m² IV days 1 and 8 q3weeks, has been associated with ORRs of 25% to 45% as a single agent in the first-line setting (250), and seldom causes nausea, diarrhea, or hair loss. It can cause myelosuppression, peripheral and sometimes autonomic neuropathy, more often in diabetics and patients with prior taxane exposure, and occasionally painful vasospasm when injected into a peripheral vein, which is why most oncologists prefer to administer it via a central line.

Oral etoposide 50 mg/m² daily for 21 days q4weeks has been reported to yield ORRs of up to 30% as second- or

subsequent-line therapy, but can cause significant hematologic and gastrointestinal toxicities.

The epothilone ixabepilone, which is derived from the soil-dwelling gram negative bacterium *Sorangium cellulosum* and interferes with microtubule disassembly by binding to tubulin at different sites than the taxanes, is typically administered at 40 mg/m² IV q3weeks. As a single agent in patients who were refractory to anthracyclines, taxanes, and capecitabine, it induced objective responses in 12.4% of patients and stable disease lasting at least 6 months in another 18.6%, while causing neutropenia, mild to moderate nausea, myalgias, fatigue, and progressive neuropathy (including grade 3 to 4 neuropathy in 14% of patients) (251).

The most recently approved chemotherapeutic agent for the treatment of MBC is eribulin, a fully synthesized analogue of the marine sponge natural product halichondrin B, which interferes with microtubule assembly necessary for formation of the mitotic spindle. In a phase III study that compared eribulin 1.4 mg/m² IV days 1 and 8 q3weeks with other chemotherapy of the physician's and patient's choice in heavily pretreated patients with MBC, patients randomized to eribulin had superior median OS (13.1 vs. 10.6 months) (252). Toxicities of the novel agent were primarily neutropenia and peripheral neuropathy.

Drugs with modest single-agent activity reported in MBC include pemetrexed, irinotecan, cisplatin, carboplatin, and cyclophosphamide.

Duration of Treatment

The optimal duration of treatment with chemotherapy in MBC is unknown. In general, studies of more prolonged administration of chemotherapy have demonstrated prolongation of TTP but little or no improvement in OS, often associated with increased toxicity and inferior quality of life. A meta-analysis of 11 trials, which compared fixed duration chemotherapy with treatment to disease progression, confirmed prolongation of PFS with a modest increase in OS. In practice, treatment is often administered until a response plateau is reached (based on imaging studies or tumor marker), the development of bothersome cumulative toxicities, or the patient requests a treatment break. In patients with HR+ disease, an effort to delay disease progression by initiating some novel (to the patient) form of endocrine therapy is reasonable, though this is not supported by any objective data. Whether to resume chemotherapy as soon as there is evidence of disease progression or to wait until the patient begins to have symptoms is not known, and best left to a joint decision between the patient and her physician.

ENDOCRINE THERAPY

The role of endocrine therapy has grown significantly over the past several years as both our understanding of breast cancer has matured and as new therapeutic options have developed. It has become increasingly clear that endocrine therapy is the backbone of treatment for hormonally responsive breast cancer, independent of stage.

Adjuvant Endocrine Therapy

Perhaps no data set has been more instructive in helping to define benefit of adjuvant hormonal therapy than the meta-analysis generated by the EBCTCG (253). One of the principles appreciated through this Overview analysis is that the proportional benefit of a given treatment is constant through risk groups (e.g., stage) and that the absolute benefit changes based on the estimated risk of systemic recurrence. For instance, if hormonal therapy

decreases the risk of cancer recurrence by 30% in a given individual, the absolute benefit would be 3% if the 10-year risk of relapse were 10%, but 18% if the 10-year risk of relapse were 60%. This concept of proportional and absolute benefit from adjuvant therapy is a guiding principle when women are counseled regarding treatment options in the adjuvant setting.

Expression of the ER or the PR is predictive of response to hormonal therapy. Therefore, essentially any woman with invasive breast cancer should receive adjuvant hormonal therapy if their tumor is ER+ and/or PR+. Conversely, hormonal therapy is inappropriate in the ER-/PR-setting. The choices for treatment and duration of therapy continue to be the subject of active investigation.

Tamoxifen was the first hormonal agent used in the adjuvant setting for breast cancer (254,255). As a selective estrogen receptor modulator (SERM), tamoxifen has differential effects on various tissues. While tamoxifen may achieve its beneficial effect in the treatment of breast cancer through multiple means, the principal mode of action appears to be through competitive binding to the ER. By preventing estrogen binding, translocation and nuclear binding of the ER is inhibited, altering transcriptional and posttranscriptional events mediated by the receptor. The antagonistic properties of tamoxifen toward breast cancer are contrasted against its agonistic effects on other tissues, such as the bone and uterus. Tamoxifen, like estrogen, improves bone mineral density in postmenopausal women and is a risk factor for endometrial cancer. Tamoxifen may negatively affect bone density in premenopausal women. The risk of endometrial cancer with the use of tamoxifen is estimated at two- to three-fold over the general population risk, though the risk is likely lower in premenopausal women and perhaps close to the general population risk as demonstrated in the NSABP P-1 trial (256). It is recommended that women on tamoxifen follow general guidelines for gynecologic screening and follow-up, but, importantly, report any menstrual changes, dysfunctional uterine bleeding, or other symptoms to their gynecologist. Women should discuss the use of tamoxifen with their gynecologist to ensure that they are being properly evaluated.

Another important risk associated with tamoxifen is that of venous thrombosis. While perhaps less so in premenopausal women, as demonstrated by the NSABP P-1 trial, tamoxifen has an approximate two-fold increase in risk for deep venous thrombosis (DVT) over the general population risk (256). This risk is sometimes described as similar to that associated with the use of oral contraceptives and may influence choice of hormonal therapy in the postmenopausal setting.

Other potential side effects of tamoxifen include hot flashes, weight gain, mood changes, increased vaginal discharge, cataracts, and rarely retinal abnormalities. Several studies have suggested an increase in risk of stroke with tamoxifen. Tamoxifen can increase fertility by increasing ovarian stimulation and is a teratogen, and is therefore contraindicated during pregnancy. Moreover, premenopausal women on tamoxifen need to ensure appropriate contraception as it is possible to become pregnant while on this medication.

Benefit from the use of tamoxifen in the adjuvant setting has been demonstrated in multiple clinical trials. The Scottish tamoxifen trial published in *The Lancet* in 1987 evaluated the use of tamoxifen 20 mg daily for 5 years in 1,312 premenopausal node-negative or postmenopausal women with any nodal status (254). This trial defined tamoxifen as an effective adjuvant in node-negative and node-positive patients as well as in the pre- and postmenopausal setting, and is considered a landmark trial. NSABP B-14 evaluated the use of tamoxifen versus placebo for 5 years in 869 premenopausal and 1,949 postmenopausal women with node-negative breast cancer, demonstrating statistically significant improvement in DFS and OS with the use of tamoxifen (255).

Although multiple dosing strategies have been tried, there is no demonstrated dose response curve between 20 and 40 mg. The recent EBCTCG report on adjuvant tamoxifen showed a trend toward improved recurrence-free survival with higher doses but no benefit in mortality (257). Thus, 20 mg per day is the recommended dose currently. Five years of tamoxifen has been considered standard, though recent data suggest that continuing tamoxifen through 10 years may further improve DFS and OS. Longer duration, therefore, can be considered, especially in higher-risk women (258,259). Therefore 5 years of treatment is recommended. The EBCTCG, which included more than 10,000 women with ER+ breast cancer, showed that treatment with 5 years of tamoxifen resulted in an improvement in DFS and OS of 39% and 30%, respectively, at 15 years (257).

Another decision-making tool in women who have an option of endocrine therapy or chemotherapy is the Oncotype DX assay. Using 668 available paraffin blocks from the B-14 trial, Paik et al. evaluated 16 cancer related genes to define an algorithm to assess risk of recurrence at 10 years (70). By creating a continuum of recurrence score based on gene expression analysis, 3 risk groups were broken out: low risk, intermediate risk, and high risk. Looking at this group of node-negative HR+ women, all of whom received tamoxifen, individuals in the low-risk category did not appear to benefit from the addition of chemotherapy to tamoxifen and are likely best served by hormonal therapy alone. Women in the high-risk group likely benefit from the addition of chemotherapy to hormonal therapy. Whether hormonal therapy alone is adequate in the intermediate-risk group is less clear and is currently being studied in a prospective randomized trial. Gene and protein expression prognostic and predictive models will continue to be developed to aid in defining appropriate therapy across risk groups and will complement established prognostic and predictive factors such as tumor size, grade, receptor status, nodal involvement, and HER2 overexpression.

While tamoxifen remains the only established hormonal agent in premenopausal women, choices in the postmenopausal setting have increased through the study and development of highly selective aromatase inhibitors. Initially, through the study of first generation aromatase inhibitors such as aminoglutethimide, these agents were found to be effective therapy for postmenopausal women. Aromatase inhibitors block estrogen production by preventing conversion of androgens produced by the adrenal gland (such as androstenedione) to estrogens, such as estrone, which is later converted to estradiol. This block occurs in the breast as well as in peripheral tissues, such as adipose tissue. The resulting decrease in circulating estrogen has been demonstrated through multiple clinical trials to be effective treatment for receptor-positive breast cancer. Of the 3 commercially available aromatase inhibitors, anastrozole and letrozole are nonsteroidal, whereas exemestane is a steroidal aromatase inhibitor. There are currently no demonstrable differences in efficacy or toxicity between these 3 products. Toxicities of aromatase inhibitors commonly include hot flashes and joint or muscle aches. Unlike tamoxifen, aromatase inhibitors can contribute to osteopenia and osteoporosis with an increased incidence of fractures, and therefore bone density should be followed carefully in women receiving these medicines. Other possible side effects include hypertension, gastrointestinal disturbance, depression, urovaginal symptoms, and possibly cardiac events. Aromatase inhibitors are not associated with an increased risk of endometrial cancer and have a lower risk for DVT compared to tamoxifen (260).

Several studies have demonstrated the efficacy of aromatase inhibitors in the adjuvant setting. The ATAC trial, one of the largest prospective adjuvant trials in breast cancer, randomized 9,300 postmenopausal women to tamoxifen, anastrozole, or the

combination (261). With a median follow-up of 120 months, there was a statistically significant benefit in DFS to anastrozole over tamoxifen with a hazard ratio of 0.91 in ER+ patients. There was no benefit to the combination. The Intergroup Exemestane Study (IES) randomized 4,700 postmenopausal women after 2 to 3 years of adjuvant tamoxifen to receive either tamoxifen or exemestane to complete 5 years of adjuvant therapy (262). With a median follow-up of 91 months, there was a statistically significant benefit in DFS for the inclusion of the aromatase inhibitor with a hazard ratio of 0.81, and a modest benefit to OS with a hazard ratio of 0.86. The MA17 initially published by Goss et al. randomized patients who had completed 5 years of adjuvant tamoxifen to 5 additional years of letrozole or placebo. After a median follow-up of 64 months, there was a statistically significant benefit to the inclusion of an aromatase inhibitor with a hazard ratio of 0.52 for DFS and 0.61 for OS (263). One important observation of this trial is that after unblinding, a large group of women assigned to placebo crossed over to letrozole. Despite an average delay of 2.8 years, treatment with letrozole after 5 years of tamoxifen significantly reduced the risk of recurrence. The Breast International Group (BIG) 1 to 98 study prospectively randomized 8,010 postmenopausal women with HR+ breast cancer to either tamoxifen for 5 years, letrozole for 5 years, tamoxifen for 2 years switching to letrozole for 3 years, or letrozole for 2 years switching to tamoxifen for 3 years. After a median follow-up of 26 months, the 2 groups that were assigned letrozole initially had a statistically significant improvement in DFS with a hazard ratio of 0.81 (264). A follow-up analysis of this trial published in 2009 showed after 71 months of follow-up that 5 years of letrozole compared to 5 years of tamoxifen reduced the risk of recurrence with a hazard ratio of 0.88; however, there was no difference between the sequential groups and continuous letrozole (265). Finally, the TEAM trial randomized more than 9,700 women to 5 years of exemestane or 2 to 2.5 years of tamoxifen followed by exemestane to complete 5 years. After 5 years of follow-up, DFS was similar in both groups (266).

Based on these trials, it is recommended that all postmenopausal women receiving adjuvant hormonal therapy receive at least 2 to 3 years of an aromatase inhibitor unless contraindicated, and treatment with an AI beyond 5 years is the subject of current investigation.

The degree of benefit and choice of hormonal therapy may be further influenced by primary tumor characteristics. The level of expression and potentially the relative expression of ER and PR positivity in breast cancer cells may be predictive of the responsiveness of the tumor to hormonal manipulation (267). It is therefore important to incorporate the degree of ER and PR positivity into adjuvant therapy decisions. Going against the conventional understanding of how the ER and PR expression predicts for benefit from endocrine therapy, the recent EBCTCG report on tamoxifen has shown uniform benefit in ER+ tumors regardless of the level of expression and no benefit in ER-tumors independent of PR expression (257). This remains an area of active investigation. The differential benefit to tamoxifen and aromatase inhibitors in the postmenopausal ER+/HER2+ setting also requires further study.

Ovarian Ablation

Ovarian ablation (OA) has long been explored as a therapeutic option for women with breast cancer. As the ovaries are the major source for estrogen, silencing the ovaries via surgical oophorectomy, radiotherapy, or the use of GnRH analogues may provide a benefit, although controversy continues as to its role in modern breast cancer management. The EBCTG overview on OA included 12 trials that compared OA by surgery or

radiation to control and encompassed 2012 women with early breast cancer. The meta-analysis concluded that OA was associated with both DFS and OS advantages when compared to observation. At 15 years, 52% were alive in those who underwent OA, compared to 46% who did not ($p = 0.001$), and 45% were disease-free, compared to 39% ($p = 0.0007$). When trials using OA versus chemotherapy following breast surgery were analyzed; however, the benefits of OA were more modest and did not achieve statistical significance. Despite these findings, OA cannot be considered equivalent to chemotherapy as these trials compared OA to chemotherapy that is considered inferior to modern adjuvant chemotherapy. Still, among premenopausal women who do not receive chemotherapy, OA may play a significant role in management.

Since the meta-analysis, several results have been published in this area. The International Breast Cancer Study Group (IBCSG) Trial VIII randomized 1,063 women with node-negative breast cancer to chemotherapy (CMF) versus Goserelin (G) versus CMF followed by G. Of note, 30% of women in this study had ER-disease. Restricting the analysis to women with ER+ disease, after median follow-up of 12.1 years, sequential therapy improved DFS compared to either treatment modality alone (DFS 77%, 68%, and 69% for CMF-G, G and CMF respectively) (269). This benefit to OA is not, however, consistently seen. Arriagada et al. randomized 926 women who had completed surgery and chemotherapy to OA (by ovarian radiation or with triptorelin) or observation (270). Ninety percent of women had positive nodes and 77% received anthracycline-based chemotherapy. Of the cohort, 63% were ER+. Estimated 10-year DFS and OS were similar in both groups, though subgroup analysis suggested that women under 40 and who had ER+ diseases benefited significantly. A plausible explanation for this observation is that younger women are more likely to recover ovarian function after chemotherapy and therefore more likely to benefit from ovarian suppression.

The ZIPP trial randomized 2,700 women to 2 years of tamoxifen (T), Goserelin (G), T+G or observation in a 2×2 factorial design. At 12 years of follow-up, the addition of G to tamoxifen versus the group receiving tamoxifen alone resulted in a small, nonstatistically significant reduction in the risk of recurrence (2.8%) (271).

The Intergroup 0101 trial examined the effect of adding OA (Goserelin) or OA and tamoxifen to anthracycline-based chemotherapy. Fifteen hundred women received 6 cycles of CAF chemotherapy alone or followed by 5 years of OA (CAF-Z) or CAF followed by 5 years of OA and tamoxifen (CAF-ZT). After 9.6 years of follow-up, there was no benefit to the addition of Z to chemotherapy. The addition of tamoxifen improved DFS but not OS (272).

The Austrian Breast Cancer Study Group randomized 1,800 premenopausal women to 3 years of Goserelin and either tamoxifen or Anastrozole with or without Zoledronic acid. After a median follow-up of 62 months, there was no difference between tamoxifen and anastrozole (DFS, 88% vs. 87%, respectively) (273). Surprisingly, it was noted that the addition of Zoledronic acid reduced the risk of recurrence by 35%. Even though none of these women received chemotherapy and despite the fact that about one-third in each group had node-positive disease, these recurrence rates are surprisingly low. For women with contraindication to chemotherapy or women who do not desire it, combining OA with tamoxifen or an aromatase inhibitor could be an effective alternative.

Contemporary trials will hopefully provide more guidance as to the role of OA in women with hormone-positive breast cancer. This is an especially important issue given the marginal benefits of chemotherapy in women with ER+ breast cancer and the availability of anti-estrogen endocrine therapy. Whether OA adds an additional benefit to endocrine therapy remains a question not sufficiently addressed.

Endocrine Therapy in Metastatic Breast Cancer

Hormonal therapy is optimal initial therapy in the setting of stage IV HR+ breast cancer unless aggressive recurrence mandates chemotherapy to maximize time to response in order to avert impending organ failure (e.g., significant hepatic metastasis). Options in the premenopausal setting include ovarian suppression with or without the addition of tamoxifen or an aromatase inhibitor, or even tamoxifen alone. In the postmenopausal setting, tamoxifen or aromatase inhibitors are effective options; however, more recent data have demonstrated improved outcome when fulvestrant is used as initial therapy as compared to an AI. Fulvestrant is a pure anti-estrogen approved for use in the postmenopausal setting and is given by monthly intramuscular injection. Data from the FIRST trial demonstrated a significantly improved TTP when 205 women were randomized to first-line fulvestrant vs. anastrozole (23.4 vs. 13.1 months) and both treatments were well tolerated (274). Aromatase inhibitors remain a good option for first-line therapy and have been clearly shown to be superior to tamoxifen. A meta-analysis of more than 8,500 patients treated with either first-line AI or tamoxifen showed a significant survival benefit favoring AI (275).

Hormonal resistance eventually evolves over time, necessitating the use of chemotherapy for cancer control. The mechanisms behind the evolution of hormonal resistance and strategies to re-induce hormonal sensitivity in stage IV breast cancer continue to be actively investigated. A recently published study looking at reversing hormonal resistance with the addition of everolimus, an mTOR inhibitor, or placebo to second-line endocrine therapy with Exemetane demonstrated a significant improvement of PFS from 3 to 7 months in favor of everolimus (276).

In the case of HER2+ metastatic breast cancer, women with HR+ tumors without aggressive disease who may not require first-line treatment with chemotherapy and trastuzumab, the combination of an aromatase inhibitor with anti-HER2 targeted therapy has improved PFS when compared to endocrine therapy alone (188,189).

Neoadjuvant Endocrine Therapy

As in the adjuvant and metastatic setting, hormonal therapy can also be beneficial for women presenting with. If chemotherapy is not being employed, neoadjuvant (preoperative) hormonal therapy in the hormonally positive setting can be effective in increasing the ability to completely surgically resect the primary tumor in locally advanced disease as well as in increasing the chances for BCS. Studies suggest that neoadjuvant aromatase inhibitors can be equally as effective as chemotherapy with comparable response rates and rates of breast conservation (114,277). In postmenopausal women, aromatase inhibitors appear to be superior to tamoxifen (278).

Endocrine Therapy for Prevention

The use of tamoxifen in early adjuvant trials appeared to have the benefit of decreasing the risk of second primary breast tumors. In addition, tamoxifen in the NSABP B-24 trial has demonstrated a decreased risk of invasive and *in situ* disease in women with a history of DCIS (87). Based on these findings, the NSABP has studied the use of tamoxifen in high-risk women. Requiring a Gail model risk for developing breast cancer over 5 years of at least 1.66%, the NSABP randomized over 13,000 high-risk women 35 years of age or older to receive tamoxifen or placebo (256). After a median follow-up of 69 months, tamoxifen decreased the risk of breast cancer by approximately 50%. Women with ADH, which, like LCIS, is a risk factor for

subsequent breast cancer, had the greatest benefit for breast cancer risk reduction of 86%. The incorporation of tamoxifen as a risk reduction strategy has been limited, however, based on potential toxicity and on the modest absolute benefit it likely provides. For example, if a woman has a risk for developing breast cancer of 1% per year, the absolute benefit of tamoxifen as risk reduction would be 0.5% per year. A meta-analysis of 4 prevention trials utilizing tamoxifen in normal or higher-risk women showed a 38% reduction in the incidence of invasive breast cancer. Only the rate of ER+ breast cancer was reduced. The risk of endometrial cancer was increased by a factor of 2.4, and the risk of thromboembolic events was increased by 1.9. Importantly, there was no detectable improvement in overall mortality or breast cancer-specific mortality rates (279).

To maintain efficacy and decrease toxicity, the NSABP P-2 trial (STAR trial) studied the use of tamoxifen or another SERM, raloxifene, as prevention for high-risk postmenopausal women. Initially published in 2006, raloxifene appeared similar to tamoxifen in decreasing the risk of invasive breast cancer, but was less effective in decreasing the risk of DCIS. However, with longer follow-up, raloxifene was inferior to tamoxifen in the prevention of invasive breast cancer (RR, 1.24; CI, 1.05–1.47), and the difference in rates of DCIS was no longer statistically significant (RR, 1.22; CI, 0.95–1.59) (280). Raloxifene was associated with a reduced incidence of endometrial cancer (RR, 0.55; CI, 0.36–0.83) and thromboembolic event (RR, 0.75; CI, 0.6–0.93) compared to tamoxifen. Overall, there was no difference in mortality.

More recently, the MAP.3 trial evaluated exemestane for prevention in postmenopausal women with increased risk of breast cancer. The eligibility criteria were similar to the NSABP-P1 trial except for the menopausal status. A total of 4,560 women were randomized to exemestane or placebo. At 35 months, treatment with exemestane reduced the risk of breast cancer by 65% (281).

Based on these trials, both raloxifene and tamoxifen are FDA approved for cancer prevention. While tamoxifen can be used in both pre- and postmenopausal women, raloxifene is reserved as a risk-reducing agent only in postmenopausal women who would have met risk eligibility for the NSABP P-2 trial. Aromatase inhibitors appear to be very promising preventive agents for postmenopausal women and offer another effective option with a different toxicity profile. Another large study exploring the use of anastrozole as a preventive agent in women with a family history of breast cancer or increased breast density is currently underway.

RADIATION THERAPY

Radiation therapy is an important and well-established treatment modality for women with breast cancer. Radiation therapy has been shown to reduce the risk of local and regional recurrence and to prevent the need for salvage mastectomy in women undergoing BCS as well as to improved local and regional control in women following mastectomy who have high-risk disease. Importantly, this reduction in local failure has been shown to translate into improved OS with long-term follow-up (282).

Breast-Conserving Therapy

Breast-conserving therapy (BCT) consisting of adjuvant radiation following BCS is the standard approach selected by the majority of women with localized, operable breast cancer. This approach has been validated through multiple randomized phase III trials (80–82,84,283–288). Relative contraindications for BCT include disease not amenable to local excision with

acceptable cosmesis, multicentric disease, persistent positive surgical margins, active pregnancy, connective tissue disorder (especially scleroderma and lupus), and prior breast irradiation.

Although one of the earliest trials evaluating BCT showed inferior results compared with mastectomy, this trial used insufficient radiation doses by modern standards. Subsequent trials conducted in both Europe and North America have all shown equivalent DFS and OS between BCT and mastectomy. The results of these trials are summarized in Table 28.7. The largest of these was NSABP B-06. This trial randomized 1,843 patients to one of 3 arms: total mastectomy, lumpectomy alone, or lumpectomy with radiation. Twenty-year follow-up results are now available. Fisher et al. reported a DFS rate of 36% and 35% ($p = 0.26$) and an OS rate of 47% and 46% ($p = 0.57$) for total mastectomy and lumpectomy with radiation, respectively (131). Local disease control was also similar: 90% and 86%, respectively.

The importance of radiation therapy as part of BCT has also been meticulously evaluated in multiple studies (Table 28.8). These studies show a consistent high rate of local failure with BCS alone, and a two-thirds reduction in failure with the addition of radiation therapy (131,285–287). NSABP B-06 again is the largest of the studies addressing this question, randomizing 1,262 patients to lumpectomy versus lumpectomy and radiation. Twenty-year follow-up results show local failure of 39% with lumpectomy alone and 14% with lumpectomy and radiation (131).

None of these trials individually have shown a difference in OS, although this is not unexpected since these studies were generally not powered to assess this endpoint. To address this shortcoming, the EBCTCG performed a meta-analysis of individual patient data from these randomized trials (289). This included 10,801 patients from 17 randomized trials of BCS with and without radiation therapy. The results show that the risk of first recurrence (local or distant) at 10 years was reduced from 35% to 19% with the addition of radiation therapy ($p < 0.0001$). More importantly, this reduction in recurrence translated into an OS benefit seen at 15 years follow-up with an absolute reduction in overall mortality of 3.8% ($p = 0.0005$). This absolute reduction in all-cause mortality was even higher in high-risk patients; 7.8% high-risk node-negative and 8.5% for node-positive patients. In general terms, for every 4 recurrences prevented with adjuvant radiation therapy, one death is prevented. The monumental undertaking of this meta-analysis of individual patient data is

very important as it demonstrates that with adequate statistical power, local disease control does in fact impact OS. Furthermore, long-term follow-up is necessary as the survival benefit was not seen until beyond 10 years. This improvement in survival is similar to what is achieved with systemic chemotherapy (215).

Despite these benefits for adjuvant radiation therapy, the question of whether some patients undergoing BCS may not require irradiation has been investigated. In 1989, the NSABP initiated the B-21 trial evaluating women with low-risk disease undergoing BCS. Women of all age with tumors less than or equal to 1 cm, ER+ and lymph node-negative were included. Patients were randomized to adjuvant treatment with tamoxifen alone versus radiation alone versus both radiation and tamoxifen with primary endpoints of in-breast tumor recurrence (IBTR) and incidence of contralateral breast cancer. This study enrolled over 1,000 women, and showed that tamoxifen was not as effective in preventing IBTR as radiation when given as a single therapy and that both were less effective than the combination of radiation and tamoxifen. The incidence of IBTR at 8 years was 16.5%, 9.3%, and 2.8%, respectively. Another sub-group felt to be at lower risk of recurrence is older patients as they tend to have more indolent tumor biology. A trial by the CALGB evaluated the additional benefit of radiotherapy in women 70 years of age or older treated by lumpectomy and tamoxifen. These women had tumors less than 2 cm in size, and were ER+ and lymph node-negative. While the rate of local recurrence was again higher among women who did not receive radiation at 5 years (4% vs. 1% in those who received breast radiation, $p < 0.001$), the absolute benefit of radiation was small, making tamoxifen alone a valid option in this patient population.

In summary, BCS with adjuvant radiation results in similar outcomes to mastectomy and is an appropriate treatment option for most patients with early-stage breast cancer. Adjuvant radiation reduces the risk of in-breast recurrence following BCS even in patients with early, low-risk disease, and should be administered as standard therapy following BCS in all patients. One notable exception is for women over the age of 70 who meet the CALGB trial criteria. These patients can be offered tamoxifen alone.

Postmastectomy Radiation Therapy

For women who undergo mastectomy and are deemed to be at moderate to high risk for local failure, radiation therapy to the chest wall and regional lymphatics is indicated. The criteria that defines “moderate” and “high” risk has evolved over time and continues to evolve as our understanding of the important factors related to local-regional recurrence grows. Early trials of postmastectomy radiation therapy showed a decrease in local recurrence but no benefit in OS (131,282,290). These trials varied greatly in radiation technique and dose, and did not include systemic therapy. Three modern-era trials have evaluated the benefit of postmastectomy radiation therapy. The Danish Breast Cancer Cooperative group (DBCCG) conducted 2 randomized trials. The first involved 1,708 premenopausal women with pathological stage II or III breast cancer who were randomized to CMF chemotherapy with or without irradiation of the chest wall and regional nodes. Radiation therapy was associated with a reduction in locoregional recurrence (alone or with evidence of distant disease) over those who received chemotherapy only, 9% versus 32%, respectively ($p < 0.001$). It was also associated with a survival benefit at 10 years where 54% who received radiation were alive, compared to 45% who had received CMF only ($p < 0.001$). The second DBCCG trial randomized postmenopausal women with stage II–III breast cancer to tamoxifen (30 mg/day for 1 year) with or without radiation therapy (292). Over 1,300 women were enrolled, and with a median follow-up of over 10 years, radiation therapy was associated with a significant reduction in locoregional

Table 28.7 Randomized Trials Comparing Breast Conservation Therapy and Mastectomy

Trial	Local Recurrence (%)		Overall Survival (%)		Follow-up (years)
	BCT	Mas	BCT	Mas	
Milan (81)	7	4	65	65	18
Institut Gustave-Roussy (83)	9	14	73	65	15
NSABP B-06 (80)	10	8	63	59	20
NCI (84)	19	6	77	75	10
EORTC (85)	20	12	65	66	10
Danish Breast Cancer Group (82)	3	4	79	82	6

BCT, breast-conservation therapy; Mas, mastectomy; NSABP, National Surgical Adjuvant Breast and Bowel Project; NCI, National Cancer Institute; EORTC, European Organization for Research and Treatment of Cancer

Table 28.8 Seminal Trials of Trastuzumab in the Adjuvant Therapy of Breast Cancer (3,4)

Trial	N	Arms	Disease-Free Survival	P-Value	Overall Survival	P-Value
NSABP B-31 (430)	2,043	AC → T	67.1%		86.6%	0.015 ^a
NCCTG 98311 (430)	3,000	AC → T + Tr	85.3%	<0.0001	91.4%	
HERA (427)	5,081	Observation	74%		89.2%	
		Tr	80.6%	<0.0001	92.4%	<0.0051
		Tr × 24 m	NR		NR	
BCIRG 006 (428)	3,222	AC → Doc	77		86%	0.004 ^b
		AC → Doc + Tr	83%	<0.00001	92%	
		Carbo + Doc + Tr	82%		91%	
FinHER (429)	210	Chemo × 9w → FEC	76.8%		88%	0.07 ^c
		Chemo + Tr × 9w → FEC	89.6%		94.8%	

NSABP, National Surgical Adjuvant Breast and Bowel Project; A, doxorubicin; C, cyclophosphamide; T, paclitaxel; NCCTG, North Central Cancer Treatment Group; Tr, trastuzumab; HERA, Herceptin Adjuvant; BCIRG, Breast Cancer International Research Group; Doc, docetaxel; Carbo, carboplatin; FinHER, Finland Herceptin; FEC, 5-fluorouracil/epirubicin/cyclophosphamide.

Unless otherwise stated, trastuzumab treatment was for a total duration of 1 year.

^aJoint analysis of 3,351 women (1,679 receiving AC → T; 1,672 receiving trastuzumab) reported survival analysis at 4 years.

^bThe second interim analysis reported survival endpoints at 4 years.

^c1,010 women were randomized in the FinHER trial to vinorelbine vs. docetaxel, followed by FEC. The subgroup with HER2/neu+ disease underwent additional randomization to trastuzumab or no trastuzumab

recurrence, 8% versus 35% with tamoxifen alone ($p < 0.001$). OS was also improved: 45% and 36%, respectively ($p = 0.03$). Over half of the women enrolled in this trial had only 1 to 3 positive axillary lymph nodes, and the benefit of postmastectomy irradiation was similar in these patients as to those who had 4 or more lymph nodes involved. The DBCCG trials have been criticized for the low number of axillary lymph nodes removed on axillary dissection and the higher than expected axillary failure rates in the control groups. Another trial conducted in British Columbia also addressed the question of postmastectomy irradiation by randomizing over 300 women to CMF chemotherapy with or without radiation therapy. This trial also showed a locoregional control benefit and OS benefit to radiation therapy, yet unlike the Danish trials, the median number of axillary lymph nodes removed on axillary dissection was 11. At 20-year follow-up, isolated recurrence was 10% versus 26% and OS was 47% versus 37% in favor of postmastectomy irradiation (291). The relative magnitude of benefit from radiation therapy was similar in women with 1 to 3 positive nodes (HR, 0.76; 95% CI, 0.50–1.15) compared to those with ≥ 4 positive nodes (HR, 0.70; 95% CI, 0.46–1.06) (292). The EBCTCG also performed a meta-analysis of individual patient data from randomized trials of postmastectomy radiation therapy (282). This analysis included 8,500 women, and for those with any involved axillary nodes, a statistically significant 17% absolute reduction in 5-year local recurrence (6% vs. 23%) and a 4.4% absolute improvement in 15-year OS (40.2% vs. 35.8%) was shown.

Postmastectomy radiation therapy, therefore, should be administered to all patients with locally advanced disease (T4 or ≥ 4 positive nodes). Radiation therapy should also be offered to patients with one to 3 positive nodes or involved surgical margins as these patients are also at moderate to high risk for local recurrence (293). Furthermore, a subset of patients with node-negative disease is at risk for recurrence and may benefit from postmastectomy radiation therapy. A combination of some of the following risk factors defines this later group: young age, T2

or greater disease, lymphovascular space invasion, close margins, and triple negative disease (ER, PR, and HER2/neu negative) (294–296).

Radiation Therapy for *In Situ* Breast Disease

Approximately 20% to 30% of patients treated with local excision alone for DCIS have a recurrence, with about half of these recurrences being invasive cancer. Given this, radiation is often delivered as a means of risk reduction. To date, 4 randomized trials have compared excision alone with excision followed by whole breast radiation therapy, and all have demonstrated that radiation therapy reduces the risk of a subsequent breast event by 38% to 62% (297).

The NSABP B-17 trial enrolled over 800 women with localized DCIS and randomized them to lumpectomy with or without radiation therapy. A statistically significant reduction was seen in both noninvasive IBTR (13.4% without radiation vs. 8.2% with radiation, $p = 0.007$) and invasive IBTR (13.4% vs. 3.9%, respectively, $p < 0.0001$) (293). EORTC 10853 enrolled over 1,000 women with surgically excised DCIS up to 5 cm in widest diameter and randomized them to observation or radiation therapy. The reported 4-year local relapse rate was 84% and 91%, respectively ($p = 0.005$), with similar reductions seen in both invasive and noninvasive recurrences. The SweDCIS trial enrolled over 1,000 women and showed a 60% relative reduction of IBTR with radiation corresponding to an absolute reduction in recurrence of 16% at 10 years (297). Lastly, Houghton et al. reported on a 2×2 randomized trial (UKANZ) in this population where over 1,700 women were randomized to both radiation and tamoxifen, either as a single agent, or to no further therapy. With a median follow-up of 53 months, radiation therapy reduced IBTR (HR, 0.68; 95% CI, 0.49–0.96). The reduction in IBTR was seen for both invasive disease (HR, 0.45; 95% CI, 0.24–0.85) and noninvasive disease (HR, 0.36; 95%

CI, 0.19–0.66). Interestingly, this is the only randomized trial to assess tamoxifen alone in the absence of radiation therapy for preventing local recurrence, and no benefit was seen. The impact of tamoxifen combined with radiation therapy was the focus of NSABP B-24. This trial showed that the addition of tamoxifen further reduced the number of invasive breast cancer events by 50%. Tamoxifen also reduced the risk of invasive disease in the contralateral breast, but had a nonsignificant effect on reducing DCIS recurrences in either breast. Finally, a recent meta-analysis of the aforementioned trials evaluated the role of radiation following breast-conservation surgery for DCIS. This analysis demonstrated a 54% reduction in local recurrence (298). The same proportional benefit was seen across all risk groups with the largest absolute benefits seen in patients with high-risk factors; size >2 cm, high grade, presence of comedonecrosis, and positive resection margins. However, even in women with small, low-grade tumors resected with negative margins, the absolute reduction in IBTR with radiation therapy at 10 years was still 18%. No significant difference in breast cancer-specific mortality or overall mortality was seen.

Attempts at identifying subgroups of patients at low risk for recurrence following excision alone have met with limited success. Wong et al. prospectively evaluated a series of patients treated with wide resection margins of at least 1.0 cm and still reported a 5-year recurrence rate of 12% (91). A prospective trial ran by ECOG evaluated patients with low-grade tumors less than 2.5 cm and high-grade tumors less than 1.0 cm. Five-year IBTR was 6.1% in the low-grade group and 15.3% in the high-grade group despite a mean tumor size of only 6 mm and 5 mm, respectively (299). Several stratification systems have been proposed (33,37,300) evaluating various clinical and pathologic factors in an attempt to identify subgroups at low risk of recurrence. Unfortunately, none have been substantiated by external validation (301–303). It appears that although many of the clinical and pathologic factors related to risk of recurrence are known, some patients with seemingly low-risk DCIS develop recurrence. It is clear that our understanding of the underlying biology of DCIS based on these factors is incomplete. Novel molecular or genetic markers may prove useful in this regard.

In summary, adjuvant radiation therapy following local excision of DCIS reduces the risk of local recurrence by approximately 50%, and tamoxifen provides an additional benefit in reducing the risk of invasive recurrence. This approach, however, has not been shown to improve DFS or OS. As such, radiation therapy as a risk reduction strategy for local recurrence should be discussed with each patient. The decision whether to proceed with treatment needs to involve the active participation of the patient, and should take into account the individual's clinical and pathologic risk factors to help assess the overall risk of recurrence, and thus the expected absolute benefit of radiation therapy, as well as the potential side effects and toxicities of therapy.

Partial Breast Irradiation

Standard radiation therapy consists of irradiating the whole breast; however, for select patients, partial breast irradiation is an option. The concept of partial breast irradiation arose out of the realization that the majority of tumor recurrences occur at or near the region of the lumpectomy site, and is supported by pathologic correlation (286,304,305). Thus, for well-selected patients, only the breast tissue surrounding the tumor bed needs radiation treatment. Limiting radiation therapy to a smaller portion of the breast results in 2 major advantages. First, there is reduction in volume of irradiated tissue thereby preserving these tissues for potential deleterious radiation effects. This includes minimal to no dose exposure to the heart and lung. Second, by reducing the volume of treatment, the overall treatment time

can be safely accelerated to deliver the entire course of radiation within a week or less. This approach is referred to as accelerated partial breast irradiation (APBI), and is generally defined as radiotherapy delivered to less than the whole breast employing fractions higher than 1.8 to 2.0 Gy per day over a period of less than 5 to 6 weeks. Multiple techniques have been developed and are being developed for the delivery of APBI. In North America, the most commonly used techniques are multicatheter interstitial brachytherapy, intracavitary brachytherapy, and 3-D conformal external beam radiation therapy. Multiple single-institutional as well as multi-institutional trials, some with follow-up beyond 10 years, have demonstrated results comparable to whole breast irradiation (306). A matched-pair analysis was performed at the William Beaumont Hospital where 199 patients who received APBI via an interstitial approach were compared to 199 patients treated with whole breast irradiation at the same institution. Shah et al. recently reported 12-year follow-up results showing no difference between the 2 groups in local control, regional control, cause-specific survival, or OS (307). The local failure was 5.0% and the cause-specific survival was 95% in both groups. To establish level I evidence for the equivalency of APBI and whole breast radiation therapy, the NSABP/Radiation Therapy Oncology Group and the Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology collaborative groups are conducting phase III randomized trials. Until these trials mature, the American Brachytherapy Society (ABS), American Society of Breast Surgeons (ASBS), and American Society of Therapeutic Radiation Oncology (ASTRO) have published guidelines for appropriate patient selection for APBI (Table 28.9) (308).

Radiation Therapy for Recurrent Disease

Recurrent disease involving the chest wall or regional lymphatics is often a marker of aggressive disease biology, and up to 80% of patients will develop subsequent distant metastatic disease (309). Aggressive local therapy with surgery and/or radiation is, however, warranted as cure can be achieved in some of these patients; furthermore, the prevention of the significant morbidity of uncontrolled, local disease is of benefit.

Table 28.9 Selection Criteria for Accelerated Partial Breast Irradiation

Criteria	ABS	ASBS
Age	≥45 years	≥45 years
Histology	IDC	IDC or DCIS
Size	≤ 3 cm	≤ 3 cm
Margin	Negative	Negative microscopic margin
Axillary Node Status	Negative	Negative

Note: ABS, American Brachytherapy Society; ASBS, American Society of Breast Surgeons; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma.

Sources: Gail MH, et al. Projecting individualized probabilities of developing breast cancer for White females who are being examined annually. *J Natl Cancer Inst.* 1989;81(24):1879–1886; Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer.* 1994;73(3):643–651; Fisher B, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347(16):1233–1241.

Radiation Therapy for Metastatic Disease

Oligometastatic disease is a condition that has been recently recognized in many solid tumors. Oligometastasis is defined as a transitional state between localized disease and widespread systemic disease, where the volume and number of metastatic deposits is limited, and local and/or systemic therapy may result in cure (310). Although only a small percentage of these patients can have long-term DFS, this is in distinct contrast to patients with widespread metastatic disease where cure is not possible. While such tumor biology is considered quite rare in breast cancer, aggressive local therapy with radiation and/or surgery should be considered for select patients. Stereotactic body radiation therapy (SBRT) or stereotactic radiosurgery (SRS) is an ideal method for radiation therapy for these patients. With this method, high ablative doses of radiation are delivered in a highly conformal manner with extreme precision. This is typically done in just 1 to 5 treatments or fractions and can be applied not just to the brain but almost any part of the body. The large radiation doses result in a high probability of local disease control, and the conformality and precision allow for a low risk of side effects and complications (311,312).

For patients with widespread metastatic disease, radiation therapy can be used effectively for palliation of lesions involving the chest wall, regional lymphatics, bone, brain, lung, and liver, among other areas. Indications for radiation in this setting include palliation of symptomatic lesions not responding or unlikely to respond to systemic therapy, and prevention of complications of local disease progression, such as impending pathologic fracture from bone metastasis, impingement of the spinal cord or nerve roots from spine metastasis, or neurologic sequelae from brain metastases. Palliative radiation courses usually last from a one-time, 8-Gy one-day treatment to a 2-to-3 week course of 2.5 to 3 Gy per fraction for a total dose of 30-37.5 Gy (313). Some well-localized lesions can also be treated with SBRT.

Radiation Therapy Techniques

Radiation treatment planning and delivery has dramatically evolved since the inception of BCT; from low-energy Cobalt units using indiscriminant en face treatment fields, to high-energy linear accelerators with rudimentary 2-D planning, and now to modern CT-based, 3-D treatment planning with sophisticated dose modulation. This is important to understand as we have come a long way in our ability to spare normal tissues, and this needs to be considered when evaluating long-term toxicity data from techniques that are clearly far inferior and posed substantial risk to underlying organs as compared to modern methods.

For modern radiation treatment planning, the process begins with the “simulation.” This is a session at which the patient position for treatment is established. For breast cancer, this is typically in the supine position with the ipsilateral arm up, although other treatment positions are sometimes used to optimize target and normal tissue geometry. Appropriate immobilization devices are used to ensure stability and reproducibility of the patient position during daily treatments. Tattoos are placed to allow for precise positioning with aid of in-room targeting lasers. A CT scan is obtained in the established treatment position. This data set is used to design treatment portals and to perform dose calculations. This allows for tailoring the treatment fields to the specific anatomy of the patient and allows for optimization of target doses and normal tissue sparing. Once an appropriate treatment plan is generated, the virtual plan is verified on the patient via imaging through the treatment portals.

The whole process undergoes rigorous quality assurance procedures to ensure the upmost accuracy in all facets of treatment delivery (314-317).

Intact Breast

Following BCS, the entire residual breast tissue is included in the irradiated volume with or without regional lymph node groups depending on the risk of subclinical disease spread to these regions. Treatment portals are oriented tangential to the breast to avoid lung and heart irradiation. Photon energies of 4 to 6 MV are preferred to treat the breast. Energies greater than 6 MV may underdose superficial tissue beneath the skin surface, but may be helpful in decreasing hot spots for patients with large breasts. Dose modulation with wedges, tissue compensators, electronic compensation (field-in-field techniques), or intensity modulated radiation therapy (IMRT) is used to optimize dose distribution and dose homogeneity across the target volumes. The prescription dose used is 45 to 50.4 Gy in 1.8 to 2.0 Gy per fraction over 25 to 28 treatments given 5 days per week over 5 to 6 weeks. This is followed by a boost to the tumor bed consisting of 10 to 16 Gy in 1.8 to 2.0 Gy per fraction to a total dose of 60 to 66 Gy over 6 to 7 weeks of treatment.

The tumor bed has the highest risk of harboring subclinical or microscopic disease, and clinical evidence has shown that it is the site at highest risk for recurrence. The value of adding a tumor bed boost was evaluated by 2 randomized trials. The EORTC 22881-10882 trial involved over 5,300 women with stage I or II breast cancer who were randomly assigned to whole breast treatment with or without a tumor bed boost of 16 Gy. At 10 years, the rate of local relapse was significantly lower in the boost arm: 10.2% versus 6.2% ($p < 0.0001$). There was no difference in OS: 82% in both arms. A subsequent randomized trial from Lyon, France also showed a reduction in local relapse with a 10 Gy boost. The boost targets the lumpectomy cavity with an appropriate margin and can be delivered using one of several techniques, including en face electrons, 3-dimensional conformal radiation therapy (3D-CRT), IMRT, Accuboot or other brachytherapy techniques.

Recent data have emerged that for select patients, hypofractionated whole breast radiation is an appropriate option. This allows for shorting the overall treatment time to about 4 weeks from 6 to 7 weeks with standard fractionation. Whelan et al. reported an update of the Canadian study which randomized over 1,200 women to either standard whole breast irradiation (50 Gy in 25 fractions) or to a hypofractionated regime (42.5 Gy in 16 fractions). The local control at 10 years was similar; 6.7% for standard fractionation and 6.2% for hypofractionation. Good to excellent cosmetic outcome was also similar; 71.3% and 69.8%, respectively. Further studies from the United Kingdom have substantiated these findings (317).

Chest Wall

For women at high risk for local or regional recurrence following mastectomy, radiation therapy is delivered to the chest wall and regional lymphatics. Similar to intact breast treatment, a 3D-CRT technique using tangentially oriented beams is used. Tissue-equivalent bolus material is used on the chest wall surface, for at least a portion of the treatment, to increase dose build-up in superficial chest wall tissues. Other techniques, such as en face electrons fields, mixed electron and photon fields, and IMRT can also be used to target the tissues at risk. The typical prescription dose is 45 to 50.4 Gy in 1.8 to 2.0 Gy per fraction over 25 to 28 treatments over 5 to 6 weeks. This can be followed by a boost to the mastectomy scar/operative bed to a total dose of 60 to 66 Gy.

For patients undergoing mastectomy, reconstructive options are an important consideration for most women. The plastic surgeon should be involved early in the multidisciplinary management of these patients as many factors can have significant implications on the ultimate cosmetic outcome. Among these factors are the type of reconstruction used, and sequencing of reconstruction and postmastectomy radiation.

Regional Lymphatics

From a radiation oncology perspective, the regional lymphatics are divided into 4 anatomical groups: low axilla (level I and lower level II), high axilla (high level II and level III), supraclavicular fossa (SCF), and internal mammary chain (IM). Each of these regions can be targeted based on risk of subclinical disease involvement. The low axilla is inadvertently included in most tangential whole breast radiation fields. This typically includes the first echelon lymph nodes as most sentinel nodes are found in these regions (318). For patients who are node-negative, the risk of failure in the axilla or SCF is uncommon, and inclusion of these nodal regions is not necessary. For patients with involved axillary lymph nodes, and particularly those with 4 or more involved nodes, the SCF is at risk and should be treated (319). The SCF is typically treated with a single anterior oblique field that is matched to the tangential breast fields. The matching technique is crucial to prevent beam overlap and thus significant dose hot spots at the beam junctions. For patients with involved axillary lymph nodes who undergo a completion axillary dissection, treatment of the high axilla is generally not necessary as the risk of failure after an *en bloc* resection is not common (319). Avoiding irradiation of the high axilla in these patients is desirable as irradiation increases the risk of arm lymphedema following axillary dissection (320). Thus treatment of the high axilla is typically reserved for patients at high risk of subsequent axillary failure. This includes patients who do not undergo axillary evaluation but are at risk for axillary lymph node involvement, patients with positive sentinel lymph nodes who do not undergo a completion dissection, and patients with involved axillary lymph nodes who undergo dissection but have high-risk factors. The high axilla is typically treated by extending the oblique SCF field laterally. Often a posterior field, posterior axillary boost, or PAB, is added to supplement dose to the posterior portion of the axilla.

The treatment of the IM nodes is controversial. Classic surgical data have shown that the risk of IM node involvement can be as high as 20%, particularly for patients who have medial tumors and involved axillary lymph nodes (321,322). However, clinical failure in the IM chain, even in these patients, is uncommon, less than 1% (323). A randomized trial evaluating the treatment of IM nodes is currently underway and will help answer this unresolved question. The IM nodes are located in the first 3 intercostal spaces adjacent to the internal mammary vessels, just lateral to the sternum. Several techniques can be used to target the IM nodes. The most common methods are either a matched en face or oblique electron field, or a modification of the whole breast tangential beams. Regional lymph nodes are treated to a total dose of 45 to 50.4 Gy in 1.8 to 2.0 Gy per fraction.

The importance of regional lymph node irradiation was the focus of the Canadian Clinical Trials Groups protocol MA.20. This study included over 900 patients with 1 to 3 involved lymph nodes undergoing BCS and were randomized to whole breast radiation therapy with or without regional nodal irradiation. Early results have been reported and they show a statistically significant improvement in DFS, isolated local-regional DFS, distant DFS, and a trend to improved OS.

Accelerated Partial Breast Irradiation

Numerous techniques for the delivery of APBI have been employed involving both external beam and brachytherapy techniques. The most common techniques used in North America are interstitial multicatheter brachytherapy (IMB), intra-cavitary balloon brachytherapy (IBB), and 3D-CRT. IMB is characterized by the percutaneous placement of multiple catheters into and surrounding the lumpectomy cavity in such a fashion as to deliver the prescription dose to the tumor bed with a margin of 1.0 to 1.5 cm. This technique is very versatile and can conform to the most complex tumor bed geometry. IBB was developed as a simplification of the IMB technique. IBB involves the percutaneous placement of a single catheter applicator into the lumpectomy cavity. This is performed either at the time of surgery under direct visualization with an open cavity, or postoperatively under US and/or CT guidance. Once the end of the applicator is positioned within the lumpectomy cavity, the balloon at the end of the applicator is inflated to conform to the cavity. Dose is prescribed to a 1.0 cm distance from the balloon surface to encompass the tumor bed with an appropriate margin. Several balloon and balloon-like catheters are commercially available including Mammosite, Contura, and SAVI. APBI using 3D-CRT is an external beam technique, which employs 4 to 5 noncoplanar, tangential-oriented beams targeted to the lumpectomy cavity. To account for breast motion, respiratory motion, patient motion, and set-up error, a larger margin of 2.5 cm is used with this technique. A prescription dose of 34.0 Gy in 10 fractions given twice daily is used for IMB and IBB and a dose of 38.5 Gy in 10 fractions is used for APBI using 3D-CRT.

Future Directions in Radiation Therapy

APBI is now an established approach to treating well-selected patients. However, several aspects of APBI remain areas of active research. Which patients are appropriate for this approach still remains to be determined. Patients defined as “appropriate” by the ASTRO criteria are clearly good candidates for this approach, but emerging data show that at least some patients in the “cautionary” and even in the “unsuitable” categories may be appropriate for APBI as well (324,325). We have learned and continue to learn about the limitations of the established techniques as long-term toxicity data emerge (326–328). Novel approaches to deliver APBI are being developed and investigated to overcome some of the limitations and shortcomings of the existing techniques. Novel approaches include electronic balloon catheter brachytherapy (Xoft), permanent breast seed implantation (PBSI), Gamma Pod, CyberKnife, prone position external beam techniques, mixed photon and electron external beam techniques, proton beam, intra-operative electrons or photons, and noninvasive image-guided breast brachytherapy (AccuBoost). It is likely that no one technique will prove superior in all scenarios, but which collection of techniques will prove to be most optimal is yet to be determined.

Another important area for future investigation is to continue to better define subgroups of patients who benefit from and those that may forgo radiation therapy. A recent analysis showed that women with triple-negative disease undergoing mastectomy had a higher rate of local-regional failure compared to women undergoing BCS and radiation therapy (329). This suggests that there are populations of patients who undergo mastectomy but are not offered radiation therapy because they are felt to be at low risk and yet ultimately develop recurrence. Further data to clearly define these at-risk groups are needed. Conversely, data need to define whether or not all patients undergoing BCS need radiation. The CALGB trial

evaluating women over the age of 70 defined one such group which can be treated without radiation therapy. Are there other low-risk groups? The answer likely is yes. But appropriately defining these groups remains a challenge. Nomograms can be useful for this purpose and are being developed (330,331). One such nomogram, IBRT!, was developed using known clinical and pathologic variables, and has undergone external validation (331). Tumor-specific genetic signatures may also prove to be helpful as they have been for determination of benefit from chemotherapy (332).

Pregnancy-Associated Breast Cancer

Breast cancer is one of the most frequently diagnosed cancers during pregnancy. Pregnancy-associated breast cancer (PABC) is defined as cancer diagnosed either during pregnancy or up to 12 months postpartum. The incidence of PABC ranges from 0.02% to 0.1% (333). As increasing numbers of women delay pregnancy, many speculate that the incidence of PABC will increase. Deciding on the best treatment of PABC is challenging due to potential conflicts between maternal and fetal well-being.

While breast examination is limited in a pregnant patient due to hormonally-induced breast engorgement, most women diagnosed with PABC present with a painless breast mass, and while the majority of palpable masses identified during pregnancy are benign, including lactating adenomas, fibroadenomas, and galactoceles, evaluation is warranted if palpable findings persist. Unfortunately, given the physiological changes associated with pregnancy, diagnostic delays are common and are believed to contribute to the advanced stages at diagnosis among pregnant women. Typically, breast US is the first diagnostic approach used to evaluate a palpable breast and/or axillary mass during pregnancy given its safety and high sensitivity and specificity (334). Following a diagnosis of breast cancer, mammography may be helpful to diagnose multicentric, multifocal and/or bilateral breast cancer. MRI has been used during pregnancy; however, as gadolinium crosses the placenta and has been associated with fetal abnormalities in rats (Category C), contrast-enhanced breast MRI is not recommended (335).

Although the usefulness of mammography during pregnancy has been questioned, recent studies have reported on both the safety and relative efficacy of mammography during pregnancy. With proper abdominal shielding, the irradiation dose to the fetus from a standard 2-view mammogram is less than 50 mrad (0.5 μ Gy). It is within the limits considered acceptable during pregnancy and well below the threshold exposure of 10 rad (100 mGy), where the estimated risk of fetal malformations and CNS problems is 1% (336).

Studies assessing the effectiveness of mammographic and ultrasonographic imaging in PABC are limited. Yang et al. performed a retrospective study of 23 women with 24 cancers diagnosed during pregnancy (337). Of those who underwent preoperative mammography, radiographic findings were “positive” in 18/20 cancers (90%) despite dense breast parenchymal patterns. The addition of ultrasonography was noted to be 100% sensitive in the work-up of the palpable mass during pregnancy. Ultrasound-guided core biopsies can be performed safely and are the preferred method for diagnosis. A percutaneous biopsy of any lesion that does not meet the criteria for a simple cyst has been recommended (338). Despite concerns to the contrary, reports of milk fistulae are rare. Furthermore, gestational changes of the breast may lead to false-positive and/or false-negative results with fine-needle aspirate cytology and should be interpreted with caution. The use of other imaging modalities should be limited to those required for treatment planning. Metastatic evaluations acceptable during pregnancy

include chest radiographs, abdominal/liver ultrasonography, and noncontrast skeletal MRI (339).

Historically, studies reported that PABC had a dismal prognosis, with survival rates of less than 20% at 5 years (340,341). These statistics likely reflect a more advanced stage of diagnosis, as PABCs are typically larger and more often node-positive (56% to 89%) compared to nonpregnant women (38% to 54%) (342). Most pregnant patients are diagnosed with infiltrating ductal adenocarcinomas associated with aggressive histologic phenotype and these are often high-grade, HR-, and *HER2/neu+* with associated LVI (343). After controlling for patient age and stage of diagnosis at presentation, the overall prognosis of patients appears similar to that of nonpregnant women, and the 5- and 10-year survival for node-negative and node-positive PABC ranges from 60% to 100%, and 31% to 52%, respectively (344,345). Despite this, controversy still persists, and a recent retrospective study demonstrated a higher risk of recurrence and death among women with PABC compared to nonpregnant controls (346).

Treatment

Treatment strategies are determined by tumor biology, stage, gestational age, and patient/family wishes. Treatment guidelines for pregnant women essentially follow those set forth for nonpregnant women with the exception of radiotherapy. There is no role for pregnancy termination with the goal of improving prognosis. A multidisciplinary approach is essential to providing optimal care, allowing for cooperation between medical, surgical, and radiation oncology, radiology, obstetrics, and neonatology.

Surgery

The safety of surgical intervention at any stage in the pregnancy is well established, and a modified radical mastectomy has traditionally been considered the standard of care. This approach virtually eliminates the need for irradiation and allows optimal control of disease within the axilla. However, given that most women with PABC will receive adjuvant or NACT, resulting in a delay of radiotherapy after delivery, BCS is increasingly seen as a reasonable alternative to pregnant women, particularly if the diagnosis is made in the latter second and third trimesters.

Lymph node staging remains the most important predictor of systemic recurrence, and accurate nodal staging is crucial to determining appropriate systemic therapy. As in nonpregnant patients, axillary ultrasonography and image-guided FNA of suspicious nodes may be helpful in diagnosing those patients with locally advanced disease. This is of particular relevance to patients for whom neoadjuvant therapy is being considered. Although the sensitivity and specificity of sentinel lymph node (SLN) biopsy in pregnancy have not been systematically evaluated, this technique has been used successfully in pregnant patients, and SLN staging with the use of Tc-99 colloid is considered safe in pregnancy (347,348). The lower radioactive dose associated with the 1 day protocol is preferred. Of note, however, both isosulfan blue dye and methylene blue dye are classified as pregnancy category C drugs. Intra-amniotic injection of methylene blue has been associated with hemolytic anemia, hyperbilirubinemia, methemoglobinemia, duodenal atresia, deep blue staining of the newborn, and even fetal death, and is best avoided (349).

Radiotherapy

Most experts consider postoperative therapeutic irradiation during pregnancy to be contraindicated. If breast conservation is chosen, adjuvant radiotherapy is typically delayed until the postpartum period. This perspective has been challenged by

some who feel that the risks of radiation to the fetus are overestimated and exposure can be reduced sufficiently by proper shielding, resulting in fetal exposure doses which fall below accepted threshold levels (350). Kouvaris et al. reported the case of a 45-year-old woman treated with radiation during the first trimester of pregnancy who delivered a healthy male neonate at 39 weeks of gestation. The lack of prospective data and the option of mastectomy for patients with PABC, however, continue to make the use of radiotherapy during PABC contraindicated.

Systemic Therapy

Given the high prevalence of node-positive disease with adverse pathologic features among women diagnosed with PABC, chemotherapy plays a crucial role in both the adjuvant and neoadjuvant treatment of these women. The effects of chemotherapy on fetal development and growth vary depending on gestational age at the time of exposure. When administered during the first trimester, chemotherapy effects are characterized as “all-or-nothing” and may result in high rates of miscarriages and congenital malformations (351). As a result, chemotherapy is generally avoided during the first trimester. The second and third trimesters of pregnancy are characterized primarily by fetal growth and maturation, as organogenesis is complete. Outside of the first trimester, chemotherapy has proven to be surprisingly safe, although all chemotherapy agents are considered category D agents. The overall incidence of major fetal malformations is reported to be ~3%, which is similar to the estimated baseline population risk for major congenital malformations (352). Studies have reported growth restriction, intrauterine and neonatal death, prematurity, and haemopoietic suppression. In a recent publication, Cardonick and colleagues reported on the experience of 104 women diagnosed with PABC who received chemotherapy during pregnancy (353). The mean gestational age at diagnosis was 13.2 weeks. All but one patient received anthracycline-based treatment, and 11 patients received additional taxane therapy. None received trastuzumab. The mean gestational age at delivery was ~36 weeks. One neonatal death was reported due to a systemic autoimmune disorder. Four (3.8%) newborns exhibited birth defects. This study showed no increased rate of growth restriction at birth or congenital anomalies compared with population controls.

Several prospective case-series have reported on the use of anthracycline-based chemotherapy administered every 3 to 4 weeks during the second and third trimesters (354). In a prospectively recorded series, Hahn and colleagues reported that among 57 women treated with FAC in the second and third trimesters, there were no stillbirths, miscarriages, or perinatal deaths (355). The median gestational age at delivery was 37 weeks (range, 29 to 42 weeks). The most common neonatal complication was respiratory distress, and 10% required ventilatory support.

Other studies have been reported recently which document the relative safety of chemotherapy for treatment of PABC. The European Institute of Oncology in Milan reported a retrospective series of 20 women with locally advanced or metastatic breast cancer treated with weekly epirubicin after the second trimester (356). The regimen was well tolerated, and the development of children was normal at a median follow-up of 2 years. Azim and colleagues reported the results of anthracycline-based treatment regimens in 26 patients with PABC (357). Chemotherapy was delivered as both adjuvant and neoadjuvant treatment during the second trimester. No growth restriction or pre-eclampsia was reported. All children met normal developmental milestones at 27 months of age.

Many of the patients who present with PABC exhibit characteristics (e.g., young age and adverse prognostic features) that in other circumstances would be treated using a combined

anthracycline- and taxane-based regimen. Historically, however, the taxanes were felt to be contraindicated due to evidence of toxicity in animal studies during organogenesis. More recently, several case reports describe the use of paclitaxel and docetaxel in the second and third trimesters (358,359). A review by Mir et al. identified 40 reports of taxanes used to treat breast, ovarian, and lung cancer in pregnant women (360). There were no spontaneous abortions or intrauterine deaths reported.

Other Therapies

Given the relative frequency of *HER2/neu* over-expressing tumors in women with PABC, treatment with trastuzumab may be considered. There are several case reports on the use of trastuzumab during pregnancy. Watson reported on a case of reversible anhydramnios following treatment with trastuzumab when used at less than 30 weeks gestation (361). Sekar and Stone reported similar results and demonstrated a 7-week delay before anhydramnios was reversed (362). Two other case reports found no fetal or neonatal complications (363,364). Trastuzumab is considered a category B drug in pregnancy, but given these data, it appears prudent to limit its use in pregnancy if possible. When used, serial monitoring of these pregnancies is warranted, particularly with regards to oligo-/anhydramnios.

Given that the majority of PABCs are HR-, the use of endocrine manipulation has been less extensively studied among pregnant women with breast cancer. There are no long-term data available of children following exposure to tamoxifen in utero. This, coupled with data from both animal and clinical studies on the potential teratogenicity of tamoxifen, suggest that tamoxifen use is best reserved until completion of the pregnancy, and the use of nonhormonal contraception is recommended during tamoxifen treatment and for 2 months after stopping, due to its extended half-life (365). Bisphosphonates have also shown promise in the treatment of premenopausal patients in combination with endocrine therapy (366); however, animal studies have shown significant fetal toxicities, including fetal underdevelopment, fetopathy, hypocalcemia, and skeletal retardation. Bisphosphonates are therefore contraindicated in pregnancy.

Developmental Effects

The potential risk of anthracycline-associated fetal cardiotoxicity later in life during childhood or adulthood remains a concern for fetuses exposed to chemotherapy in utero. Meyer-Wittkopf et al. did not identify any abnormalities on echocardiograms performed in utero and up to 2 years of age on infants exposed to doxorubicin and cyclophosphamide starting at 24 weeks gestation (367). Additionally, evaluation of 81 children who received anthracycline treatment in utero detected no abnormalities at a median follow-up of 17 years (368).

Others have voiced unease over the potential long-term developmental sequelae of in utero exposure to chemotherapy. Aviles and Neri reported on a cohort of 84 children born to mothers who received combination chemotherapy during pregnancy for hematological malignancies (369). Physical, neurological, and psychological development were normal for all children, and there were no malignancies diagnosed in this group of children. Finally, a recent study by Amant et al. documented the outcomes of 70 children exposed to chemotherapy during pregnancy. No differences were reported in general health and growth, CNS, cardiac, and auditory function. Prematurity was frequently reported, however, and was associated with cognitive impairment, stressing the importance of avoiding iatrogenic premature delivery whenever possible. At present, the dosing recommendations for chemotherapy during pregnancy are weight-based. Current recommendations are to avoid the administration of chemotherapy approximately one

month prior to delivery in order to minimize the possibility of infectious complications or hemorrhage to both the mother and the fetus from pancytopenia.

Pregnancy After Breast Cancer Treatment

It has been reported that approximately 5% to 15% of young breast cancer survivors will become pregnant. To date, there are no prospective studies evaluating the safety of a subsequent pregnancy after a diagnosis of breast cancer. Several retrospective studies have demonstrated no worsening of survival or increased risk of recurrence, although these studies are subject to significant biases and limitations (370). Of note, a number of studies reported an improved survival in women who became pregnant after breast cancer (371), and the issue of the “healthy mother effect” as a potential confounder has been reported. The reasoning is that only women who feel physically and emotionally healthy will attempt pregnancy, while those who continue to be affected by the disease do not. Alternatively, it is possible that the high hormonal levels of pregnancy have a beneficial effect given the documented anti-tumor effects seen both *in vitro* and *in vivo* animal models of high-dose estrogens and progestins.

For those women who become pregnant following breast cancer treatment, successful breast-feeding following breast conservation and irradiation has been reported. Higgins and Haffty reported on 11 patients who subsequently experienced 13 pregnancies (372). Following delivery, lactation was possible in the treated breast in 4 instances but not in 6 others. In 3 women, lactation was pharmacologically suppressed. In the majority of cases, lactation was possible in the untreated breast. The time interval from initial treatment did not appear to impact successful lactation; however, in 4 instances where lactation was not successful, a circumareolar incision was performed, suggesting that lactation may be less likely to occur in the case of centrally located lesions where the anatomy of central ducts may be altered.

It may seem helpful to wait a period of time prior to attempting pregnancy since this is the time of highest risk of recurrence, but the available data have not clearly shown a worse prognosis if pregnancy is achieved sooner. Furthermore, women with a risk of breast cancer may develop recurrent disease many years after, such that a waiting period of 2 years may not be as reassuring as it seems. In this regard, studies have highlighted patients’ concerns regarding the impact of adjuvant treatment on subsequent fertility options (373,374). Discussing fertility options after receiving treatment for breast cancer may be too late. Thewes et al. found that women prefer to discuss these issues at the time of treatment planning and early follow-up, suggesting that options for preserving fertility should be addressed early, including a referral to a fertility specialist as needed. Recently, ASCO convened an expert panel to develop guidelines for fertility preservation.

Breast Cancer in the Elderly Patient

Age is a well-documented risk factor for the development of breast cancer, and decisions regarding effective therapy can be complicated by a real or perceived limited life expectancy, multiple competing comorbidities, and limited level I evidence. Data from the Surveillance Epidemiology and End Results (SEER) database shows that more than half of all cancers occur in patients aged > 65 years, including approximately 25% aged 75 to 84 years, and almost 10% aged > 85 years. Given the overall increase in life expectancy among women in industrialized countries, higher numbers of otherwise healthy elderly women with breast cancer are anticipated. Unfortunately, large national multi-institutional trials include only a small fraction of these older women. Furthermore, defining the “elderly population” is

problematic. Much of the literature defines “elderly” broadly, and includes women as young as 65 years of age and may even exclude women older than 80 years of age. Despite the high prevalence of breast cancer in older women, there is substantial evidence that they are less likely to receive standard care (375,376) and may have worse outcomes as a result (377,378). Ideally, age alone should not dictate the management of older women with breast cancer. Treatment should be based on a careful, individualized assessment of physiological age, estimated life expectancy, risks, benefits, treatment tolerance, patient preference, and potential treatment barriers (379). While there is currently no standard method of geriatric assessment, tools such as Adjuvant! Online (www.adjuvantonline.com) and the Comprehensive Geriatric Assessment (380) have attempted to estimate the relative benefit of treatment, taking into account both tumor biologic characteristics as well as a patient’s life expectancy.

Compared to younger women, older women are more likely to have breast cancers that are estrogen receptor (ER)- and PR+ and HER2/neu-, and well- or moderately differentiated with a low proliferation index (381,382). Despite these apparently favorable characteristics, some studies indicate that survival from breast cancer appears to be worse among older women. One recent study documented lower 5-year and 10-year relative survival among patients 70 years or older compared to patients aged 40 to 70 years, even when adjusting for disease stage (383). The determinants underlying this finding remain unclear.

Age-related differences in breast cancer survival may be related to differences in disease stage at diagnosis. Tumor size and nodal involvement have been shown to increase with age (381,384), and one analysis of SEER registry data shows older women are diagnosed with metastatic disease more frequently than younger women (385). Conversely, a recent single-institutional study of 1,267 women demonstrated older women had more early-stage cancers and a longer recurrence-free and OS (386). Analysis of 2 large Italian databases has confirmed these data (387).

Surgery

Despite earlier studies suggesting that primary medical treatment with tamoxifen was as effective as surgery for the treatment of operable breast cancer in elderly patients, more recent randomized studies have demonstrated a more favorable outcome following surgical management of these patients (388). A recent Cochrane review also concluded that primary endocrine therapy alone is inferior to surgery for local control of operable breast cancer in older women, and suggests that the option of endocrine therapy alone should be limited to those women whose competing comorbidities preclude them from proceeding to surgery or women who refuse surgery at all (389).

Standard of care for operable breast cancer includes BCS plus whole-breast radiotherapy (WBRT) or mastectomy followed by postmastectomy radiotherapy, as appropriate. Older patients tolerate surgery as well as their younger counterparts, and the operative mortality of patients who are in reasonable health with a reasonable functional status is negligible (390). Careful evaluation of significant comorbidities will identify the small group of women who would suffer significant morbidity and/or mortality from surgery. Furthermore, the widespread adoption and acceptance of axillary sentinel node biopsy has served to decrease further the risk associated with operative management of breast cancer. In fact, some have questioned whether there is any benefit of axillary evaluation in elderly women at all, particularly in the presence of endocrine-responsive disease. The International Breast Cancer Study Group compared the outcome of axillary clearance versus no

clearance in women older than 60 years (median age, 74 years) with clinically negative, operable breast cancer. All women with endocrine-responsive breast cancer received 5 years of tamoxifen. Although axillary relapse was not the primary endpoint, the results were reassuring in this subgroup, showing a relapse rate of ~2% after 5 years of follow-up. Avoiding axillary clearance was associated with an improvement in early quality of life measures (391). A nonrandomized, retrospective study of elderly patients with clinical T1N0 disease treated by surgery and adjuvant tamoxifen with or without axillary lymph node dissection (ALND) showed no difference in OS after a median follow-up of 15 years. The axillary recurrence rate, however, was 5.8% in the group with no ALND compared to 0% in the group with ALND. No data are available regarding quality of life (392).

The recent publication of the ACOSOG Z-0011 trial has called into question the routine use of completion ALND in patients with SLN-positive disease. Women with one or two positive SLNs were randomized to no ALND or ALND with removal of at least 10 nodes. All patients underwent BCS with WBRT. The trial closed prematurely prior to full recruitment. Axillary recurrence rates were 0.9% in the SLN-alone group and 0.5% in the SLN plus ALND group, with no differences in distant recurrence or OS. While some still consider a sentinel lymph node dissection (SLND) followed by a completion ALND in patients with SLN-positive disease to be both useful and the standard of care for all patients (393), the omission of a SLNB and/or completion ALND may be reasonable in some elderly patients since ALND does not appear to affect breast cancer mortality and symptomatic axillary recurrences are rare. Furthermore, particularly in patients with endocrine-responsive disease, the information gained by a sentinel node biopsy is unlikely to have a significant impact on systemic treatment recommendations.

Radiotherapy

While the role of postoperative radiotherapy in decreasing local control following BCS has been well established, recent retrospective and prospective trials have evaluated the benefit in older women. While the omission of WBRT after BCS in elderly patients remains controversial, recent data suggest clinical circumstances in which WBRT may be safely avoided, particularly as it appears that despite a benefit in terms of locoregional recurrence, there is no obvious benefit in terms of OS. The CALGB 9343 trial randomized women 70 years or older with a clinical stage 1, ER+ breast cancer to lumpectomy plus tamoxifen with or without WBRT (394). At completion of 5-year median follow-up, the locoregional recurrence was 1% among patients receiving WBRT compared to 4% for those who did not receive WBRT. No OS difference was noted. Despite a lower beneficial therapeutic margin, the subset of patients who underwent radiotherapy still had a 3% lower risk of breast recurrences. The United Kingdom START trials (317,395) and a Canadian trial (316) have shown equivalent local control for standard WBRT and a hypofractionation schedule, and included a substantial number of elderly patients. Similar results were reported in a nonrandomized series of elderly patients (396).

While there may be a group of women whose margin of therapeutic benefit for postoperative radiotherapy is small enough that radiation can be safely omitted, currently, breast irradiation following BCS remains the standard of care. The decision to forego radiation therapy must take into account the best prognostic estimates and balance carefully a patient's life expectancy with the risk of serious adverse events from radiotherapy. Current trials evaluating IORT and APBI, such as the NSABP B-39 trial, may help to define better the options of postoperative radiotherapy for elderly patients. Additional data are expected following analysis of the PRIME II trial, which is evaluating the

effect of WBRT omission following BCS and endocrine therapy in patients (≥ 65 years) with T1–2 (≤ 3 cm), node-negative disease on ipsilateral breast recurrence rates, regional recurrence rates, contralateral recurrence, distant metastases, DFS, and OS (<http://homepages.ed.ac.uk/prime/prime2.html>).

Systemic Therapy

The confirmed benefit of adjuvant hormonal therapy for endocrine-responsive breast cancers is of particular relevance of elderly patients given that ~80% older women have ER+ cancers. Despite this, serious toxicities of tamoxifen may include rare cases of endometrial cancers and an increase in thromboembolic disease. With this in mind, it is notable that patients with small (<1 cm), node-negative tumors with other serious comorbid conditions and a life expectancy of less than 10 years are unlikely to benefit significantly from endocrine manipulation (397). More recently, the Danish Breast Cancer Cooperative Group study identified a subgroup of patients who might not benefit from adjuvant systemic therapy (398). In the absence of any systemic treatment, women aged 60 to 74 years with small (<1 cm), node-negative, endocrine-response, grade 1 ductal carcinomas or grade 1 or 2 lobular carcinomas did not demonstrate any increase in mortality compared to age-matched controls. In this patient population, it seems reasonable to omit endocrine therapy altogether.

Until recently, tamoxifen was the most commonly used hormonal treatment for ER+ breast cancers. However, data from the ATAC trial confirmed a DFS advantage for anastrozole over tamoxifen and a longer time to recurrence (399). In addition, anastrozole was associated with fewer thromboembolic and ischemic cerebrovascular events, and less endometrial cancer and vaginal bleeding, but a greater incidence of bone loss. Two analyses specifically reported on the outcomes following treatment with aromatase inhibitors among older women. The MA.17 trial evaluated the additional advantage of extended letrozole after 5 years of tamoxifen and demonstrated no additional benefit among women older than 60 years. The Breast International Group (BIG) I-98 trial compared letrozole with tamoxifen and showed a significant benefit in favor of letrozole (264). The study confirmed a higher incidence of bone loss and fractures. Thus in regards to elderly women who are at increased risk of osteoporosis and bone fractures, the long-term risks of aromatase inhibitors may be significant and must be taken into account when recommending adjuvant endocrine therapy.

Despite an overall favorable biologic profile in breast cancer in the elderly, a significant number of women have a substantial risk of recurrence and should be considered candidates for chemotherapy. Approximately 20% of elderly women evaluated in the SEER registry are diagnosed with node-positive cancers, and 10% to 25% have other poor prognostic features (397). Retrospective analyses of the SEER database have reported a statistically significant reduction in all-cause mortality of 15% to 28% among elderly women with ER- cancers treated with chemotherapy, particularly node-positive patients (400,401). Most experts suggest limiting chemotherapy to elderly women with HR- tumors that are considered high risk and whose life expectancy exceeds 5 years. Few women with node-negative, HR+ breast cancers are likely to benefit from chemotherapy. Newer gene-based risk assessment tools may help to distinguish those women with node-negative tumors whose risk is sufficiently high enough to warrant chemotherapy.

The optimal chemotherapy regimen, dose, and schedule for elderly patients remain undefined. CMF has been studied in this population and is reasonable, but it may be tolerated poorly and anthracycline-related toxicity may be an issue for elderly patients (379). In a retrospective observational study, docetaxel and cyclophosphamide treatment was determined to be feasible

(402). This regimen was shown to be superior to doxorubicin and cyclophosphamide in terms of DFS and OS (216). When combined with chemotherapy, trastuzumab has been shown to significantly improve the chances of cure among women with *HER2/neu* overexpressing tumors. As the number of long-term survivors of breast cancer increases, it remains important to identify and minimize the late effects of treatments. Cardiac toxicity is a significant side effect of trastuzumab and may be compounded by the joint use of anthracycline-based chemotherapy. Recent studies evaluating newer nonanthracycline regimens may change standard regimens, and incorporating these regimens with biologic agents such as trastuzumab may lead to improvements in survival while decreasing the cardiac toxicity associated with combined anthracycline and trastuzumab therapy. Currently, there are no data available for treatment with trastuzumab alone in patients who are poor candidates for chemotherapy, although the 2011 St. Gallen consensus states that if chemotherapy cannot be given, it may be reasonable to give trastuzumab alone (403).

Despite competing comorbidities, breast cancer is the direct cause of death for a substantial number of older patients, and up to 40% of women age 80 years or older at diagnosis die as a direct result of their breast cancer (383). Approximately 30% of older patients present with an aggressive biologic phenotype characterized by negative ER/PR expression. To what extent undertreatment of these patients based on an underestimation of life expectancy and treatment-related efficacy is the cause remains unclear. Surgical management of these patients is typically the same as in younger patients. While the absolute benefit of adjuvant radiotherapy may be limited, the current data demonstrate similar relative benefits to adjuvant radiotherapy, in the absence of endocrine-responsive disease; the option of chemotherapy needs to be discussed with the patient. The decision to forego or proceed with radiotherapy and/or chemotherapy must take into account both the tumor characteristics and the ensuing risk of relapse, as well as the patient's overall functional status and competing comorbidities. Extrapolation from earlier trials regarding the potential benefits or toxicity of chemotherapy is complicated by the small number of elderly patients accrued to these trials. Furthermore, in earlier trials that included elderly patients, inherent biases resulted in the recruitment of very "fit," or healthy, patients. Thus how these data may relate to patients who are less fit is unclear.

Disparities in Breast Cancer

Despite significant advances in the diagnosis and treatment of breast cancer, which have resulted in continued improvements in survival rates and overall outcomes, there exists a vast body of literature highlighting disparities in the mortality burden among population subsets. While the incidence rates for breast cancer in African-American (AA) women are lower than Whites (113 vs. 123.5 per 100,000), mortality rates are disproportionately higher among AA women (33 deaths vs. 23.9 per 100,000 cases) (404). Similar patterns have emerged among the Latina population, where breast cancer is now the leading cause of cancer death.

A variety of factors have been proposed to explain this difference in breast cancer outcome, including variations in access and adequacy of medical care, differences in breast cancer risk factors, and differences in genetics and biology. In fact, health insurance coverage and socioeconomic status is an important factor in determining health care outcomes in general, but it does not appear to be the only explanation for ethnicity-related outcome disparities with regards to breast cancer. Newman et al. conducted a meta-analysis of studies reporting on survival of AA versus White breast-cancer patients (405). After adjusting

for socioeconomic status, age, and stage of diagnosis, they found that AA women still experienced a higher risk of mortality, with a mortality hazard ratio of 1.27 (95% CI, 1.18–1.38). Similarly, Field et al. evaluated survival among AA and White breast-cancer patients receiving care through the Cancer Research Network, which covers patients using managed care health plans (406). Despite similar health coverage and access to care, 5-year survival was lower for AA women (74% vs. 82%). They concluded that among women with invasive breast cancer, being insured and having access to medical care does not eliminate the survival disparity for AA women. Therefore, it appears that inequalities in access to health care, while a reality for many AA women in the United States and likely partially accounting for differences in outcomes, are not solely responsible for the racial disparities evident among women diagnosed with breast cancer.

Another argument is that differences in tumor biology or other extrinsic factors account for a significant proportion of the disparity evidenced among different racial/ethnic groups (407). Invasive ductal carcinoma remains the most common histologic type of breast cancer identified, regardless of ethnicity. However, reports suggest a higher frequency of aggressive subtypes among AA women, such as basaloid and IBC (342,408,409). In a population-based study of the California Cancer Registry, Bauer et al. demonstrated that the greatest risk factor for a triple-negative subtype was age younger than 40, Black race, and, to a lesser extent, Hispanic race (66). Elledge et al. identified no significant differences in the frequency of HER2+ breast cancers among different racial groups (407). A study comparing a group of Hispanic women to White women reported that Hispanic women presented more often with larger, triple-negative cancers at a younger age, despite equal access to health care (410). Others have demonstrated similar findings (411,412).

Studies evaluating the incidence of *BRCA1* and *BRCA2* mutations in the Hispanic population have been reported, and among non-White minorities, Hispanics with breast cancer have the highest reported incidence of pathogenic *BRCA1* mutations (413). Recently, Weitzel et al. reported on a large deletion identified in 5 unrelated Mexican families (414). A large multiplex panel that tests for 18 mutations in *BRCA1/BRCA2* is currently being developed for testing in Hispanic patients (415). For their part, the frequency of *BRCA1/BRCA2* mutations among AAs appears to be lower than that observed among White women, Ashkenazi Jewish individuals, and Hispanic women (413,415).

Disparities in the delivery of adjuvant chemotherapy to eligible patients may account for disparities among AAs, and studies do show a disturbing trend. White et al. (416) reported in 2003 that among 1,263 patients with node-positive breast cancer eligible for chemotherapy, 85.3% of White women received the indicated treatment, compared to 78.7% of AA and Latina patients. More recently, Bickell et al. (416,417) reported data from 6 New York City hospitals and found that AAs were twice as likely to be undertreated with regards to either chemotherapy, radiation therapy, and/or endocrine therapy compared with White patients. Others have reported similar findings (418).

Disparities also appear to exist in surgical management of breast cancer. In their review of the SEER database (417,419), AA breast cancer patients were 36% less likely to receive sentinel node biopsy compared with White breast-cancer patients. This is similar to that which was reported by Bickell et al. Several groups have reported lower rates of breast reconstruction following mastectomy (419,420). In their analysis, Tseng et al. not only noted a lower pattern of referral for breast reconstruction, but they also reported lower rates of reconstruction being offered if indeed a consultation took place. The extent to which these decisions reflect patient preferences is unknown.

Despite this, most studies comparing BCS between AA and White women have shown equal rates of BCS. Similar studies are unavailable in Hispanic women. There are concerning data, however, regarding inadequate margin control in lumpectomy specimens, failure to receive postoperative radiation therapy, and inequalities in axillary staging procedures (421).

Effective evaluation of the determinants of racial disparities in breast cancer treatment will require adequate participation in randomized clinical trials. Currently, the percentage of AAs, Latinas, and other ethnic groups in multicentered trials is low. In their study, Simon et al. demonstrated that only 21% of AA patients were offered a clinical trial, compared to 42% of the White patients. That study did not control for trial eligibility. In their study evaluating barriers to enrollment of minorities onto clinical trials, Adams-Campbell et al. reported that among 235 AA patients with breast cancer, only 8.5% were eligible for trial participation. Most of these women were excluded due to comorbid disease.

There is one underlying assumption that is made as we strive to eliminate racial disparities in breast cancer treatment outcomes. That is, that equal treatments will yield equal results. Recent retrospective analysis of data from the NSABP trials seems to support this belief (422,423). A recent study from MDACC further supported this contention (424). Similar responses to neoadjuvant therapy were reported when comparing AA women to White women. Data from analysis of SWOG trials, on the other hand, showed that despite similar treatment with adjuvant therapy, AA women with node-positive breast cancer had higher mortality compared with White women, even when controlled for differences in socioeconomic status and ER status (425). A similar evaluation of Cancer and Leukemia group B (CALG-B) data showed a worse outcome on univariate analysis, but this did not persist on multivariate analysis (426), emphasizing the need for greater representation of different ethnicities in large, cooperative trials in order to address better the question of a differential response to treatment.

Documented racial disparities exist in the incidence, treatment, and outcomes of women with breast cancer. Of great concern, the mortality among AA and Latina women diagnosed with breast cancer exceeds that of White women, despite an overall lower incidence of disease overall. The determinants of these disparities are likely multifactorial, and despite numerous studies, they remain incompletely understood. Increasingly, studies point to a combination of variable access to care, resulting in more advanced stages at diagnosis, differing risk factors to breast cancer, and differences in genetics, biology, and treatment.

Summary

The field of breast oncology has evolved significantly, with gains made in prevention, screening, diagnosis, and management. All of these have led to a reduction in the mortality rate from breast cancer, with a resultant increase in the population who are considered breast cancer survivors. Despite this, multiple questions remain: how should new radiologic technologies, such as tomosynthesis, be incorporated into routine screening practice? Should breast MRI utilization be expanded to all women with a new diagnosis of breast cancer? How can we maximize the use of neoadjuvant chemotherapy in women with invasive disease? How should we treat patients who have persistent disease following primary chemotherapy? Is partial breast radiation as safe as whole breast radiation? These are only a few of the issues that oncology will need to address as we look forward into the future.

There is no one standard of care in the management of the patient with breast cancer. The indications for the use of

chemotherapy continue to evolve as evidence mounts that women with breast cancer cannot be considered one in the same. HR status can predict who will benefit from endocrine therapy, and appears to also predict who has little to gain from chemotherapy. Our current understanding of the treatment landscape in breast cancer has reinforced one point: that treatment must be individualized, especially since multiple options are considered reasonable. The evolution of breast cancer management will undoubtedly continue as researchers seek to define more targets for treatment and refine the appropriate therapies for the patient with breast cancer, tailored to hormone and HER2/neu status. Utilization of new technologies for treatment and follow-up will be better characterized, such as the use of APBI or the use of circulating tumor cells. Hopefully, we will continue to improve the outcomes for our patients with breast cancer, and increase the chances more women will be cured.

KEY POINTS

1. Technological advances have improved our ability to classify breast cancers, going from histopathologic characterization of a tumor into the genomic signature that the tumor carries. Luminal, basaloid, and HER-2 overamplified breast cancers are a part of this new classification, which may yet help determine the best way to individualize treatments.
2. The mammogram remains the key screening test for women. Ultrasound is useful in distinguishing a benign versus malignant lesion or in the evaluation of a non-mammographically apparent mass. Breast MRI is indicated in selected populations as a screening tool and as an adjunct to mammography for treatment planning purposes.
3. Mastectomy and breastconservation surgeries achieve equivalent outcomes, the latter of which is possible with the use of adjuvant radiation therapy. Sentinel node biopsy is the standard of care in the surgical management of the new patient with breast cancer, with a clinically negative axillary examination. Completion axillary dissection in those patients with a positive sentinel node remains standard of care, though considerable controversy exists as to whether this standard must be applied uniformly.
4. The adjuvant treatment of breast cancer must be individualized. While chemotherapy plays an important role in the adjuvant setting, we are recognizing the variable response and benefits that can be achieved, particularly in those women who are ER+ and even in those women who are HER2/neu-. Patients with high-risk node-negative (1 cm or more if ER-, 2 cm or more if ER+ or node-positive breast cancer who are HER2/neu+, warrant treatment with an anthracycline, taxane treatment and adjuvant trastuzumab therapy.
5. Endocrine therapy remains the most potent agents for women with ER+ breast cancer.
6. Radiotherapy achieves a reduction in local recurrence when used as an adjuvant modality. This becomes important as evidence indicates that local recurrence is a predictor of mortality from breast cancer.

The treatment of breast cancer calls for a coordinated multimodality approach that ensures all aspects of the disease are being expeditiously and appropriately addressed.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures* 2012. Atlanta, GA: American Cancer Society, Inc.; 2012.
2. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *J Am Med Assoc*. 2003;289(24):3243–3253.
3. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *J Am Med Assoc*. 2006;295(14):1647–1657.
4. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med*. 2002;346(26):2025–2032.
5. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer*. 1994;73(3):643–651.
6. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879–1886.
7. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*. 1994;266(5182):66–71.
8. Wooster R, Swensen J, Shattuck-Eidens D, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12–13. *Science*. 1994;265(5181):2088–2090.
9. Tokunaga M, Land CE, Yamamoto T, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1980. *Radiat Res*. 1987;112(2):243–272.
10. Aisenberg AC, Finkelstein DM, Doppke KP, et al. High risk of breast carcinoma after irradiation of young women with Hodgkin's disease. *Cancer*. 1997;79(6):1203–1210.
11. Michels KB, Mohllajee AP, Roset-Bahmanyar E, et al. Diet and breast cancer: a review of the prospective observational studies. *Cancer*. 2007;109(suppl. 12):2712–2749.
12. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med*. 2005;353(3):229–237.
13. Worsham MJ, Abrams J, Raju U, et al. Breast cancer incidence in a cohort of women with benign breast disease from a multiethnic, primary health care population. *Breast J*. 2007;13(2):115–121.
14. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356(3):227–236.
15. Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. *J Natl Cancer Inst*. 1975;55(2):231–273.
16. Faverly DR, Burgers L, Bult P, et al. Three dimensional imaging of mammary ductal carcinoma *in situ*: clinical implications. *Semin Diagn Pathol*. 1994;11(3):193–198.
17. Gaffney DK, Tsodikov A, Wiggins CL. Diminished survival in patients with inner versus outer quadrant breast cancers. *J Clin Oncol*. 2003;21(3):467–472.
18. Tulinius H, Sigvaldason H, Olafsdottir G. Left and right sided breast cancer. *Pathol Res Pract*. 1990;186(1):92–94.
19. Lee YT. Breast carcinoma: pattern of metastasis at autopsy. *J Surg Oncol*. 1983;23(3):175–180.
20. Valagussa P, Bonadonna G, Veronesi U. Patterns of relapse and survival following radical mastectomy. Analysis of 716 consecutive patients. *Cancer*. 1978;41(3):1170–1178.
21. Fisher B. Laboratory and clinical research in breast cancer—a personal adventure: the David A. Karnofsky memorial lecture. *Cancer Res*. 1980;40(11):3863–3874.
22. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2000;355(9217):1757–1770.
23. Hellman S. Karnofsky Memorial Lecture. Natural history of small breast cancers. *J Clin Oncol*. 1994;12(10):2229–2234.
24. Perry S. Recommendations of the consensus development panel on breast cancer screening. *Cancer Res*. 1978;38(2):476–477.
25. Santen RJ, Mansel R. Benign breast disorders. *N Engl J Med*. 2005;353(3):275–285.
26. Schnitt SJ, Connolly JL, Tavassoli FA, et al. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. *Am J Surg Pathol*. 1992;16(12):1133–1143.
27. Margenthaler JA, Duke D, Monsees BS, et al. Correlation between core biopsy and excisional biopsy in breast high-risk lesions. *Am J Surg*. 2006;192(4):534–537.
28. Fraser JL, Raza S, Chorny K, et al. Columnar alteration with prominent apical snouts and secretions: a spectrum of changes frequently present in breast biopsies performed for microcalcifications. *Am J Surg Pathol*. 1998;22(12):1521–1527.
29. Collins LC, Achacoso NA, Nekhyudov L, et al. Clinical and pathologic features of ductal carcinoma *in situ* associated with the presence of flat epithelial atypia: an analysis of 543 patients. *Mod Pathol*. 2007;20(11):1149–1155.
30. Fernandez-Aguilar S, Simon P, Buxant F, et al. Tubular carcinoma of the breast and associated intra-epithelial lesions: a comparative study with invasive low-grade ductal carcinomas. *Virchows Arch*. 2005;447(4):683–687.
31. Wells WA, Carney PA, Eliassen MS, et al. Pathologists' agreement with experts and reproducibility of breast ductal carcinoma-in-situ classification schemes. *Am J Surg Pathol*. 2000;24(5):651–659.
32. Schackmuth EM, Harlow CL, Norton LW. Milk fistula: a complication after core breast biopsy. *AJR Am J Roentgenol*. 1993;161(5):961–962.
33. Silverstein MJ, Poller DN, Waisman JR, et al. Prognostic classification of breast ductal carcinoma-in-situ. *Lancet*. 1995;345(8958):1154–1157.
34. de Mascarel I, MacGrogan G, Mathoulin-Pélissier S, et al. Breast ductal carcinoma *in situ* with microinvasion: a definition supported by a long-term study of 1248 serially sectioned ductal carcinomas. *Cancer*. 2002;94(8):2134–2142.
35. Douglas-Jones AG, Logan J, Morgan JM, et al. Effect of margins of excision on recurrence after local excision of ductal carcinoma *in situ* of the breast. *J Clin Pathol*. 2002;55(8):581–586.
36. Neuschatz AC, DiPetrillo T, Steinhoff M, et al. The value of breast lumpectomy margin assessment as a predictor of residual tumor burden in ductal carcinoma *in situ* of the breast. *Cancer*. 2002;94(7):1917–1924.
37. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma *in situ* of the breast. *N Engl J Med*. 1999;340(19):1455–1461.
38. Deutsch M, Land SR, Begovic M, et al. The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy. Results of National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials B-04 and B-06. *Cancer*. 2003;98(7):1362–1368.
39. Arpino G, Allred DC, Mohsin SK, et al. Lobular neoplasia on core-needle biopsy—clinical significance. *Cancer*. 2004;101(2):242–250.
40. Elsheikh TM, Silverman JF. Follow-up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma *in situ*: a correlative study of 33 patients with review of the literature. *Am J Surg Pathol*. 2005;29(4):534–543.
41. Sullivan ME, Khan SA, Sullu Y, et al. Lobular carcinoma *in situ* variants in breast cores: potential for misdiagnosis, upgrade rates at surgical excision, and practical implications. *Arch Pathol Lab Med*. 2010;134(7):1024–1028.
42. O'Malley FP. Lobular neoplasia: morphology, biological potential and management in core biopsies. *Mod Pathol*. 2010;23(suppl. 2):S14–S25.
43. Elston CW, Ellis IO. Pathology and breast screening. *Histopathology*. 1990;16(2):109–118.
44. Bane AL, Tjan S, Parkes RK, et al. Invasive lobular carcinoma: to grade or not to grade. *Mod Pathol*. 2005;18(5):621–628.
45. Diab SG, Clark GM, Osborne CK, et al. Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas. *J Clin Oncol*. 1999;17(5):1442–1448.
46. Goldstein NS, Kestin LL, Vicini FA. Refined morphologic criteria for tubular carcinoma to retain its favorable outcome status in contemporary breast carcinoma patients. *Am J Clin Pathol*. 2004;122(5):728–739.
47. Walsh MM, Bleiweiss JJ. Invasive micropapillary carcinoma of the breast: eighty cases of an underrecognized entity. *Hum Pathol*. 2001;32(6):583–589.
48. Pettinato G, Manivel CJ, Panico L, et al. Invasive micropapillary carcinoma of the breast: clinicopathologic study of 62 cases of a poorly recognized variant with highly aggressive behavior. *Am J Clin Pathol*. 2004;121(6):857–866.
49. Collins LC, Carlo VP, Hwang H, et al. Intracystic papillary carcinomas of the breast: a reevaluation using a panel of myoepithelial cell markers. *Am J Surg Pathol*. 2006;30(8):1002–1007.
50. Solorzano CC, Middleton LP, Hunt KK, et al. Treatment and outcome of patients with intracystic papillary carcinoma of the breast. *Am J Surg*. 2002;184(4):364–368.
51. Moatamed NA, Apple SK. Extensive sampling changes T-staging of infiltrating lobular carcinoma of breast: a comparative study of gross versus microscopic tumor sizes. *Breast J*. 2006;12(6):511–517.
52. Daling JR, Malone KE, Doody DR, et al. Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. *Cancer*. 2002;95(12):2455–2464.
53. Tse GM, Tan PH, Putti TC, et al. Metaplastic carcinoma of the breast: a clinicopathological review. *J Clin Pathol*. 2006;59(10):1079–1083.
54. Chaney AW, Pollack A, McNeese MD, et al. Primary treatment of cystosarcoma phylloides of the breast. *Cancer*. 2000;89(7):1502–1511.
55. Telli ML, Horst KC, Guardino AE, et al. Phylloides tumors of the breast: natural history, diagnosis, and treatment. *J Natl Compr Canc Netw*. 2007;5(3):324–330.

56. Sher T, Hennessy BT, Valero V, et al. Primary angiosarcomas of the breast. *Cancer*. 2007;110(1):173–178.
57. Vorburger SA, Xing Y, Hunt KK, et al. Angiosarcoma of the breast. *Cancer*. 2005;104(12):2682–2688.
58. Allred DC. The utility of conventional and molecular pathology in managing breast cancer. *Breast Cancer Res*. 2008;10(suppl. 4):S4.
59. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med*. 2010;134(7):e48–e72.
60. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–792.
61. Emens LA. Trastuzumab: targeted therapy for the management of HER-2/neu-overexpressing metastatic breast cancer. *Am J Ther*. 2005;12(3):243–253.
62. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007;25(1):118–145.
63. Livasy CA, Karaca G, Nanda R, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. *Mod Pathol*. 2006;19(2):264–271.
64. Rakha EA, El-Sayed ME, Green AR, et al. Prognostic markers in triple-negative breast cancer. *Cancer*. 2007;109(1):25–32.
65. Fulford LG, Easton DF, Reis-Filho JS, et al. Specific morphological features predictive for the basal phenotype in grade 3 invasive ductal carcinoma of breast. *Histopathology*. 2006;49(1):22–34.
66. Bauer KR, Brown M, Cress RD, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. *Cancer*. 2007;109(9):1721–1728.
67. Lakhani SR, Reis-Filho JS, Fulford L, et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. *Clin Cancer Res*. 2005;11(14):5175–5180.
68. Daidone MG, Silvestrini R. Prognostic and predictive role of proliferation indices in adjuvant therapy of breast cancer. *J Natl Cancer Inst Monogr*. 2001;30(3):27–35.
69. Dowsett M, Nielsen TO, A'hern R, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst*. 2011;103(22):1656–1664.
70. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351(27):2817–2826.
71. Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification, prognostication, and prediction. *Lancet*. 2011;378(9805):1812–1823.
72. Weigelt B, Horlings HM, Kreike B, et al. Refinement of breast cancer classification by molecular characterization of histological special types. *J Pathol*. 2008;216(2):141–150.
73. Halsted WS. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Johns Hopkins Hosp Rep*. 1894;4:297.
74. Meyer W. An improved method of the radical operation for carcinoma of the breast. *Med Rec*. 1894;46:746.
75. Halsted WS. The results of radical operations for the cure of carcinoma of the breast. *Ann Surg*. 1907;46:1.
76. Urban JA. Radical excision of the chest wall for mammary cancer. *Cancer*. 1951;4(6):1263–1285.
77. Halsted WS. Parasternal invasion of the thorax in breast cancer and its suppression by the use of radium tubes as an operative precaution. *Surg Gynecol Obstet*. 1927;45:721–782.
78. McWhirter R. The value of simple mastectomy and radiotherapy in the treatment of cancer of the breast. *Br J Radiol*. 1948;21:599.
79. Patey DH, Dyson WH. The prognosis of carcinoma of the breast in relation to the type of operation performed. *Br J Cancer*. 1948;2:7–13.
80. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233–1241.
81. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227–1232.
82. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr*. 1992;11:19–25.
83. Arriagada R, Le MG, Rochard F, et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol*. 1996;14(5):1558–1564.
84. Poggi MM, Danforth DN, Sciuto LC, et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. *Cancer*. 2003;98(4):697–702.
85. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst*. 2000;92(14):1143–1150.
86. Veronesi U, Zurrada S. Optimal surgical treatment of breast cancer. *Oncologist*. 1996;1:340–346.
87. Fisher B, Land S, Mamounas E, et al. Prevention of invasive breast cancer in women with ductal carcinoma *in situ*: an update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol*. 2001;28:400–418.
88. Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol*. 2007;8(10):881–888.
89. Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma *in situ*: a meta-analysis. *Cancer*. 1999;85(3):616–628.
90. Silverstein MJ, Lagios MD, Craig PH, et al. A prognostic index for ductal carcinoma *in situ* of the breast. *Cancer*. 1996;77(11):2267–2274.
91. Wong JS, Kaelin CM, Troyan SL, et al. Prospective study of wide excision alone for ductal carcinoma *in situ* of the breast. *J Clin Oncol*. 2006;24:1031–1036.
92. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma *in situ*: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet*. 2000;355(9203):528–533.
93. Patani N, Cutuli B, Mokbel K. Current management of DCIS: a review. *Breast Cancer Res Treat*. 2008;111(1):1–10.
94. Wilkie C, White L, Dupont E, et al. An update of sentinel lymph node mapping in patients with ductal carcinoma *in situ*. *Am J Surg*. 2005;190(4):563–566.
95. Yen TW, Hunt KK, Ross MI, et al. Predictors of invasive breast cancer in patients with an initial diagnosis of ductal carcinoma *in situ*: a guide to selective use of sentinel lymph node biopsy in management of ductal carcinoma *in situ*. *J Am Coll Surg*. 2005;200(4):516–526.
96. Klauber-DeMore N, Tan LK, Liberman L, et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? *Ann Surg Oncol*. 2000;7(9):636–642.
97. Gutierrez RL, DeMartini WB, Silbergeld JJ, et al. High cancer yield and positive predictive value: outcomes at a center routinely using preoperative breast MRI for staging. *AJR Am J Roentgenol*. 2011;196(1):W93–W99.
98. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet*. 2010;375(9714):563–571.
99. Haid A, Knauer M, Dunzinger S, et al. Intra-operative Sonography: a valuable aid during breast-conserving surgery for occult breast cancer. *Ann Surg Oncol*. 2007;14(11):3090–3101.
100. Duarte GM, Cabello C, Torresan RZ, et al. Radioguided Intraoperative Margins Evaluation (RIME): preliminary results of a new technique to aid breast cancer resection. *Eur J Surg Oncol*. 2007;33:1150–1157.
101. Morrow M. Breast conservation and negative margins: how much is enough? *Breast*. 2009;18(suppl. 3):S84–S86.
102. Singletary SE. Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg*. 2002;184(5):383–393.
103. Neuschatz AC, DiPetrillo T, Safaii H, et al. Long-term follow-up of a prospective policy of margin-directed radiation dose escalation in breast-conserving therapy. *Cancer*. 2003;97(1):30–39.
104. Chia S, Bryce C, Gelmon K. The 2000 EBCTCG overview: a widening gap. *Lancet*. 2005;365(9472):1665–1666.
105. Klimberg VS, Kepple J, Shafirstein G, et al. eRFA: excision followed by RFA—a new technique to improve local control in breast cancer. *Ann Surg Oncol*. 2006;13(11):1422–1433.
106. Allweis TM, Kaufman Z, Lelcuk S, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. *Am J Surg*. 2008;196(4):483–489.
107. Oruwari JU, Chung MA, Koelliker S, et al. Axillary staging using ultrasound-guided fine needle aspiration biopsy in locally advanced breast cancer. *Am J Surg*. 2002;184(4):307–309.
108. Lee MC, Newman LA. Management of patients with locally advanced breast cancer. *Surg Clin North Am*. 2007;87(2):379–398.
109. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional

- disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol*. 1997;15(7):2483–2493.
110. Mansour EG, Gray R, Shatila AH, et al. Survival advantage of adjuvant chemotherapy in high-risk node-negative breast cancer: ten-year analysis—an intergroup study. *J Clin Oncol*. 1998;16:3486–3492.
 111. Khan A, Sabel MS, Nees A, et al. Comprehensive axillary evaluation in neoadjuvant chemotherapy patients with ultrasonography and sentinel lymph node biopsy. *Ann Surg Oncol*. 2005;12:697–704.
 112. Kuerer HM, Sahin AA, Hunt KK, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. *Ann Surg*. 1999;230(1):72–78.
 113. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796–1804.
 114. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype—ACOSOG Z1031. *J Clin Oncol*. 2011;29(17):2342–2349.
 115. Davies GC, Millis RR, Hayward JL. Assessment of axillary lymph node status. *Ann Surg*. 1980;192(2):148–151.
 116. Petrek JA, Blackwood MM. Axillary dissection: current practice and technique. *Curr Probl Surg*. 1995;32(4):257–323.
 117. Vlastos G, Fornage BD, Mirza NQ, et al. The correlation of axillary ultrasonography with histologic breast cancer downstaging after induction chemotherapy. *Am J Surg*. 2000;179(6):446–452.
 118. Bonnema J, van Geel AN, van Ooijen B, et al. Ultrasound-guided aspiration biopsy for detection of nonpalpable axillary node metastases in breast cancer patients: new diagnostic method. *World J Surg*. 1997;21(3):270–274.
 119. Somasundar P, Gass J, Steinhoff M, et al. Role of ultrasound-guided axillary fine-needle aspiration in the management of invasive breast cancer. *Am J Surg*. 2006;192(4):458–461.
 120. Krishnamurthy S, Sneige N, Bedi DG, et al. Role of ultrasound-guided fine-needle aspiration of indeterminate and suspicious axillary lymph nodes in the initial staging of breast carcinoma. *Cancer*. 2002;95(5):982–988.
 121. van Rijk MC, Deurloo EE, Nieweg OE, et al. Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. *Ann Surg Oncol*. 2006;13(1):31–35.
 122. Chagpar AB, Scoggins CR, Martin RC 2nd, et al. Prediction of sentinel lymph node-only disease in women with invasive breast cancer. *Am J Surg*. 2006;192(6):882–887.
 123. Newman LA, Sabel MS, Nees AV, et al. Sentinel lymph node biopsy performed after neoadjuvant chemotherapy is accurate in patients with documented node-positive breast cancer at presentation. *Ann Surg Oncol*. 2007;14(10):2946–2952.
 124. Samant R, Ganguly P. Staging investigations in patients with breast cancer: the role of bone scans and liver imaging. *Arch Surg*. 1999;134(5):551–553.
 125. Newman LA, Buzdar AU, Singletary SE, et al. A prospective trial of preoperative chemotherapy in resectable breast cancer: predictors of breast-conservation therapy feasibility. *Ann Surg Oncol*. 2002;9(3):228–234.
 126. Helvie MA, Joynt LK, Cody RL, et al. Locally advanced breast carcinoma: accuracy of mammography versus clinical examination in the prediction of residual disease after chemotherapy. *Radiology*. 1996;198(2):327–332.
 127. Delille JP, Slanetz PJ, Yeh ED, et al. Invasive ductal breast carcinoma response to neoadjuvant chemotherapy: noninvasive monitoring with functional MR imaging pilot study. *Radiology*. 2003;228(1):63–69.
 128. Chagpar AB, Middleton LP, Sahin AA, et al. Accuracy of physical examination, ultrasonography, and mammography in predicting residual pathologic tumor size in patients treated with neoadjuvant chemotherapy. *Ann Surg*. 2006;243(2):257–264.
 129. Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma *in situ* in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. *J Clin Oncol*. 2007;25(19):2650–2655.
 130. Chung CS, Harris JR. Post-mastectomy radiation therapy: translating local benefits into improved survival. *Breast*. 2007;16(suppl. 2):S78–S83.
 131. Fisher B, Jeong JH, Anderson S, et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347(8):567–575.
 132. Johansen H, Kaae S, Schiødt T. Simple mastectomy with postoperative irradiation versus extended radical mastectomy in breast cancer. A twenty-five-year follow-up of a randomized trial. *Acta Oncol*. 1990;29(6):709–715.
 133. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305(6):569–575.
 134. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg*. 2010;252(3):426–432; discussion 432–433.
 135. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. *Cancer*. 1998;83(12 Suppl American):2776–2781.
 136. Petrek JA, Senie RT, Peters M, et al. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer*. 2001;92(6):1368–1377.
 137. Nos C, Kaufmann G, Clough KB, et al. Combined axillary reverse mapping (ARM) technique for breast cancer patients requiring axillary dissection. *Ann Surg Oncol*. 2008;15(9):2550–2555.
 138. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer*. 2006;106(1):4–16.
 139. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127(4):392–399.
 140. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg*. 1994;220(3):391–398.
 141. Chagpar AB, Martin RC, Scoggins CR, et al. Factors predicting failure to identify a sentinel lymph node in breast cancer. *Surgery*. 2005;138(1):56–63.
 142. Tuttle TM. Technical advances in sentinel lymph node biopsy for breast cancer. *Am Surg*. 2004;70(5):407–413.
 143. Ting AC, Kumarasingam B, Szeto ER. Successful internal mammary visualization with periareolar injections of Tc-99m antimony sulfur colloid in sentinel node breast lymphoscintigraphy. *Clin Nucl Med*. 2006;31(10):593–597.
 144. Bezu C, Coutant C, Salengro A, et al. Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surg Oncol*. 2011;20(1):e55–e59.
 145. Clough KB, Nasr R, Nos C, et al. New anatomical classification of the axilla with implications for sentinel node biopsy. *Br J Surg*. 2010;97(11):1659–1665.
 146. van der Ploeg IM, Tanis PJ, Valdés Olmos RA, et al. Breast cancer patients with extra-axillary sentinel nodes only may be spared axillary lymph node dissection. *Ann Surg Oncol*. 2008;15(11):3239–3243.
 147. Krag DN, Weaver DL, Alex JC, et al. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol*. 1993;2(6):335–339; discussion 340.
 148. Van Diest PJ, Torrens H, Borgstein PJ, et al. Reliability of intraoperative frozen section and imprint cytological investigation of sentinel lymph nodes in breast cancer. *Histopathology*. 1999;35(1):14–18.
 149. Naik AM, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. *Ann Surg*. 2004;240(3):462–468; discussion 468–471.
 150. Park J, Fey JV, Naik AM, et al. A declining rate of completion axillary dissection in sentinel lymph node-positive breast cancer patients is associated with the use of a multivariate nomogram. *Ann Surg*. 2007;245(3):462–468.
 151. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol*. 2003;10(10):1140–1151.
 152. Pyszel A, Malyszczak K, Pyszel K, et al. Disability, psychological distress and quality of life in breast cancer survivors with arm lymphedema. *Lymphology*. 2006;39(4):185–192.
 153. Boneti C, Korourian S, Bland K, et al. Axillary reverse mapping: mapping and preserving arm lymphatics may be important in preventing lymphedema during sentinel lymph node biopsy. *J Am Coll Surg*. 2008;206(5):1038–1042; discussion 1042–1044.
 154. Noone RB, Frazier TG, Noone GC, et al. Recurrence of breast carcinoma following immediate reconstruction: a 13-year review. *Plast Reconstr Surg*. 1994;93(1):96–106; discussion 107–108.
 155. Simmons RM, Fish SK, Gayle L, et al. Local and distant recurrence rates in skin-sparing mastectomies compared with non-skin-sparing mastectomies. *Ann Surg Oncol*. 1999;6(7):676–681.
 156. Foster RD, Esserman LJ, Anthony JP, et al. Skin-sparing mastectomy and immediate breast reconstruction: a prospective cohort study for the treatment of advanced stages of breast carcinoma. *Ann Surg Oncol*. 2002;9(5):462–466.
 157. Vaughan A, Dietz JR, Aft R, et al. Scientific Presentation Award. Patterns of local breast cancer recurrence after skin-sparing mastectomy and

- immediate breast reconstruction. *Am J Surg.* 2007;194(4):438–443.
158. Simmons RM, Brennan M, Christos P, et al. Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved? *Ann Surg Oncol.* 2002;9(2):165–168.
 159. Sacchini V, Pinotti JA, Barros AC, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg.* 2006;203(5):704–714.
 160. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol.* 2008;34(2):143–148.
 161. Lanitis S, Tekkis PP, Sgourakis G, et al. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. *Ann Surg.* 2010;251(4):632–639.
 162. Peled AW, Foster RD, Stover AC, et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. *Ann Surg Oncol.* 2012.
 163. Clough KB, Kaufman GJ, Nos C, et al. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. *Ann Surg Oncol.* 2010;17(5):1375–1391.
 164. Petit JY, Veronesi U, Orecchia R, et al. Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): a new type of mastectomy for breast cancer treatment. *Breast Cancer Res Treat.* 2006;96(1):47–51.
 165. Chen CY, Calhoun KE, Masetti R, et al. Oncoplastic breast conserving surgery: a renaissance of anatomically-based surgical technique. *Minerva Chir.* 2006;61(5):421–434.
 166. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med.* 2007;131(1):18–43.
 167. Hugh J, Hanson J, Cheang MC, et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial. *J Clin Oncol.* 2009;27(8):1168–1176.
 168. Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med.* 2007;357(15):1496–1506.
 169. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol.* 2011;29(25):3366–3373.
 170. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol.* 2011;12(3):236–244.
 171. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011;365(14):1273–1283.
 172. Perez EA, Suman VJ, Davidson NE, et al. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 2011;29(34):4491–4497.
 173. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol.* 2009;27(34):5685–5692.
 174. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol.* 2009;27(34):5700–5706.
 175. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol.* 2005;23(16):3676–3685.
 176. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet.* 2010;375(9712):377–384.
 177. Petrelli F, Borgonovo K, Cabiddu M, et al. Neoadjuvant chemotherapy and concomitant trastuzumab in breast cancer: a pooled analysis of two randomized trials. *Anticancer Drugs.* 2011;22(2):128–135.
 178. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2012;379(9816):633–640.
 179. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(1):25–32.
 180. Hamberg P, Bos MM, Braun HJ, et al. Randomized phase II study comparing efficacy and safety of combination-therapy trastuzumab and docetaxel vs. sequential therapy of trastuzumab followed by docetaxel alone at progression as first-line chemotherapy in patients with HER2+ metastatic breast cancer: HERTAX trial. *Clin Breast Cancer.* 2011;11(2):103–113.
 181. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol.* 2006;24(18):2786–2792.
 182. Valero V, Forbes J, Pegram MD, et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. *J Clin Oncol.* 2011;29(2):149–156.
 183. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. *J Clin Oncol.* 2009;27(12):1999–2006.
 184. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat.* 2008;112(3):533–543.
 185. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol.* 2010;28(7):1124–1130.
 186. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012;366(2):109–119.
 187. De Laurentiis M, Arpino G, Massarelli E, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. *Clin Cancer Res.* 2005;11(13):4741–4748.
 188. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAndEM study. *J Clin Oncol.* 2009;27(33):5529–5537.
 189. Johnston S, Pippet J Jr, Pivov X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009;27(33):5538–5546.
 190. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357(26):2666–2676.
 191. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med.* 2012;366(4):299–309.
 192. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. *N Engl J Med.* 2012;366(4):310–320.
 193. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist.* 2008;13(5):503–514.
 194. Coleman RE, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med.* 2011;365(15):1396–1405.
 195. Nonaka D, Rosai J, Spagnolo D, et al. Cylindroma of the breast of skin adnexal type: a study of 4 cases. *Am J Surg Pathol.* 2004;28(8):1070–1075.
 196. Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. *J Natl Cancer Inst.* 1998;90(18):1346–1360.
 197. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol.* 2003;21(6):976–983.
 198. Berry DA, Ueno NT, Johnson MM, et al. High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials. *J Clin Oncol.* 2011;29(24):3214–3223.
 199. Seidman AD, Berry D, Cirincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol.* 2008;26(10):1642–1649.

200. Citron ML, Berry DA, Cirincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol.* 2003;21(8):1431–1439.
201. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med.* 2008;358(16):1663–1671.
202. Wong NS, Buckman RA, Clemons M, et al. Phase I/II trial of metronomic chemotherapy with daily dalteparin and cyclophosphamide, twice-weekly methotrexate, and daily prednisone as therapy for metastatic breast cancer using vascular endothelial growth factor and soluble vascular endothelial growth factor receptor levels as markers of response. *J Clin Oncol.* 2010;28(5):723–730.
203. Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol.* 2002;20(6):1456–1466.
204. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *J Clin Oncol.* 2006;24(36):5664–5671.
205. Martin M, Rodríguez-Lescure A, Ruiz A, et al. Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by paclitaxel for early breast cancer. *J Natl Cancer Inst.* 2008;100(11):805–814.
206. Amar S, McCullough AE, Tan W, et al. Prognosis and outcome of small (≤ 1 cm), node-negative breast cancer on the basis of hormonal and HER-2 status. *Oncologist.* 2010;15(10):1043–1049.
207. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst.* 1997;89(22):1673–1682.
208. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol.* 2010;11(1):55–65.
209. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol.* 2010;28(11):1829–1834.
210. Goldstein LJ, Gray R, Badve S, et al. Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. *J Clin Oncol.* 2008;26(25):4063–4071.
211. Tang G, Cuzick J, Costantino JP, et al. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. *J Clin Oncol.* 2011;29(33):4365–4372.
212. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med.* 2002;347(25):1999–2009.
213. Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst.* 2006;98(17):1183–1192.
214. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA.* 2001;98(19):10869–10874.
215. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet.* 2012;379(9814):432–444.
216. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-Year follow-up of US Oncology Research Trial 9735. *J Clin Oncol.* 2009;27(8):1177–1183.
217. Muss HB, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med.* 2009;360(20):2055–2065.
218. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352(22):2302–2313.
219. Goldstein LJ, O'Neill A, Sparano JA, et al. Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup Trial E 2197. *J Clin Oncol.* 2008;26(25):4092–4099.
220. Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol.* 2005;23(16):3686–3696.
221. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst.* 2005;97(3):188–194.
222. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and bowel project protocols B-18 and B-27. *J Clin Oncol.* 2008;26(5):778–785.
223. Yuan Y, Chen XS, Liu SY, et al. Accuracy of MRI in prediction of pathologic complete remission in breast cancer after preoperative therapy: a meta-analysis. *AJR Am J Roentgenol.* 2010;195(1):260–268.
224. Dunnwald LK, Gralow JR, Ellis GK, et al. Tumor metabolism and blood flow changes by positron emission tomography: relation to survival in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. *J Clin Oncol.* 2008;26(27):4449–4457.
225. Rouzier R, Extra JM, Klijanienko J, et al. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. *J Clin Oncol.* 2002;20(5):1304–1310.
226. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol.* 1999;17(2):460–469.
227. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2006;24(13):2019–2027.
228. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol.* 2012;30(15):1796–1804.
229. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res.* 2007;13(8):2329–2334.
230. Ogston KN, Miller ID, Payne S, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *Breast.* 2003;12(5):320–327.
231. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol.* 2007;25(28):4414–4422.
232. von Minckwitz G, Raab G, Caputo A, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. *J Clin Oncol.* 2005;23(12):2676–2685.
233. Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol.* 2005;23(25):5983–5992.
234. Untch M, Möbus V, Kuhn W, et al. Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. *J Clin Oncol.* 2009;27(18):2938–2945.
235. von Minckwitz G, Rezaei M, Loibl S, et al. Capecitabine in addition to anthracycline- and taxane-based neoadjuvant treatment in patients with primary breast cancer: phase III GeparQuattro study. *J Clin Oncol.* 2010;28(12):2015–2023.
236. Byrski T, Gronwald J, Huzarski T, et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *J Clin Oncol.* 2010;28(3):375–379.
237. Carrick S, Parker S, Wilcken N, et al. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev.* 2005;(2):CD003372.
238. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol.* 2002;20(12):2812–2823.
239. Blum JL, Dees EC, Chacko A, et al. Phase II trial of capecitabine and weekly paclitaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol.* 2006;24(27):4384–4390.
240. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol.* 2008;26(24):3950–3957.
241. Tomova A, Bartsch R, Brodowicz T, et al. Concomitant docetaxel plus gemcitabine versus sequential docetaxel followed by gemcitabine in anthracycline-pretreated metastatic or locally recurrent inoperable breast cancer patients: a prospective multicentre trial of the Central European Cooperative Oncology Group (CECOG). *Breast Cancer Res Treat.* 2010;119(1):169–176.
242. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer

- progressing after anthracycline and taxane treatment. *J Clin Oncol*. 2007;25(33):5210–5217.
243. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol*. 2008;26(12):1980–1986.
 244. Mauri D, Kamposioras K, Tsali L, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer Treat Rev*. 2010;36(1):69–74.
 245. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol*. 2005;23(24):5542–5551.
 246. Yonemori K, Katsumata N, Uno H, et al. Efficacy of weekly paclitaxel in patients with docetaxel-resistant metastatic breast cancer. *Breast Cancer Res Treat*. 2005;89(3):237–241.
 247. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23(31):7794–7803.
 248. Zielinski C, Gralow J, Martin M. Optimising the dose of capecitabine in metastatic breast cancer: confused, clarified or confirmed? *Ann Oncol*. 2010;21(11):2145–2152.
 249. Blackstein M, Vogel CL, Ambinder R, et al. Gemcitabine as first-line therapy in patients with metastatic breast cancer: a phase II trial. *Oncology*. 2002;62(1):2–8.
 250. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol*. 2007;25(23):3407–3414.
 251. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377(9769):914–923.
 252. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol*. 2011;29(16):2144–2149.
 253. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687–1717.
 254. Breast Cancer Trials Committee, Scottish Cancer Trials Office. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish Trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. *Lancet*. 1987;2(8552):171–175.
 255. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med*. 1989;320(8):479–484.
 256. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90(18):1371–1388.
 257. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378(9793):771–784.
 258. Benson JR. Re: Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 Randomized Trial. *J Natl Cancer Inst*. 2001;93(19):1493–1494.
 259. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomized trial. *Lancet*. 2012;doi:10.1016/S0140-6736(12)61963-1.
 260. Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011;103(17):1299–1309.
 261. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol*. 2010;11(12):1135–1141.
 262. Bliss JM, Kilburn LS, Coleman RE, et al. Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study. *J Clin Oncol*. 2012;30(7):709–717.
 263. Jin H, Tu D, Zhao N, et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol*. 2012;30(7):718–721.
 264. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353(26):2747–2757.
 265. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med*. 2009;361(8):766–776.
 266. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet*. 2011;377(9762):321–331.
 267. Coombes RC, Kilburn LS, Snowden CE, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet*. 2007;369(9561):559–570.
 268. Legare CH. Exploring explanation: explaining inconsistent evidence informs exploratory, hypothesis-testing behavior in young children. *Child Dev*. 2012;83(1):173–185.
 269. Karlsson P, Sun Z, Braun D, et al. Long-term results of International Breast Cancer Study Group Trial VIII: adjuvant chemotherapy plus goserelin compared with either therapy alone for premenopausal patients with node-negative breast cancer. *Ann Oncol*. 2011;22(10):2216–2226.
 270. Arriagada R, Lê MG, Spielmann M, et al. Randomized trial of adjuvant ovarian suppression in 926 premenopausal patients with early breast cancer treated with adjuvant chemotherapy. *Ann Oncol*. 2005;16(3):389–396.
 271. Hackshaw A, Baum M, Fornander T, et al. Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. *J Natl Cancer Inst*. 2009;101(5):341–349.
 272. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol*. 2005;23(25):5973–5982.
 273. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol*. 2011;12(7):631–641.
 274. Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol*. 2009;27(27):4530–4535.
 275. Mauri D, Pavlidis N, Polyzos NP, et al. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst*. 2006;98(18):1285–1291.
 276. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520–529.
 277. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer*. 2007;110(2):244–254.
 278. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. *Breast Cancer Res Treat*. 2007;105(suppl. 1):33–43.
 279. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet*. 2003;361(9354):296–300.
 280. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. *Cancer Prev Res (Phila)*. 2010;3(6):696–706.
 281. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med*. 2011;364(25):2381–2391.
 282. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366(9503):2087–2106.
 283. Sarrazin D, Lê MG, Arriagada R, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol*. 1989;14(3):177–184.
 284. van Dongen JA, Bartelink H, Fentiman IS, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *J Natl Cancer Inst Monogr*. 1992;(11):15–18.
 285. Liljegren G, Holmberg L, Adami HO, et al. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. *J Natl Cancer Inst*. 1994;86(9):717–722.
 286. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol*. 2001;12(7):997–1003.
 287. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst*. 1996;88(22):1659–1664.
 288. Winzer KJ, Sauer R, Sauerbrei W, et al. Radiation therapy after breast-conserving surgery: first results of a randomised clinical trial in patients with low risk of recurrence. *Eur J Cancer*. 2004;40(7):998–1005.

289. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707–1716.
290. Host H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer—long-term results from the Oslo study. *Int J Radiat Oncol Biol Phys*. 1986;12(5):727–732.
291. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet*. 1999;353(9165):1641–1648.
292. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol*. 2006;24(15):2268–2275.
293. Katz A, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. *J Clin Oncol*. 2000;18(15):2817–2827.
294. Jagsi R, Raad RA, Goldberg S, et al. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys*. 2005;62(4):1035–1039.
295. Freedman GM, Fowble BL, Hanlon AL, et al. A close or positive margin after mastectomy is not an indication for chest wall irradiation except in women aged fifty or younger. *Int J Radiat Oncol Biol Phys*. 1998;41(3):599–605.
296. Wang J, Shi M, Ling R, et al. Adjuvant chemotherapy and radiotherapy in triple-negative breast carcinoma: a prospective randomized controlled multi-center trial. *Radiother Oncol*. 2011;100(2):200–204.
297. Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma *in situ* of the breast. *J Clin Oncol*. 2008;26(8):1247–1252.
298. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma *in situ* of the breast. *J Natl Cancer Inst Monogr*. 2010;2010(41):162–177.
299. Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma *in situ* of the breast: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009;27(32):5319–5324.
300. Rudloff U, Jacks LM, Goldberg JL, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma *in situ*. *J Clin Oncol*. 2010;28(23):3762–3769.
301. Bijker N, Peterse JL, Duchateau L, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol*. 2001;19(8):2263–2271.
302. MacAusland SG, Heipel JT, Chong FK, et al. An attempt to independently verify the utility of the Van Nuys Prognostic Index for ductal carcinoma *in situ*. *Cancer*. 2007;110(12):2648–2653.
303. Yi M, Meric-Bernstam F, Kuerer HM, et al. Evaluation of a breast cancer nomogram for predicting risk of ipsilateral breast tumor recurrences in patients with ductal carcinoma *in situ* after local excision. *J Clin Oncol*. 2012;30(6):600–607.
304. Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst*. 1992;84(9):683–689.
305. Vicini FA, Kestin LL, Goldstein NS. Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: a pathologic analysis. *Int J Radiat Oncol Biol Phys*. 2004;60(3):722–730.
306. Heipel JT, Wazer DE. A comparison of brachytherapy techniques for partial breast irradiation. *Brachytherapy*. 2012;11(3):163–175.
307. Shah C, Antonucci JV, Wilkinson JB, et al. Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: results of a matched-pair analysis. *Radiother Oncol*. 2011;100(2):210–214.
308. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009;74(4):987–1001.
309. Bedwinek JM, Lee J, Fineberg B, et al. Prognostic indicators in patients with isolated local-regional recurrence of breast cancer. *Cancer*. 1981;47(9):2232–2235.
310. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8–10.
311. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol*. 2009;27(10):1572–1578.
312. Wang XS, Rhines LD, Shiu AS, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial. *Lancet Oncol*. 2012;13(4):395–402.
313. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys*. 2011;79(4):965–976.
314. Kutcher GJ, Coia L, Gillin M, et al. Comprehensive QA for radiation oncology: report of AAPM Radiation Therapy Committee Task Group 40. *Med Phys*. 1994;21(4):581–618.
315. Klein EE, Hanley J, Bayouth J, et al. Task Group 142 report: quality assurance of medical accelerators. *Med Phys*. 2009;36(9):4197–4212.
316. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362(6):513–520.
317. START Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. 2008;371(9618):1098–1107.
318. Schlembach PJ, Buchholz TA, Ross MI, et al. Relationship of sentinel and axillary level I–II lymph nodes to tangential fields used in breast irradiation. *Int J Radiat Oncol Biol Phys*. 2001;51(3):671–678.
319. Strom EA, Woodward WA, Katz A, et al. Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1508–1513.
320. Hayes SB, Freedman GM, Li T, et al. Does axillary boost increase lymphedema compared with supraclavicular radiation alone after breast conservation? *Int J Radiat Oncol Biol Phys*. 2008;72(5):1449–1455.
321. Morrow M, Foster RS Jr. Staging of breast cancer: a new rationale for internal mammary node biopsy. *Arch Surg*. 1981;116(6):748–751.
322. Veronesi U, Cascinelli N, Bufalino R, et al. Risk of internal mammary lymph node metastases and its relevance on prognosis of breast cancer patients. *Ann Surg*. 1983;198(6):681–684.
323. Freedman GM, Fowble BL, Nicolaou N, et al. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? *Int J Radiat Oncol Biol Phys*. 2000;46(4):805–814.
324. Vicini F, Arthur D, Wazer D, et al. Limitations of the American Society of Therapeutic Radiology and Oncology Consensus Panel guidelines on the use of accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2011;79(4):977–984.
325. Shaitelman SF, Vicini FA, Beitsch P, et al. Five-year outcome of patients classified using the American Society for Radiation Oncology consensus statement guidelines for the application of accelerated partial breast irradiation: an analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. *Cancer*. 2010;116(20):4677–4685.
326. Wazer DE, Kaufman S, Cuttino L, et al. Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. *Int J Radiat Oncol Biol Phys*. 2006;64(2):489–495.
327. Evans SB, Kaufman SA, Price LL, et al. Persistent seroma after intraoperative placement of MammoSite for accelerated partial breast irradiation: incidence, pathologic anatomy, and contributing factors. *Int J Radiat Oncol Biol Phys*. 2006;65(2):333–339.
328. Heipel JT, Tokita M, MacAusland SG, et al. Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1290–1296.
329. Abdulkarim BS, Cuartero J, Hanson J, et al. Increased risk of locoregional recurrence for women with T1–2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. *J Clin Oncol*. 2011;29(21):2852–2858.
330. Sanghani M, Balk E, Cady B, et al. Predicting the risk of local recurrence in patients with breast cancer: an approach to a new computer-based predictive tool. *Am J Clin Oncol*. 2007;30(5):473–480.
331. Sanghani M, Truong PT, Raad RA, et al. Validation of a web-based predictive nomogram for ipsilateral breast tumor recurrence after breast conserving therapy. *J Clin Oncol*. 2010;28(5):718–722.
332. Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol*. 2010;28(10):1677–1683.
333. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer*. 2006;42(2):126–140.
334. Navrozoglu I, Vrekoussis T, Kontostolis E, et al. Breast cancer during pregnancy: a mini-review. *Eur J Surg Oncol*. 2008;34(8):837–843.

335. Oto A, Ernst R, Jesse MK, et al. Magnetic resonance imaging of the chest, abdomen, and pelvis in the evaluation of pregnant patients with neoplasms. *Am J Perinatol*. 2007;24(4):243–250.
336. Streffer C, Shore R, Konermann G, et al. Biological effects after prenatal irradiation (embryo and fetus). A report of the International Commission on Radiological Protection. *Ann ICRP*. 2003;33(1)–(2):5–206.
337. Yang WT, Dryden MJ, Gwyn K, et al. Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. *Radiology*. 2006;239(1):52–60.
338. Taylor D, Lazberger J, Ives A, et al. Reducing delay in the diagnosis of pregnancy-associated breast cancer: how imaging can help us. *J Med Imaging Radiat Oncol*. 2011;55(1):33–42.
339. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. *Lancet*. 2012;379(9815):570–579.
340. Haagensen CD, Stout AP. Carcinoma of the Breast: II. Criteria of operability. *Ann Surg*. 1943;118(5):859–870.
341. White TT. Carcinoma of the breast and pregnancy; analysis of 920 cases collected from the literature and 22 new cases. *Ann Surg*. 1954;139(1):9–18.
342. Middleton LP, Chen V, Perkins GH, et al. Histopathology of breast cancer among African-American women. *Cancer*. 2003;97(suppl. 1):253–257.
343. Murphy CG, Mallam D, Stein S, et al. Current or recent pregnancy is associated with adverse pathologic features but not impaired survival in early breast cancer. *Cancer*. 2012;118(13):3254–3259.
344. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer*. 2006;106(2):237–246.
345. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. *Arch Surg*. 2003;138(1):91–98; discussion 99.
346. Ali SA, Gupta S, Sehgal R, et al. Survival outcomes in pregnancy associated breast cancer: a retrospective case control study. *Breast J*. 2012;18(2):139–144.
347. Gentilini O, Cremonesi M, Toesca A, et al. Sentinel lymph node biopsy in pregnant patients with breast cancer. *Eur J Nucl Med Mol Imaging*. 2010;37(1):78–83.
348. Khara SY, Kiluk JV, Hasson DM, et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. *Breast J*. 2008;14(3):250–254.
349. Cragan JD. Teratogen update: methylene blue. *Teratology*. 1999;60(1):42–48.
350. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol*. 2005;6(5):328–333.
351. Ring AE, Smith IE, Ellis PA. Breast cancer and pregnancy. *Ann Oncol*. 2005;16(12):1855–1860.
352. Kalter H, Warkany J. Congenital malformations (second of two parts). *N Engl J Med*. 1983;308(9):491–497.
353. Cardonick E, Dougherty R, Grana G, et al. Breast cancer during pregnancy: maternal and fetal outcomes. *Cancer J*. 2010;16(1):76–82.
354. Berry DL, Theriault RL, Holmes FA, et al. Management of breast cancer during pregnancy using a standardized protocol. *J Clin Oncol*. 1999;17(3):855–861.
355. Hahn KM, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. *Cancer*. 2006;107(6):1219–1226.
356. Peccatori FA, Azim HA Jr, Scarfone G, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat*. 2009;115(3):591–594.
357. Azim HA Jr, Peccatori FA, Scarfone G, et al. Anthracyclines for gestational breast cancer: course and outcome of pregnancy. *Ann Oncol*. 2008;19(8):1511–1512.
358. Garcia-Manero M, Royo MP, Espinos J, et al. Pregnancy associated breast cancer. *Eur J Surg Oncol*. 2009;35(2):215–218.
359. Morris PG, King F, Kennedy MJ. Cytotoxic chemotherapy for pregnancy-associated breast cancer: single institution case series. *J Oncol Pharm Pract*. 2009;15(4):241–247.
360. Mir O, Berveiller P, Goffinet F, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Ann Oncol*. 2010;21(2):425–426.
361. Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. *Obstet Gynecol*. 2005;105(3):642–643.
362. Sekar R, Stone PR. Trastuzumab use for metastatic breast cancer in pregnancy. *Obstet Gynecol*. 2007;110(2 Pt 2):507–510.
363. Waterston AM, Graham J. Effect of adjuvant trastuzumab on pregnancy. *J Clin Oncol*. 2006;24(2):321–322.
364. Fanale MA, Uyei AR, Theriault RL, et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. *Clin Breast Cancer*. 2005;6(4):354–356.
365. Barthelme L, Gateley CA. Tamoxifen and pregnancy. *Breast*. 2004;13(6):446–451.
366. Gnani M, Mlineritsch B, Schipfinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009;360(7):679–691.
367. Meyer-Wittkopf M, Barth H, Emons G, et al. Fetal cardiac effects of doxorubicin therapy for carcinoma of the breast during pregnancy: case report and review of the literature. *Ultrasound Obstet Gynecol*. 2001;18(1):62–66.
368. Aviles A, Neri N, Nambo MJ. Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. *Ann Oncol*. 2006;17(2):286–288.
369. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. *Clin Lymphoma*. 2001;2(3):173–177.
370. Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer. *Breast*. 2007;16(suppl 2):S175–S181.
371. Gemignani ML, Petrek JA. Pregnancy after breast cancer. *Cancer Control*. 1999;6(3):272–276.
372. Sankila R, Heinavaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: “healthy mother effect”. *Am J Obstet Gynecol*. 1994;170(3):818–823.
373. Higgins S, Haffty BG. Pregnancy and lactation after breast-conserving therapy for early stage breast cancer. *Cancer*. 1994;73(8):2175–2180.
374. Duffy CM, Allen SM, Clark MA. Discussions regarding reproductive health for young women with breast cancer undergoing chemotherapy. *J Clin Oncol*. 2005;23(4):766–773.
375. Lavelle K, Todd C, Moran A, et al. Non-standard management of breast cancer increases with age in the UK: a population based cohort of women > or =65 years. *Br J Cancer*. 2007;96(8):1197–1203.
376. Gennari R, Audisio RA. Breast cancer in elderly women. Optimizing the treatment. *Breast Cancer Res Treat*. 2008;110(2):199–209.
377. Bouchardy C, Rapiti E, Fioretta G, et al. Under-treatment strongly decreases prognosis of breast cancer in elderly women. *J Clin Oncol*. 2003;21(19):3580–3587.
378. Yood MU, Owusu C, Buist DS, et al. Mortality impact of less-than-standard therapy in older breast cancer patients. *J Am Coll Surg*. 2008;206(1):66–75.
379. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol*. 2012;13(4):e148–e160.
380. Pallis AG, Fortpied C, Wedding U, et al. EORTC elderly task force position paper: approach to the older cancer patient. *Eur J Cancer*. 2010;46(9):1502–1513.
381. Schonberg MA, Marcantonio ER, Li D, et al. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. *J Clin Oncol*. 2010;28(12):2038–2045.
382. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst*. 2000;92(7):550–556.
383. Rosso S, Gondos A, Zanetti R, et al. Up-to-date estimates of breast cancer survival for the years 2000–2004 in 11 European countries: the role of screening and a comparison with data from the United States. *Eur J Cancer*. 2010;46(18):3351–3357.
384. Wildiers H, Van Calster B, van de Poll-Franse LV, et al. Relationship between age and axillary lymph node involvement in women with breast cancer. *J Clin Oncol*. 2009;27(18):2931–2937.
385. Yancik R, Ries LG, Yates JW. Breast cancer in aging women. A population-based study of contrasts in stage, surgery, and survival. *Cancer*. 1989;63(5):976–981.
386. Lyman GH, Lyman S, Balducci L, et al. Age and the risk of breast cancer recurrence. *Cancer Control*. 1996;3(5):421–427.
387. Molino A, Giovannini M, Auriemma A, et al. Pathological, biological and clinical characteristics, and surgical management, of elderly women with breast cancer. *Crit Rev Oncol Hematol*. 2006;59(3):226–233.
388. Mustacchi G, Ceccherini R, Milani S, et al. Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the phase III randomized controlled multicenter GRETA trial. *Ann Oncol*. 2003;14(3):414–420.
389. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. *Br J Cancer*. 2007;96(7):1025–1029.
390. Audisio RA, Bozzetti F, Gennari R, et al. The surgical management of elderly cancer patients; recommendations of the SIOG surgical task force. *Eur J Cancer*. 2004;40(7):926–938.
391. Rudenstam CM, Zahrieh D, Forbes JF, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol*. 2006;24(3):337–344.
392. Martelli G, Miceli R, Daidone MG, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. *Ann Surg Oncol*. 2011;18(1):125–133.
393. McMahon LE, Gray RJ, Pockaj BA. Is breast cancer sentinel lymph node mapping valuable for patients in their seventies and beyond? *Am J Surg*. 2005;190(3):366–370.
394. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation

- in women 70 years of age or older with early breast cancer. *N Engl J Med*. 2004;351(10):971–977.
395. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol*. 2008;9(4):331–341.
 396. Kirova YM, Campana F, Savignoni A, et al. Breast-conserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2009;75(1):76–81.
 397. Crivellari D, Aapro M, Leonard R, et al. Breast cancer in the elderly. *J Clin Oncol*. 2007;25(14):1882–1890.
 398. Christiansen P, Bjerre K, Ejlersen B, et al. Mortality rates among early-stage hormone receptor-positive breast cancer patients: a population-based cohort study in Denmark. *J Natl Cancer Inst*. 2011;103(18):1363–1372.
 399. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365(9453):60–62.
 400. Elkin EB, Hurria A, Mitra N, et al. Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: assessing outcome in a population-based, observational cohort. *J Clin Oncol*. 2006;24(18):2757–2764.
 401. Giordano SH, Duan Z, Kuo YF, et al. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. *J Clin Oncol*. 2006;24(18):2750–2756.
 402. Freyer G, Campone M, Peron J, et al. Adjuvant docetaxel/cyclophosphamide in breast cancer patients over the age of 70: results of an observational study. *Crit Rev Oncol Hematol*. 2011;80(3):466–473.
 403. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St.Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011;22(8):1736–1747.
 404. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277–300.
 405. Newman LA, Griffith KA, Jatoi I, et al. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. *J Clin Oncol*. 2006;24(9):1342–1349.
 406. Field TS, Buist DS, Doubeni C, et al. Disparities and survival among breast cancer patients. *J Natl Cancer Inst Monogr*. 2005;(35):88–95.
 407. Elledge RM, Clark GM, Chamness GC, et al. Tumor biologic factors and breast cancer prognosis among white, hispanic, and black women in the United States. *J Natl Cancer Inst*. 1994;86(9):705–712.
 408. Li CI, Malone KE, Daling JR. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. *Cancer Epidemiol Biomarkers Prev*. 2002;11(7):601–607.
 409. Hance KW, Anderson WF, Devesa SS, et al. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. *J Natl Cancer Inst*. 2005;97(13):966–975.
 410. Watlington AT, Byers T, Mouchawar J, et al. Does having insurance affect differences in clinical presentation between Hispanic and non-Hispanic white women with breast cancer? *Cancer*. 2007;109(10):2093–2099.
 411. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006;295(21):2492–2502.
 412. Setiawan VW, Monroe KR, Wilkens LR, et al. Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. *Am J Epidemiol*. 2009;169(10):1251–1259.
 413. John EM, Miron A, Gong G, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. *JAMA*. 2007;298(24):2869–2876.
 414. Weitzel JN, Lagos VI, Herzog JS, et al. Evidence for common ancestral origin of a recurring BRCA1 genomic rearrangement identified in high-risk Hispanic families. *Cancer Epidemiol Biomarkers Prev*. 2007;16(8):1615–1620.
 415. Patel TA, Colon-Otero G, Bueno Hume C, et al. Breast cancer in Latinas: gene expression, differential response to treatments, and differential toxicities in Latinas compared with other population groups. *Oncologist*. 2010;15(5):466–475.
 416. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *J Am Med Assoc*. 2005;294(15):1925–1933.
 417. Bickell NA, Wang JJ, Oluwole S, et al. Missed opportunities: racial disparities in adjuvant breast cancer treatment. *J Clin Oncol*. 2006;24(9):1357–1362.
 418. White J, Morrow M, Moughan J, et al. Compliance with breast-conservation standards for patients with early-stage breast carcinoma. *Cancer*. 2003;97(4):893–904.
 419. Maggard MA, Lane KE, O'Connell JB, et al. Beyond the clinical trials: how often is sentinel lymph node dissection performed for breast cancer? *Ann Surg Oncol*. 2005;12(1):41–47.
 420. Hershman D, McBride R, Jacobson JS, et al. Racial disparities in treatment and survival among women with early-stage breast cancer. *J Clin Oncol*. 2005;23(27):6639–6646.
 421. Morrow M, Scott SK, Menck HR, et al. Factors influencing the use of breast reconstruction post-mastectomy: a National Cancer Database study. *J Am Coll Surg*. 2001;192(1):1–8.
 422. Tseng JF, Kronowitz SJ, Sun CC, et al. The effect of ethnicity on immediate reconstruction rates after mastectomy for breast cancer. *Cancer*. 2004;101(7):1514–1523.
 423. Newman LA, Martin IK. Disparities in breast cancer. *Curr Probl Cancer*. 2007;31(3):134–156.
 424. Dignam JJ. Differences in breast cancer prognosis among African-American and Caucasian women. *CA Cancer J Clin*. 2000;50(1):50–64.
 425. Dignam JJ. Efficacy of systemic adjuvant therapy for breast cancer in African-American and Caucasian women. *J Natl Cancer Inst Monogr*. 2001;(30):36–43.
 426. Dawood S, Broglio K, Kau SW, et al. Triple receptor-negative breast cancer: the effect of race on response to primary systemic treatment and survival outcomes. *J Clin Oncol*. 2009;27(2):220–226.
 427. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1659–1672.
 428. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273–1283.
 429. Joensuu H, Kellokumpui-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354(8):809–820.
 430. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673–1684.
 430. Azzopardi J. *G. Problems in Breast Pathology*. London, England: WB Saunders Co Ltd; 1979:193–203.

29

Management of Infections
in Patients with Gynecologic
MalignancyAMAR SAFDAR ■ KENNETH ROLSTON ■ GENEVIEVE L. BENNETT
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Patients with gynecologic cancer are susceptible to infections. The risk of developing an infection can arise from a number of factors that may relate to the neoplasm and antineoplastic therapy, or both. Tumor encroachment and invasion of adjacent structures, necrosis of expanding tumor mass, surgical tumor excision, and removal of internal organs including lymph nodes and diversion procedures that disrupt protective barriers in the lower and upper female reproductive tract are a few such causes. Patients with these malignancies may also be susceptible to a host of infections due to presence of drug- or radiation-induced mucositis, severe neutropenia, long-term sequelae of prior abdominopelvic radiation therapy, and presence of indwelling foreign devices (1,2).

The wide spectrum of causative microorganisms most frequently arises from endogenous vaginal, urethral, and intestinal tract colonization with bacteria and *Candida* species. The normal aerobic and anaerobic vaginal bacterial flora may be altered in patients undergoing antimicrobial and antineoplastic therapy. Among factors that influence changes in colonization are hormonal dysfunction, factors influencing alteration in the composition of mucosal secretions including innate immune functions, frequent exposure to broad-spectrum antimicrobial agents, antineoplastic drug and radiation therapy, instrumentation and prolonged, often multiple hospitalizations. In a recent report, however, patients receiving external-beam radiotherapy for gynecologic malignancy did not experience changes in aerobic microflora in the vagina, cervix, or rectum (3,4). Whereas a significant growth in vaginal yeasts occurred during the first 2 weeks after radiation therapy commenced; *Candida albicans* and *Candida tropicalis* were prominent. The increase of vaginal growth of *Candida* species returned to preradiation levels after 4 weeks (5). Exposure to health care facilities, especially centers that care for immunocompromised oncology patients, has been recognized as a major influence, albeit transient in most instances, in promoting change in cutaneous, orointestinal, and genitourinary microflora. The changes in vaginal and lower urinary tract microflora occur less commonly, even in patients following repeated exposure to the hospital environment, and are often limited to patients who undergo instrumentation. The health care-associated microorganisms are frequently less susceptible to commonly prescribed antibiotics, and optimum selection of antimicrobial drugs poses a daunting challenge. It is, however, important to appreciate that changes in a host's microflora are in most cases transient and restitution of normal intestinal and vaginal flora occurs once factors promoting the change have been removed.

The female genital tract is rich in anaerobic microflora. *Peptococcaceae* are prominent in the normal vaginal bacterial flora. Quantitative vaginal cultures in recent studies showed that anaerobic bacteria outnumbered aerobic bacteria by nearly 10:1;

peptococci, *Lactobacillus*, *Corynebacterium*, *Eubacterium*, and *Bacteroides* species are frequently isolated (6). *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species are the aerobic Gram negatives, and streptococci, enterococci, and coagulase-negative staphylococcus are gram-positive bacteria isolated from the lower female genital tract. These organisms provide an important reference to local and invasive infections seen in patients undergoing treatment for gynecologic malignancy.

This chapter provides an overview of infections encountered in patients receiving treatment for cancers involving the female reproductive system. A detailed review of specific diseases such as postsurgical abdominopelvic infections, febrile neutropenia, and bacteremia is presented. A focused discussion regarding the changing epidemiology of causative organisms, the increasing rate of infection due to drug-resistant organisms, and an update on new antimicrobial agents is briefly discussed.

PATIENTS WITH FEVER

The factors that increase the risk for infection are shown in Table 29.1. Knowledge of underlying predisposing factor(s) is necessary in the selection of appropriate empiric therapy. Antibiotic prophylaxis and/or recent treatment with broad-spectrum antimicrobial drugs have been associated with the risk of infection(s) due to non-drug-susceptible microorganisms, including systemic candidiasis. Awareness of specific cancer and cancer-therapy-associated risks and the host's underlying immune dysfunction may allow for proper selection of empiric antibiotic therapy in critically ill patients prior to the results of diagnostic microbiologic and radiographic studies are known. It is important to note that patients with gynecologic cancer may have a high risk of polymicrobial infections due to the presence of physiologic microflora resulting from anatomic proximity to the lower intestinal and urinary tracts. In certain infections, such as deep-tissue abscess, cellulitis in patients with chronic fistula tract, presence of large necrotic tumor, and history of multiple recent instrumentation, the probability of polymicrobial infection remains high (7). Furthermore, in patients with a known anaerobic bloodstream infection, concurrent bacteremia due to aerobic organism(s) is not uncommon (7). Patients with advanced cancer, history of radiation therapy, and extensive pelvic surgery may develop obstruction to the pelvic venous and lymphatic flow. The aberration in physiologic/anatomic defenses and stagnation heightens the risk for cellulitis, abscess formation, and septic thrombophlebitis. Furthermore, these factors also unfavorably influence response to antimicrobial therapy. Several Comprehensive Cancer Centers and other institutions that care for large numbers of patients with cancer have

Table 29.1 Predisposing Risk Factors and Infections in Patients with Gynecologic Tumor*Tumor Related*

Obstruction of gastrointestinal or urinary tract

Erosion into bowel, urinary tract, peritoneum, or retroperitoneal space

Necrosis of rapidly growing cancer promotes abscess formation

Lymphatic obstruction

Surgery

Aspiration pneumonia

Hospital-acquired pneumonia, including ventilator-associated pneumonia

Wound infection; skin, and skin structure infection

Tissue necrosis due to disruption of blood supply

Infected hematoma

Fistula tract communication between intestinal and urinary tracts

Complicated peritonitis

Septic deep thrombophlebitis

Fasciitis, myositis, and gas gangrene are rare complications

Chemotherapy

Febrile neutropenia

Pneumonia

Neutropenic enterocolitis

Radiation Therapy

Enteritis

Urinary tract infection

Poor wound healing

Catheter and Implantable Devices

Device infection

Peritonitis

Bloodstream infection

Urinary tract infection

Table 29.2 Infectious Diseases Consultations Performed for the Gynecologic Oncology Clinical Service at MD Anderson Cancer Center, Houston, Texas,^a n = 373

Reason for Consultation	Number (%)
Intra-abdominal/Pelvic Abscess	43 (12)
Surgical Wound Infection	41 (11)
Complicated Urinary Tract Infection	38 (10)
Neutropenic Fever	36 (10)
Pneumonia	35 (9)
Unexplained Fever (Including tumor fever)	35 (9)
Bacteremia	32 (9)
Diarrhea (Including <i>C. difficile</i> associated)	30 (8)
Nonspecific Cutaneous Eruption (Rash)	21 (6)
Leukocytosis/Leukemoid Reaction	19 (5)
Infection with MDR—Organism ^b	16 (4)
Fungemia	11 (3)
Varicella-Zoster Infection	5 (1)
Meningitis	2 (1)
Miscellaneous ^c	9 (2)

^a Consultations performed by K.R. from January 2001 to December 2011.^b MDR—Multidrug resistant, defined as resistance to three or more different classes of antimicrobial agents, included cellulitis, and wound breakdown/dehiscence.^c Included travel and other immunizations.

developed Infectious Disease consultative services with a special interest and expertise in infections seen in this high-risk patient population. Table 29.2 provides a breakdown of the various infectious and noninfectious causes that resulted in Infectious Disease consultation requests from the gynecologic oncology clinical service at the MD Anderson Cancer Center.

TUMOR RELATED

Tumor-associated infections are dependent on the anatomic site, type, and extent of tumor involvement. In patients with an early-stage, locally involved cancer such as stage I cervical cancer, most infections remain localized to the vagina, whereas in

patients with advanced cervical cancer, infections may involve the uterus, fallopian tubes, ovaries and other deep pelvic structures, and retroperitoneum. Infections may present as tubo-ovarian or deep pelvic abscess, endometritis, and less frequently seen pyometra (Figs. 29.1, 29.2, and 29.3). Extension of these infections to adjacent structures may present as ascending pyelonephritis, rectal abscess, and complicated peritonitis, which are often serious requiring surgical debridement or intervention by invasive radiology (8,9). It is also important to note that an infection may be the primary presentation of an undiagnosed malignancy involving the female reproductive tract. In a study of postmenopausal women who presented with tubo-ovarian abscess, nearly half of these patients were subsequently diagnosed with a gynecologic malignancy (10). Therefore, a thorough investigation for possible underlying cancer should be considered in postmenopausal women or those in the absence of sexually transmitted diseases who present with tubo-ovarian abscess or pyometra.

In a large study conducted at the MD Anderson Cancer Center in the 1970s, septicemia, pneumonia, and peritonitis in patients with gynecologic cancer were associated with high infection-associated mortality (11). In the last 2 decades, in patients at an increased risk for infections, early diagnosis, identification of factors associated with poor treatment outcome, empiric therapy with new generation broad-spectrum antimicrobial drugs, advances in antineoplastic and target-centered radiation therapy, and improved surgical techniques have substantially improved outcomes. The recent favorable outcomes

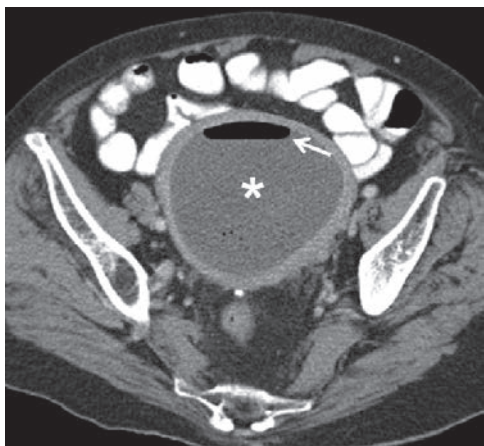


FIGURE 29.1. A 73-year-old woman with endometrial cancer presented with pelvic pain, fever and vaginal bleeding. Axial CT scan performed with enteric and IV contrast demonstrates a markedly distended endometrial cavity containing fluid (*). There is air also present, with an air-fluid level (arrow). In a febrile patient, this is highly suggestive of infection/endometritis. At D&C, blood and pus were drained from the uterine cavity compatible with pyohematometra.

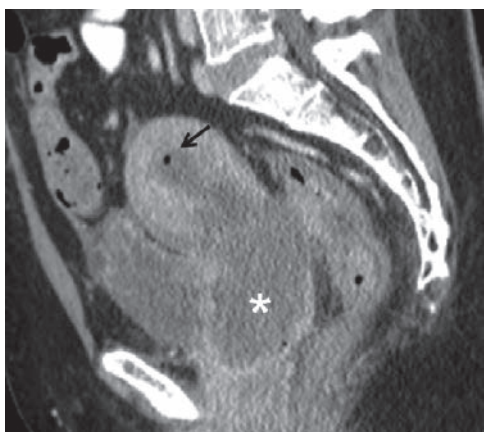


FIGURE 29.2. A 46-year-old woman with cervical cancer presented with pelvic pain and fever. Sagittal contrast enhanced CT image demonstrates a large cervical mass (*). There is obstruction of the endometrial cavity which is mildly distended and contains fluid and air (arrow), compatible with infection/pyometra.

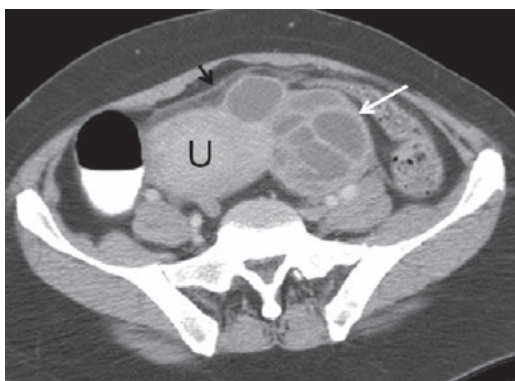


FIGURE 29.3. A 40-year-old woman with cervical cancer presented with fever, left lower quadrant pain and diagnosed with tubo-ovarian abscess. Axial contrast enhanced CT scan demonstrates a complex multiloculated mass with thick septations (white arrow) to the left of the uterine fundus (U). There are inflammatory changes in the pelvic fat (black arrow).

for serious systemic bacterial and *Candida* species infections are in most part due to the availability of well-tolerated broad-spectrum antimicrobial drugs. The recent emergence and spread of multidrug-resistant (MDR) organisms, however, may mitigate these advances, and even patients with solid-organ cancer with limited immune suppression, life-threatening septicemia, pneumonia, peritonitis and abdominopelvic infections may mimic the antibiotic nascent era (11).

SURGERY RELATED

Patients undergoing surgery for cervical cancer have a higher rate of infectious complications, compared with patients with endometrial cancer who tolerate surgery better and have fewer infections during the early and late postoperative period (12). Pelvic exenteration is performed in patients with advanced and/or treatment refractory cervical and upper reproductive tract malignancies. Infections remain as serious complications following pelvic exenteration; early postsurgical wound infection and wound dehiscence are not uncommon (13,14). Urinary tract infections frequently occur in patients with urinary fistula and/or those who develop urethral obstruction. Studies show that greater than 40% of patients undergoing pelvic exenteration for gynecologic and rectal cancer had urinary tract infection and wound dehiscence, or both (13). Late infections such as ascending pyelonephritis may be serious, as they frequently recur and are usually seen in patients with irreparable structural damage to the urinary reservoir such as those with a neobladder or with stenosis of the urethra or surgical anastomosis site. Ureterointestinal fistula; stones in the urinary reservoir; and surgical, radiation, or chronic/recurrent infection/inflammation-induced narrowing all contribute to increased risk of infections, and unless the anatomical abnormality is corrected, these patients remain at increased risk for recurrent urinary tract infections and complications arising from prolonged systemic antibiotic therapy and repeat hospitalizations. Empiric therapy includes adequate coverage for possible polymicrobial infection, and the choice should include drugs that provide adequate coverage for enteric coliforms, enterococci, including vancomycin-resistant *Enterococcus* species, especially in patients with known prior intestinal or genitourinary tract colonization due to these drug-resistant bacteria and/or receiving care at centers with known high prevalence for these pathogens (15). As most infections in this setting may also have an anaerobe as a copathogen, even in patients with negative microbiologic evidence of anaerobic infection, antibiotic selection should entertain nonisolated anaerobic bacteria. We recommend secondary suppressive antimicrobial therapy in patients with recurrent deep pelvic infection to reduce morbidity and subsequent hospitalization and surgeries. It is critical to select high-risk patients judiciously so patients are not given prolonged courses of broad-spectrum antibiotics, which is the single most important factor in promoting selection for or, less commonly, development of *de novo* drug-resistant bacteria and fungi.

Infections remain the main concern in patients following radical vulvar resection and inguinal lymph node dissection. In 67 patients undergoing 112 inguinal lymphadenectomy, early postoperative cellulitis is noted in nearly one-third of patients undergoing inguinal lymphadenectomy, and in over 20%, early surgical wound breakdown also occurred (16). Furthermore, they observed late surgery-site cellulitis in patients with chronic lymphedema, whereas, in most patients the surgical wound was not compromised (16).

Wound Infection

Infected surgical wounds in patients following female genital tract surgery include *Staphylococcus aureus*, including MDR

or semisynthetic penicillin resistant *S. aureus* (MRSA) obtained from health care microflora (health care associated [HA]) or community acquired (CA)-MRSA, which has now become the leading source of MRSA infections in the United States and globally. *Streptococcus* species (group A, B, C, non-Enterococcus D and G) are also common pathogens in this population, and nearly one-third of infections, especially those with involvement of the lower intestinal tract and urinary tract, are less likely to be monomicrobial.

In certain subpopulations of patients who have been receiving systemic corticosteroids for extended periods, patients with morbid obesity, malnutrition, cancer related cachexia and those with poorly controlled diabetes mellitus have a higher risk of developing postoperative wound infections. Coagulase-negative *Staphylococcus*, *Streptococcus* species, *S. aureus*, enteric gram-negative bacteria, and *Bacteroides* species are potential pathogens.

Patients who have a complicated hospital course following surgery may develop infections due to organisms acquired from the health care microenvironment. In critically ill patients, infections are treated empirically, and the spectrum of causative organism(s) may not be available at the time of medical decision making. Knowledge of regional and institutional prevalence of drug-resistant organisms is required in prescribing an appropriate treatment regimen. The empiric therapy in patients with prolonged hospitalization and anatomic abnormalities such as enterourethral, entero- or rectovaginal, or enterovesicular fistula increases the probability of recurrent infection due to resistant HA-gram-negative bacteria, such as *Pseudomonas* species, and extended-spectrum beta-lactamases-producing and carbapenemases-producing *Enterobacteriaceae*, such as *E. coli* and *Klebsiella pneumoniae*. Other nonfermentative gram-negative bacteria such as nosocomial *Acinetobacter* spp. and *Stenotrophomonas maltophilia* are often resistant to a wide variety of commonly used broad-spectrum antibiotics; successful treatment for MDR bacterial disease remains a consternant task (17,18).

Intra-abdominal and Pelvic Abscess

An infected collection within the peritoneal cavity may develop as a consequence of breach in the physical barriers resulting from tumor progression or tumor necrosis and may also occur in patients undergoing instrumentation, or as a consequence of reconstructive surgery and implantation of prosthetic devices. The secondary seeding of the intraperitoneal tumor mass in patients with bloodstream infection arising from a different primary source, such as the urinary tract, antineoplastic therapy-induced orointestinal mucositis, or indwelling vascular device may also occur. The spectrum of causative organisms includes enteric bacteria such as *E. coli*, *Enterococcus*, *Staphylococcus* species, *Bacteroides*, and other anaerobes. *Candida* species infection is less frequent in nonneutropenic patients, although patients with high yeast counts in multiple body sites referred as high *Candida* colonization index, exposure to prolonged broad-spectrum antibiotics, poorly controlled diabetes mellitus, systemic corticosteroid use, as well as stay in critical care units and presence of foreign devices may increase the risk for tissue invasive candidiasis.

Hematogenous or direct seeding of the retroperitoneal space may lead to paraspinal and psoas abscess; these infections escape early detection as patients may not have high-grade fever, and increase in chronic low back pain remains subject to interpretation. In the absence of a direct extension from the intestinal or urinary tract, these retroperitoneal infections are usually monomicrobial, and diagnosis requires prompt computed tomography or magnetic resonance imaging scans and aspiration of the infected collection (Figs. 29.4 and 29.5). In tuberculosis endemic regions, *Mycobacterium tuberculosis* must

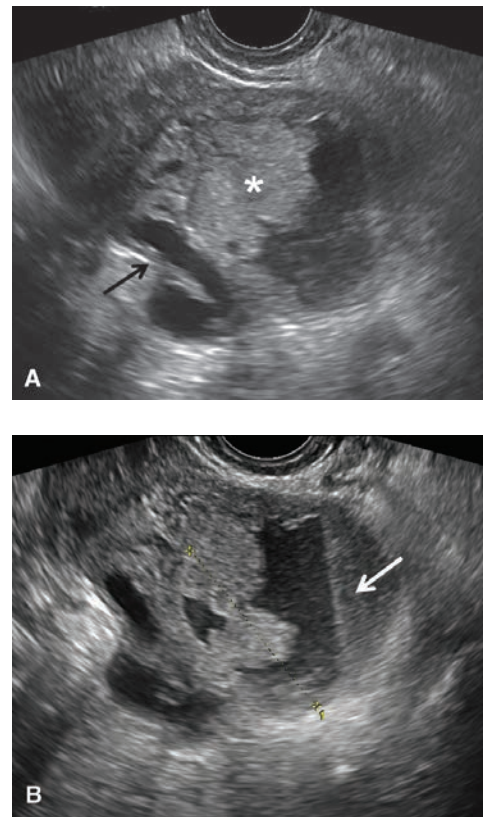


FIGURE 29.4. A 52-year-old woman with fallopian tube carcinoma initially diagnosed as tubo-ovarian abscess. She presented to the emergency department with left lower quadrant pain, and fever. **A:** Transvaginal ultrasound demonstrates a complex left adnexal mass with a tubular in configuration fluid-filled component (arrow) and a solid component (*). **B:** Additional image demonstrates a fluid-debris level within this mass (arrow). Initially, this was thought to represent a tubo-ovarian abscess; however, the patient had no risk factors for pelvic inflammatory disease. At surgery, fallopian tube carcinoma was found.

be considered in determining the etiology of these infections, especially in patients in whom the vertebral column is involved.

Pelvic abscesses that develop after instrumentation or following surgery are often polymicrobial, and treatment is directed toward normal intestinal tract and cutaneous microflora.

Peritoneal infections following bowel perforation, anastomotic leaks, or fistula tracts may present with fever, abdominal pain, and fistula drainage and/or surgical wound dehiscence. Most infections, as expected, are polymicrobial, and *Enterobacteriaceae*, *S. aureus*, *Streptococcus*, and *Enterococcus* species including vancomycin-resistant strains are frequently encountered. *Bacteroides fragilis* and *Clostridium* species are common anaerobes; *Fusobacterium*, *Peptostreptococcus*, and *Eubacterium* occur less commonly. Patients with peritoneal infections following surgery involving the nonsterile bowel and lower genitourinary tract may also have an increased risk for *Pseudomonas* species infection involving the deep pelvic and lower abdominal tissue and/or organs.

CHEMOTHERAPY AND RADIATION RELATED

Patients receiving chemotherapy may have an increased risk of infection; neutropenia for less than a week increases risk for systemic bacterial infections due to *S. aureus*, *Pseudomonas*, *E. coli* and other coliform bacteria. Patients who remain neutropenic

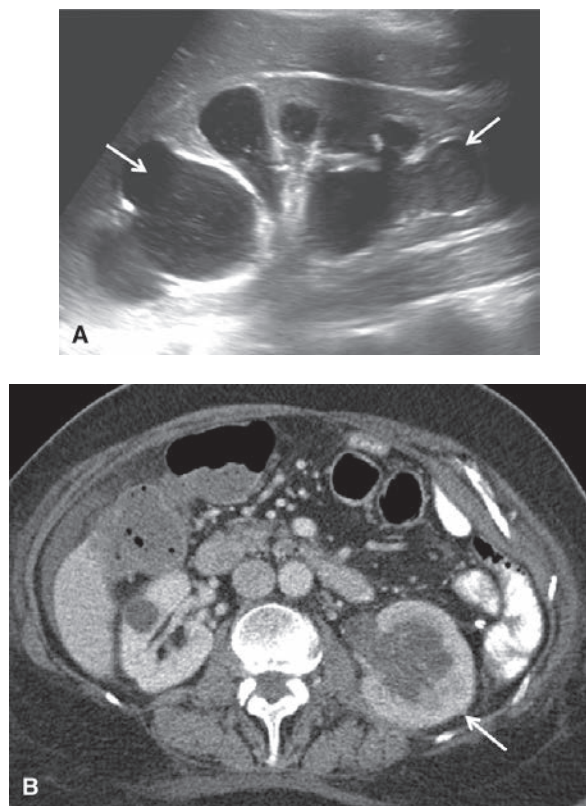


FIGURE 29.5. A 48-year-old woman with cervical cancer presents with left flank pain and fever: **A:** Sagittal gray-scale ultrasound image of the left kidney demonstrates marked hydronephrosis compatible with ureteral obstruction secondary to the patient's cervical neoplasm. There is echogenic debris present in the dilated collecting system (arrows) compatible with pus in the setting of pyonephrosis. **B:** Axial contrast-enhanced CT scan in the same patient demonstrates the enlarged left kidney with hydronephrosis (arrow). There is a delayed nephrogram compared with the right, compatible with obstruction. The left nephrogram is also heterogeneous and there is perinephric inflammatory change compatible with pyelonephritis. The right kidney is normal with the exception of a small cyst.

for longer than 5 to 7 days are also at increased risk for developing tissue-invasive *Candida* species infection (1,2). Disruption of orointestinal and genitourinary tract mucosa compromises an important barrier in the prevention of bacterial and fungal invasion. In patients with severe treatment-induced mucositis, α -hemolytic streptococcal and anaerobic septicemia may lead to devastating consequences, including rapidly progressive multiorgan failure, disseminated intravascular coagulation, hemodynamic collapse, and death (19).

Radiation therapy in patients with vulvar, vaginal, and cervical cancer causes microvascular damage to the tissue and may lead to difficult-to-treat intestinal, vaginal, and urologic complications.

Increased doses of radiation for gynecologic cancer have been associated with improved cancer-free survival (20). However, with increased radiation dose, the rate of complications has also risen (21). Noninfectious complications arising from high-dose radiotherapy include damage to the organs in radiation field, including necrosis of tissue and bone, fistula formation, enteritis, proctitis, aseptic degenerative arthritis of pelvic, and sacroiliac joints increasing the risk for pathologic fracture. Radiation-induced fibrosis may result in vaginal, rectal, and ureteric stenosis, and predisposes to secondary infection due to stagnation and inadequate physiologic drainage (22). In rare cases, patients with radiation-induced necrosis of pelvic bones may present with osteomyelitis; for these patients, a challenging

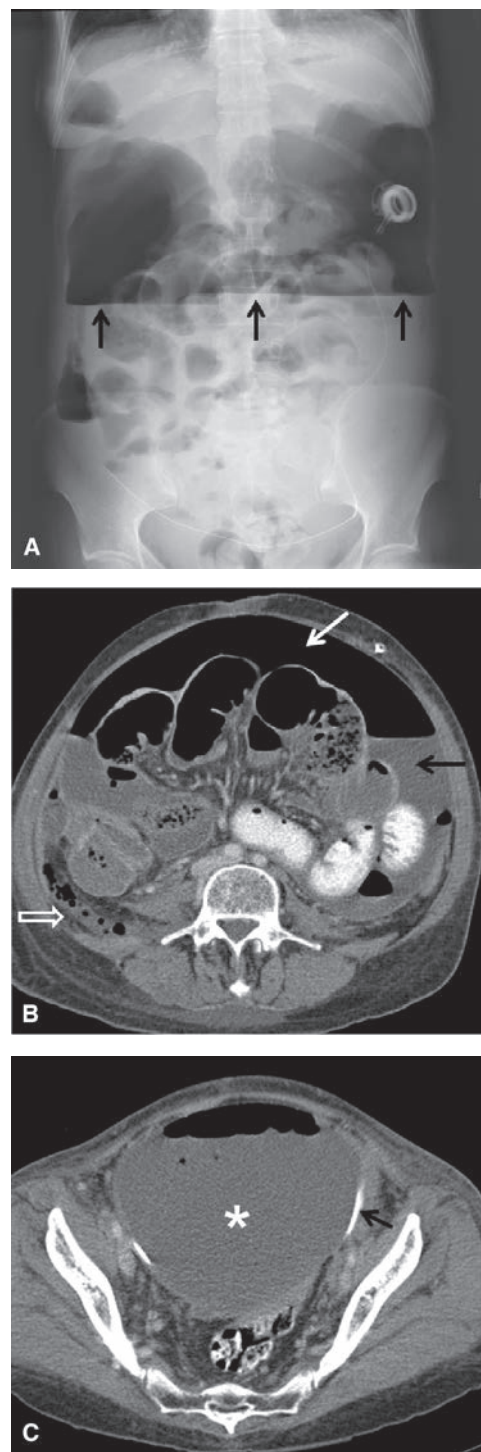


FIGURE 29.6. A 53-year-old woman with recurrent papillary serous carcinoma of the ovary with serosal bowel implants undergoing treatment with intraperitoneal chemotherapy presents with abdominal pain, vomiting and fever: **A:** Upright abdominal radiograph demonstrates large amount of free intraperitoneal air with air-fluid level due to the presence of ascites fluid (arrows). Multiple dilated air-filled loops of bowel are noted. Intraperitoneal chemotherapy infusion catheter is in place with port in left upper abdomen. These findings are compatible with perforated viscus. **B:** Axial contrast enhanced CT scan in the same patient demonstrates a large amount of free intraperitoneal air (white arrow) and ascites fluid (black arrow). There are multiple dilated loops of bowel. There is a mottled gas collection in the right lower quadrant posterior to the cecum (open white arrow). At surgery, the cecum was found to be perforated. **C:** Large loculated fluid and gas-containing collection in the pelvis is compatible with an abscess (*). The chemotherapy infusion catheter is visualized at the posterior wall of the abscess (black arrow).

and multifaceted treatment approach is needed for successful outcomes (23) (Fig. 29.6). A patient with osteomyelitis in the setting of radiation-induced bone necrosis may need extensive surgical debridement and an appropriate selection of antibiotics for a prolonged period. The excisional defects create additional complexity due to placement of prosthetic or autologous or cadaveric biologic grafts. A high clinical suspicion remains critical in the timely diagnosis of radiation-related infectious and noninfectious complications.

Bacteremia

Most hematogenous bloodstream infections in adult neutropenic cancer patients are due to coagulase-negative *Staphylococcus*, viridans streptococci, *E. coli*, *Pseudomonas aeruginosa*, and *S. aureus* observed in prospective case-controlled study (24). In patients with solid-organ cancer, *E. coli* and coagulase-negative *Staphylococcus* account for nearly 40% of bacteremia, whereas *Pseudomonas*, *S. aureus*, and enterococcal bloodstream infections each account for 10% or less (25). *Klebsiella* species, other *Enterobacteriaceae*, and *S. maltophilia* are a serious concern and may become prominent bloodstream infections in certain geographic regions.

Cancer patients with bacteremia who present with extensive tissue involvement/infection are significantly less likely to respond to antimicrobial therapy (26). Other factors associated with poor prognosis in bacteremic adult patients with an underlying malignancy include shock, infection due to multidrug-resistant bacteria, and *Pseudomonas* and *Clostridium* species infection (26).

Bacteroides and *Clostridium* species are the most frequent cause of anaerobic bacteremia, which is most frequently seen in patients with abdominal and pelvic malignancy (26,27). In cancer patients with nonsporulating anaerobes bacteremia, *B. fragilis*, and *Fusobacterium* are isolated more frequently compared with *Peptostreptococcus* and *Eubacterium* species (28). Polymicrobial infections are more frequent in patients with anaerobic bacteremia compared with aerobic bacterial infections. *E. coli*, *Pseudomonas*, *Klebsiella* species, and among gram-positive cocci, *Streptococcus*, *Enterococcus*, and *Staphylococcus epidermidis* may accompany anaerobic bloodstream infection (28). Concurrent candidemia is uncommon in patients with bacteremia due to anaerobic bacteria, unless patients have (a) high *Candida* colonization index, (b) indwelling intravascular catheter, (c) are receiving care in critical care unit, or have (d) poorly controlled diabetes, (e) parenteral nutritional support, or (f) severe and prolonged treatment-induced neutropenia. Over 90% of patients with nonsporulating anaerobic bacteremia may also have a deep-tissue abscess (28). The authors suggest that all patients with gynecologic malignancy who present with anaerobic bacteremia be thoroughly evaluated for an infected abdominopelvic or pelvic collection, which may not be clinically apparent at the time of initial presentation.

Hematogenous *Clostridium* species infection is often seen in patients with gastrointestinal or genitourinary cancer, and acute leukemia (29). Nearly one-third of patients with bacteremia with *Clostridium* species alone and nearly half with polymicrobial infection present with septic shock (29). *Clostridium perfringens* is a common species, and *Clostridium septicum* is uncommon, albeit serious *C. septicum* infections are seen in patients with intra-abdominal neoplasms (29,30). Diffuse, rapidly spreading cellulitis involving the abdominal wall, groin, and upper thigh area, gas gangrene, and acute intravascular hemolysis indicate the possibility of clostridial infection (29). Early appropriate therapy remains critical in improved response and outcome for patients with deep-tissue anaerobic infection with or without accompanying bacteremia.

Febrile Neutropenia

The organisms associated with infections in patients with neutropenia are shown in Table 29.3. *Pseudomonas* spp. is a well-recognized cause of serious systemic infections in febrile neutropenic patients. The other nonfermentative gram-negative bacteria such as *S. maltophilia* have emerged and present as life-threatening pneumonia, bacteremia, or deep-tissue infection; these infections are commonly resistant to standard broad-spectrum antipseudomonal antibiotics, and despite appropriate therapy response may remain suboptimum (17). Patients with peripheral absolute blood neutrophil counts of less than 500 have significantly higher risk of serious infection, especially if the duration of neutropenia is more than 5 to 7 days (1,2). During the first 5 days of neutropenia, bacterial infections are prominent; if neutropenia extends beyond a week, invasive candidiasis becomes a concern; and in patients with greater than 2 weeks of profound neutropenia invasive mold infections such as aspergillosis may be occasionally encountered. In most patients with gynecologic malignancy, isolation of a mold even from sterile samples does not indicate invasive fungal disease; in patients with no known established predisposing factors (31), these saprophytic molds usually represent colonization or laboratory contamination (32).

Catheter-Related Bloodstream Infection

In patients with solid-organ cancer, nearly 70% of gram-positive bacteremias are associated with an infected indwelling vascular catheter; similarly, 60% of gram-negative bacteremias are also related to an infected catheter, whereas only 19% of

Table 29.3 Microorganisms Commonly Associated with Infection in Neutropenic Patients

Gram-Negative Organisms

Escherichia coli

Klebsiella spp.

Pseudomonas aeruginosa

Stenotrophomonas maltophilia

Enterobacter spp.

Gram-Positive Organisms

Staphylococcus spp. including vancomycin-tolerant organisms

Staphylococcus aureus

Coagulase-negative *Staphylococcus* such as *S. epidermidis* and *S. saprophyticus*

Beta-hemolytic streptococci, group A, B, G

α -Hemolytic streptococci (viridans streptococcus spp.)

Enterococcus spp. including vancomycin-resistant strains

Fungi^a

Candida spp. including *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*

^aPatients receiving multiple courses of fluconazole therapy or prolonged antifungal suppression or prophylaxis are at higher risk for infections due to drug-resistant *C. glabrata* and *C. krusei*.

gram-negative bacteremias in patients with hematologic cancer is due to an infected catheter (33). Coagulase-negative *Staphylococcus* remains the most commonly isolated microorganism in blood cultures drawn from an indwelling central venous catheter and is frequently regarded as catheter-related bloodstream infection. Similarly, *S. aureus*, including MRSA bacteremia, may result from an infected indwelling catheter, and successful therapy requires selection of antimicrobial agents that penetrate the biofilm and are effective against the sessile nongrowth stationary phase of the bacteria (34). *S. aureus* bloodstream infections are associated with high rates of complications (35). Patients with solid-organ cancer with catheter-related *S. aureus* bacteremia have a fivefold higher probability of developing intravascular complications such as septic thrombosis and less commonly infective endocarditis (35).

Patients with gynecologic malignancy have a higher rate of postoperative infection, catheter malfunction, and unplanned catheter removal following external intravascular catheters compared with subcutaneous/implantable venous access devices (36,37). Nearly one-third of all intravascular catheters were associated with delayed complications in this cancer population; bacteremia was significantly more common in patients with nonimplantable (Hickman catheters) compared with implantable indwelling intravenous devices such as infusaport or peripheral access system ports (38).

IMPLANTABLE DEVICE INFECTIONS

Peritoneal, hepatic, and pleural implantable devices for delivering chemotherapy or drainage of recurring malignant effusions have been successfully used in the last 2 decades. These devices are well tolerated; major complications including bowel perforation are uncommon, and serious infections are seen in less than 5% of cases (39–44). Overall, infections are seen in less than 20% of cases. While serious infections including pocket infections are seldom noticed, when infections such as these do occur, they should be treated aggressively, requiring prompt removal of the infected reservoir and appropriate systemic antimicrobial therapy (39). Abdominal pain and chemotherapy-related discomfort remain as the major problems with these chemotherapy infusion devices.

Urinary Tract Infection

Patients with gynecologic cancer have an increased risk for urinary tract infection. The factors that promote infections are listed in Table 29.4. Nearly one-third of patients, while undergoing pelvic radiotherapy for gynecologic cancer, may have symptoms of urinary tract infection at the onset of therapy or develop infection during the course of radiation therapy (45). Despite appropriate therapy, infections may recur and require several courses of antibiotic therapy (45). Patients who have undergone pelvic exenteration remain at increased risk for ascending urinary tract infection (14); recurrent pyelonephritis in these patients leads to an increased risk of scarring and permanent renal damage. Older patients with advanced gynecologic and urologic malignancies are also recently being considered for pelvic exenteration surgery (46). In these and other patients with lower renal reserves, a severe episode of pyelonephritis may precipitate irreversible renal failure prompting prolonged renal replacement therapy. We suggest that in selected high-risk patients, preemptive antimicrobial therapy or even secondary antibiotic prophylaxis be considered after an episode of urinary tract infection, especially pyelonephritis.

Table 29.4 Factors Promoting Urinary Tract Infections

Tumor Obstruction

Retrograde urine flow leading to ascending pyelonephritis

Stagnation in patients with outlet obstruction and abscess formation

Instrumentation

Cystoscopy-related introduction of pathogens

Dilatation of strictures

Foreign Body

Urethral stent

Percutaneous nephrostomy tube placement/replacement^a

Surgical drains for extended duration

Radiotherapy

Inflammation of bladder mucosa

Suppression of local innate cellular and a cellular immune response

Surgery

Urinary diversions

Organ resection

Lymph node dissection

Anastomotic leak

Chronic surgical wound breakdown

Chemotherapy

Neutropenia

Suppression of local immune surveillance and response to bacterial invasion

Mucosal damage and disruption

^a Patients undergoing routine replacement of percutaneous nephrostomy tubes may develop transient bacteremia in the event of prior colonization.

ANTIMICROBIAL AGENTS

It is important to refer to the spectrum of local and regional drug resistance among commonly encountered pathogens in selecting appropriate antimicrobials, especially when treatment is initiated empirically or in patients awaiting microbiologic drug susceptibility results.

SURGICAL ANTIMICROBIAL PROPHYLAXIS

Operative Site

Guidelines for the administration of antibiotics to uninfected patients undergoing pelvic surgical procedures were first proposed by Ledger et al. in 1975 (47). Prophylactic antibiotics are indicated for women undergoing pelvic surgery for malignancy. There have been few studies evaluating this prophylaxis

in such cases. Recently, cefazolin was showed to be inferior to cefotetan as a single-dose prophylaxis in women undergoing elective abdominal hysterectomy (48). A placebo-controlled trial showed that using a broad-spectrum cephalosporin plus beta-lactamase inhibitor significantly reduced the risk of major operation-site infection from 27% in patients not given antimicrobial prophylaxis, whereas none given antibiotic developed operative-site infection (49).

The overall postoperative infection rate has been as high as 46%, and surgical-site infection is seen in nearly one-fourth of patients (50). The risk of postoperative infection is adversely affected by prolonged duration of surgery for >5 hours, presence of remote infection at the time of surgery, and duration of hospitalization for longer than 3 weeks; in patients with all 3 risk factors the relative risk of infections increases to 7.3% compared with 3% in patients who have only one of these risk factors (50). Risk factors that have been associated with an increased incidence of infection in patients undergoing surgery for reproductive tract neoplasms include lower socioeconomic status, preoperative colonization, failure to administer perioperative heparin, obesity, advanced patient age, a longer operative period, and a longer hospital stay prior to surgery (51,52). Extent of surgery plays a central role in predicting probability and severity of postoperative infections (12–14,52). However, these risk factors were not uniform among investigators' evaluations.

Clinical Investigation

The overall operative-site infection rate ranges from 6.7% to 44%. Interestingly, patients with preoperative cervical colonization did not have an increase in postoperative complications including duration of hospitalization, operative time, or febrile episodes compared with patients in whom no cervical colonization was demonstrated (53). An overall decrease in significant postoperative infections was reported in retrospective studies among patients undergoing radical hysterectomy (54,55). The benefit, however, was thought to be associated only with reduced local wound infections (56).

Prospective data have not resolved this issue. Numbers of patients in comparative arms have been small, and the data may, therefore, be inadequate for detecting a statistically significant infection rate. Rosenshein et al. noted no significant difference in overall operative-site infection after preoperative prophylaxis (57), an observation shared by Marsden et al (58). In contrast, significantly lower incidences of infection following preoperative antimicrobial prophylaxis were reported by Sevin et al. (59) and Micha et al. (60). Sevin et al. reported that a short course (3 doses) of prophylaxis was as effective as a long course consisting of 12 doses in preventing major infection after radical hysterectomy (61). If separate operative-site data from prospective studies are combined, the overall incidence of pelvic infection and wound infection was significantly reduced by the administration of prophylactic antimicrobials.

A cost-benefit analysis of 3 doses of cefazolin antimicrobial prophylaxis showed a 29% reduction in infectious morbidity following vaginal hysterectomy and an 18% reduction in postoperative infections in patients following abdominal hysterectomy (62).

One patient population that has a significant surgical incision breakdown is that of women undergoing radical vulvectomy. Anecdotal experience indicates the principal pathogens to be *S. aureus* and *S. epidermidis*. The administration of broad-spectrum medications, such as piperacillin or mezlocillin, not unexpectedly, did not significantly reduce the incidence of postoperative wound infection; 8 of 12 women undergoing radical vulvectomy for vulvar carcinoma who were given single-dose piperacillin or mezlocillin developed postoperative infections

(63). We recommend *Staphylococcus* active drug should be considered for women undergoing radical or modified vulvectomy for vulvar carcinoma. Drain sites fall into the same category. The foreign body undoubtedly contributes to the infections; in our opinion, local attention, rather than parenteral or oral antibiotics, is the appropriate preventive approach.

AGENT ADMINISTRATION

Intravenous administration of antibiotics is recommended to achieve high serum and tissue drug concentration and should be given before anesthesia. Antibiotics administered to women undergoing hysterectomy for benign indications by suppository, by spray, and orally, with significant reduction in operative-site infection (64–66). There are no similar data for women undergoing hysterectomy for gynecologic cancer, and these routes of administration are presently not advised.

Timing of Drug Administration

The first dose of an antibiotic should be given intravenously in the operating room. Combination regimens and prolonged administration did not appear to offer superior infection prevention when compared with that provided by a single agent given once. If the interval between the first dose and opening the vagina exceeds 2.5 to 3 hours, a second intravenous dose should be given 15 to 30 minutes before the anticipated vaginal entry. This conclusion is based on data provided by Shapiro et al. (67). This has not been clinically studied, but administration at longer fixed intervals has not enhanced protection at hysterectomy for benign indications. In cancer patients who are expected to undergo a prolonged surgical procedure (>4 hours), the dose may be repeated after 4 to 6 hours.

Recommendations

Intravenous administration of 2 g cefazolin should be given in the operating room. Cefazolin provides activity against gram-negative and gram-positive aerobic and anaerobic bacteria; it is an uncommon therapeutic agent and is comparatively inexpensive—beneficial attributes for a prophylactic antibiotic. A single dose of a prophylactic agent did not result in the selection of a resistant species, as did 3 doses of antibiotics at hysterectomy for benign disease (68). A 1-g dose may suffice, but 2 g was superior to 1 g for vaginal hysterectomy, and three 1-g doses over 16 hours were statistically inferior to a single 2-g dose for cesarean delivery (69). A single dose (1 g) of cefotetan was significantly ($p < 0.05$) superior to 1 g of cefazolin in preventing operative-site infection after elective abdominal hysterectomy for benign diagnoses. The high drug acquisition cost was offset by an overall reduction in hospital costs owing to fewer infections and shorter hospital stays in patients given cefotetan compared with cefazolin (70). Kobamatsu et al. also found superior protection for women undergoing radical hysterectomy when using expanded-spectrum cephalosporins compared with first-generation agents (71). Other alternatives include ampicillin-sulbactam, although there is little evidence to support this practice; similarly, using metronidazole as a single agent may be less effective at preventing infection compared with broad-spectrum cephalosporin agents (72). More prospective data are necessary in patients with gynecologic cancer undergoing surgery.

If the patient is allergic to cephalosporins, or if she has a history of a type I immediate hypersensitivity reaction to a penicillin, and if she is not allergic to a tetracycline, the recommendation is 100 mg doxycycline orally at bedtime the night

before surgery and again the day of surgery about 3 hours before departure for the operating room. This regimen has been evaluated prospectively in Parkland Memorial Hospital, but in a nonrandomized study using very few patients and no control regimen. If the woman is allergic to tetracycline, the recommendation is intravenous administration of 900 mg of clindamycin given preoperatively, as for cefazolin. The new generation of fluoroquinolones such as moxifloxacin may be particularly suited for the gynecologic cancer patient scheduled for pelvic surgery because of its aerobic and anaerobic spectrum of antibacterial activity and extended drug half-life. Prospective, controlled studies are needed.

BOWEL PREPARATION

Unobstructed Bowel

There are approximately 10^{11} bacteria in a gram of feces, making sepsis a major hazard if the colon is opened. It is desirable to reduce the patient's normal colonic microflora to diminish the postoperative infection rate in case it is necessary to perform colonic resection and reanastomosis. Preparation for colonoscopy is a regimen of clear liquids the day before surgery and 3 tablespoons of Fleet Phospho-Soda in one-half cup of cold water at 4:00 PM and 6:00 PM the day before surgery. Patients should be cautioned to drink eight to ten 8-ounce glasses of clear liquids the day before surgery. Additional clear fluid is acceptable. Some surgeons prefer to add a Fleet enema 2 hours before surgery. An alternative mechanical preparation is whole gut irrigation with chilled polyethylene glycol and electrolyte therapy or a similar lavage solution given orally at a rate of approximately 1 L/hour until the rectal effluent is colorless, but for not more than 4 hours. A large cohort multicenter, recently randomized a trial, has placed routine mechanical bowel preparation practice into serious question; in patients who underwent elective colorectal surgery, no difference in anastomotic leak or other septic complications such as fascia dehiscence were noted in the group who had preoperative bowel preparation (73).

In the antimicrobial approach, 1 g each of erythromycin and neomycin is given orally at 1:00 PM, 2:00 PM, and 11:00 PM the day before surgery. This regimen was initially proposed in 1971 by Nichols and Condon (74). An alternative is 1 g each of metronidazole and neomycin at 2:00 PM and at 11:00 PM the day before surgery. There should be no need to add further antimicrobial prophylaxis to 2 g of cefazolin or other agents. Because this may alter hydration status and serum electrolytes, many administer intravenous fluids to patients undergoing mechanical bowel preparation (75).

Obstructed Bowel

There can be no mechanical prophylaxis for preoperative management of the obstructed bowel. Treatment principles include fluid and electrolyte therapy with mechanical decompression of the bowel from above and timed surgical intervention. Women with mechanical intestinal obstruction immediately after surgery may be able to be treated conservatively with decompression only. If necessary, surgery should be performed within 24 hours of the mechanical obstruction; these patients have the lowest mortality rate. A dose of intravenous antibiotic should be given in the operating room before the procedure, with a second dose given in the recovery room, and a third 8 hours later if it is necessary to enter the bowel lumen. The single-agent or combination regimen should provide broad coverage of both gram-positive and gram-negative aerobic and anaerobic bacterial species with a broader spectrum of antibacterial activity

than with cefazolin. Evaluation has produced no evidence for a superior regimen. A single agent usually suffices unless the patient is septic, in which case antibiotic combination is appropriate because therapy, not prophylaxis, is necessary.

CLINICAL SYNDROMES

Peritonitis and Intra-abdominal Abscess

Etiology

Infection in the patient with pelvic cancer most commonly involves the pelvis and abdomen. The potential causes of infection include complications of the primary tumor, surgery, and antineoplastic therapy including radiation and chemotherapy. The tumor can compromise the integrity of the vaginal wall and allow seeding of endogenous vaginal flora into the pelvic and peritoneal cavities. Previous antibiotics, radiation therapy, and the tumor itself may alter the normal genital flora. The tumor can also erode into the bowel and allow entry of fecal material into the peritoneal cavity. Rare cases of several other syndromes arising from untreated pelvic tumor, including spontaneous clostridial gas gangrene and pneumoperitoneum, have been reported (76,77). Peritonitis, with or without abscess formation, may occur postoperatively after hysterectomy or with bowel injury. Radiation therapy to the pelvis can cause radiation enteritis, leading to a chronic diarrheal syndrome, which may develop years after radiation therapy is completed. These patients are also at higher risk for bowel adhesions and subsequent obstruction, and subclinical perforation may present as late insidious intra-abdominal or deep pelvic abscess. Macro and micronutrient malabsorption in patients with chronic diarrheal state may enhance susceptibility for severe systemic infections and extenuate healing process.

Signs and Symptoms

In patients with pelvic cancer, peritonitis may develop at any time, including at initial diagnosis (e.g., tumor infiltration of bowel), immediately postoperatively, or days or weeks after surgery (e.g., tumor infiltration or radiation therapy). The signs are generally dramatic and familiar: abdominal pain, fever, and signs of peritoneal irritation. However, among postoperative patients or patients who have received radiation or corticosteroid therapy, the physical findings may resemble those of a routine postoperative patient, making the diagnosis more difficult. To ensure proper diagnosis, frequent physical examinations, and computed tomography scan should be obtained early in the course of the disease.

Abscess formation can also occur in several settings. In some patients, a subclinical microperforation of the bowel is successfully walled off by the body's immune system, forming a pericolic or intraperitoneal abscess. This has been shown to occur 7 to 10 days after microperforation (78). Fever or mechanical obstruction may be the only presenting sign. Subphrenic, psoas, or liver abscesses may present as a fever of unknown origin and may require a methodical, diligent evaluation for diagnosis. A fistula, usually caused by tumor but also occurring postoperatively, may form between any 2 organ systems, including the bladder, vagina, bowel, or skin. Persistent suppuration despite therapy or the presence of a feculent discharge from the skin, bladder, or vagina may suggest the development of a fistula.

Diagnosis

The diagnosis of peritonitis is usually made on clinical grounds. In patients who have clinical evidence of peritonitis but are

unable to undergo surgery because of bulky tumor, multiple prior surgeries, or general debility, paracentesis with appropriate cultures may be useful in guiding antibiotic therapy. Radiologic investigation is generally required to diagnose an abscess. Regular plain X-ray films of the abdomen are seldom revealing. A sonogram, computed tomographic (CT) scan, or magnetic resonance image (MRI) of the abdomen may show the collection (Figs. 29.7 and 29.8). A gallium scan may also be helpful. In a particularly confusing case in which abnormalities of scans can represent an abscess, metastatic tumor, or postoperative changes, a labeled leukocyte scan may be needed to diagnose the abscess with certainty; these scans are presently seldom used due to inconsistent results and several days to complete the process.

The diagnosis of a fistula requires demonstration of abnormal drainage from one organ system to another. This can be shown by intravenous or intravesical injection of dye for fistulae arising from the bladder, oral or rectal instillation of dye for those arising from the gastrointestinal tract, or a fistulogram for a fistula involving the skin (Fig. 29.9).

In all cases, laboratory abnormalities, including an elevated leukocyte count, reactive thrombocytosis, an elevated erythrocyte sedimentation rate, C-reactive protein and abnormal liver function tests, may suggest the diagnosis and direct the workup. The microbiologic diagnosis in each of these syndromes requires culture for aerobes and anaerobes. Blood cultures are only rarely positive. Some patients may have an unexplained bacteremia of enteric aerobic gram-negative rods or anaerobes. This is probably from a microperforation of the bowel. Any patient with pelvic tumor and enteric gram-negative rods or anaerobic bacteremia should be radiologically evaluated for evidence of perforation.

Therapy

Acute, generalized peritonitis where gastrointestinal perforation is suspected usually requires urgent surgery to irrigate the

peritoneum and repair any perforation. Broad-spectrum antibiotic coverage with agents such as cefoxitin, ticarcillin–clavulanic acid, piperacillin–tazobactam; metronidazole, clindamycin with ampicillin, and an aminoglycoside such as tobramycin or amikacin is generally effective for the polymicrobial infection. Addition of the aminoglycosides is particularly important for patients who have been recently or frequently hospitalized or who have had past courses of antibiotics. These situations predispose the patient to the development of resistant organisms.

Effective treatment of an abscess requires drainage. Percutaneous drainage is adequate in many cases, but laparotomy is occasionally required. Large or persistent abscesses may require placement of a suction drain. Patients with fistulae generally require resection of the involved tissue.

For intra-abdominal infection, intravenous antibiotics directed at the recovered bacteria should continue for at least 10 to 14 days after drainage. Some patients who have been on antibiotics may have evidence of pus but no growth on cultures. In this situation, broad-spectrum antibiotics directed at enteric gram-negative rods and anaerobes should be administered.



FIGURE 29.7. A 58-year-old woman with metastatic ovarian cancer presents with fever, abdominal pain, and elevated white blood cell count. Coronal contrast enhanced CT scan shows multiple loculated fluid collections in the abdomen and pelvis (*) with central displacement of small bowel loops. There is thickening and enhancement of the peritoneal reflection (arrows). These findings could be seen with either peritoneal carcinomatosis or peritonitis. Aspiration of the fluid was compatible with infection and peritonitis.

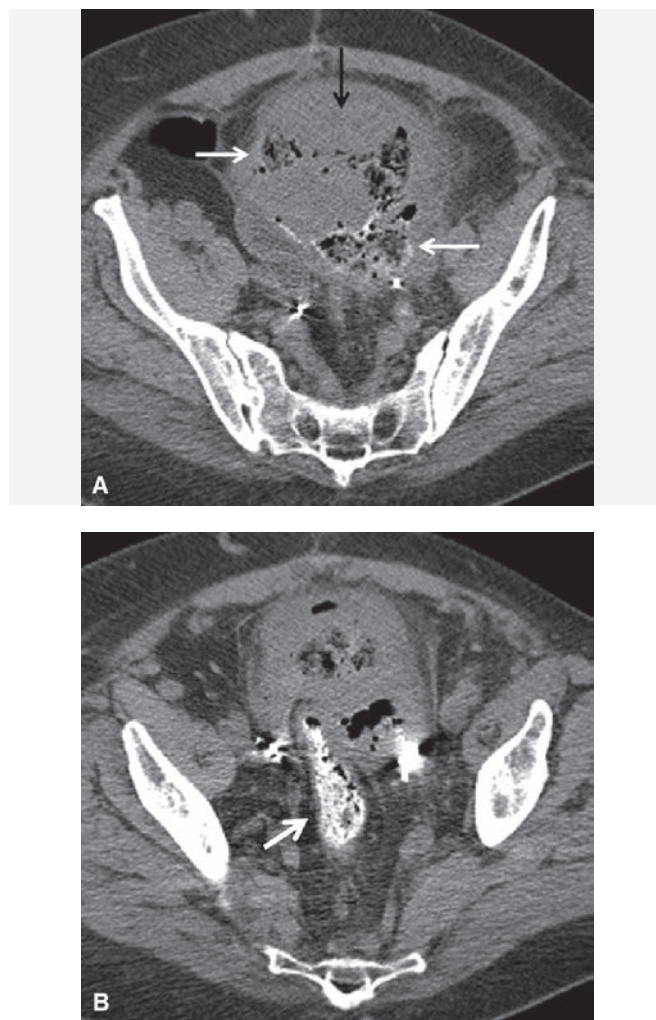


FIGURE 29.8. A 65-year-old woman with recurrent cervical cancer and fistula tract with the rectum. **A:** Axial CT image performed with enteric contrast shows the large recurrent mass in the midline pelvis (black arrow). There are mottled collections of gas and enteric contrast present within this mass (white arrows) suggesting fistulization with bowel. **B:** Slightly more inferior image demonstrates the contrast-filled rectum (arrow) partially encased by the mass. This was the site of fistulization.



FIGURE 29.9. A 61-year-old woman with recurrent fallopian tube carcinoma and carcinomatosis status post exploratory laparotomy, partial small bowel resection with draining anterior abdominal wall wound. Axial CT scan performed with enteric and IV contrast demonstrates a loop of small bowel adherent to the anterior abdominal wall with enteric contrast-containing tract within the abdominal wall soft tissues (black arrows). There is a contrast-containing collection in the overlying subcutaneous soft tissues. These findings are compatible with enterocutaneous fistula. Additional intraperitoneal abscess is noted (white arrow).

Laboratory parameters such as leukocyte counts should be followed to determine the exact duration.

Patients who are inoperable can be treated with chronic suppressive therapy, intravenously or orally. Oral agents such as amoxicillin-clavulanic acid (875 mg bid) or clindamycin (450 mg q 6 to 8 hours) may be effective. Ciprofloxacin, moxifloxacin, or levofloxacin alone should not be used in this situation because they provide limited coverage for *Enterococcus* species.

Patients with infections due to vancomycin-resistant enterococci and/or vancomycin-tolerant (79) *Streptococcus* or *Staphylococcus* species may be treated with daptomycin (6 mg/kg daily) or linezolid (600 mg twice daily), usually in combination with drugs with gram-negative and anaerobic activity. Tigecycline may also be used as an alternative; it has broad spectrum antimicrobial activity including promising *in vitro* results against multidrug-resistant bacteria such as extended-spectrum beta-lactamase positive *E. coli*, multidrug-resistant *Acinetobacter*, *S. maltophilia*, carbapenemases producing *K. pneumoniae*, vancomycin-resistant enterococci, and multidrug-resistant *S. aureus*. There is limited clinical data for its use in patients with gynecologic malignancy, and due to poor activity against *Pseudomonas* species it should be used cautiously in neutropenic patients and those with prior invasive *Pseudomonas* infection or known bacterial colonization. Furthermore, emergence of drug-resistant bacteria or selection of less-susceptible organisms remains a concern for widespread use of drugs with broad-spectrum antimicrobial coverage. Similarly, antipseudomonal carbapenems such as imipenem-cilastatin and meropenem should also be reserved for seriously ill patients with polymicrobial infection, as emergence and spread of multidrug-resistant gram-negative bacteria are increasing in immunosuppressed cancer patients (80). Ertapenem, a carbapenem without antipseudomonal activity, was as effective as piperacillin-tazobactam for the treatment of acute pelvic infection (81), and can be administered as a single daily dose, albeit due to lack of enterococcal coverage it is important to select patients carefully.

Urinary Tract Infection

Etiology

Many clinical situations predispose a patient to urinary tract infection. Urinary tract infection continues to be the leading cause of infectious morbidity in this population. One study showed that half of the patients with pelvic cancer admitted to the hospital because of infection had a urinary tract infection; *E. coli* was the most common organism isolated (82). Another report found that the frequency of urinary tract infections is increased as much as threefold in patients undergoing pelvic irradiation (20–22). Many patients who undergo pelvic surgery require prolonged bladder catheterization, usually with a Foley catheter. These patients may develop well-recognized infectious complications of chronic bladder catheterization, the most common of which is recurrent infection. In addition, tumor can cause urinary obstruction and subsequent infection. The role of antiseptic or antibiotic-impregnated urinary catheters has not yet been defined.

Signs and Symptoms

Some patients with gynecologic malignancy and urinary tract infection have the familiar clinical picture of dysuria, fever, flank or suprapubic tenderness, elevated leukocyte count, and abnormal urinalysis. In many others, these signs and symptoms are obscured by the rest of the clinical picture. For instance, a postoperative patient may be expected to have abdominal tenderness, an elevated leukocyte count, and fever. The physician should consider the entire clinical setting before embarking on a course of therapy.

Diagnosis

Diagnosis is generally made on the basis of a urine culture, from a “clean catch” or through a catheter, but the initial urinalysis is extremely helpful. Pyuria is expected in any nongranulocytopenic patient with a urinary tract infection. Gram stain of urinary sediment can direct antibiotic therapy in advance of the culture results. A common problem confronting the physician is when patients, especially those with indwelling catheters or nephrostomy tubes, have positive urine cultures but do not appear to be ill. Differentiating colonization from invasive infection is frequently not simple and requires clinical judgment. Any patient who is not severely neutropenic should also have pyuria along with positive urine cultures. The absence of pyuria in a patient with a positive urine culture suggests the likelihood of simple asymptomatic bacteriuria. From a practical standpoint, in a clinically stable patient, it is reasonable to withhold antibiotics pending repeated urinalysis and urine culture. If an organism persists, therapy may be considered.

Therapy

Therapy should be based on the sensitivity pattern of the recovered organism, and intravenous antibiotics are reserved for patients with drug-resistant bacteria and those with systemic infection, ascending infection, or pyelonephritis. Optimum duration of therapy in a patient with a urethral stent or a permanent indwelling catheter is often difficult to determine. It is virtually impossible to eradicate an infection in the presence of a foreign body, and removal of the foreign object is highly desirable, however, removal is not always feasible. A patient with a urinary tract infection and a foreign body in the urinary collecting system should be considered for chronic suppressive therapy if she has recurrent infection. In general, among patients with gram-negative rods, chronic suppressive therapy may include ampicillin, trimethoprim-sulfamethoxazole, doxycycline, or

an oral fluoroquinolone such as ciprofloxacin. Patients with a chronic enterococcal infection may benefit from chronic suppressive therapy with amoxicillin–clavulanic acid (Augmentin) or amoxicillin alone or doxycycline.

In patients with pyuria and fever in whom a urinary tract infection is suspected, empiric antibiotic therapy should be given pending urine culture results. Gram stain of urinary sediment may be helpful in directing treatment. However, for those cases in which Gram stain is not helpful, broad-spectrum coverage should be given. For a patient who has had frequent or prolonged hospitalizations, effective coverage of potentially resistant gram-negative rods dictates that 2 drugs be given, preferably a beta-lactam and an aminoglycoside. Cefazolin (1 to 2 g IV, q 8 hours) and gentamicin (4 to 5 mg/kg per day IV in 3 divided doses) is a good empiric combination for many patients. For more debilitated patients or those with prolonged hospitalizations and frequent past courses of antibiotics, advanced generation cephalosporin, such as ceftazidime (1 to 2 g IV, q 8 hours) or ceftepime (1 gram IV, q 8 hours) should be substituted for cefazolin. After culture results are known, antibiotics can be adjusted and the spectrum narrowed. For any gynecologic cancer patient with an unexplained predisposition to recurrent urinary tract infection, a full investigation should be undertaken to exclude obstruction from tumor as the cause.

Wound Infections

There are important variables that influence the development of wound infection after surgery. These include hospital flora, patient microflora, operative technique and variables, patient nutritional status, and competency of innate and adaptive immune function. Women being treated for reproductive tract cancer may be at risk because of specific problems with immunocompetency, possible prior chemotherapy or radiotherapy, poor nutritional status, hypoproteinemia, economically disadvantaged, or advanced cancer-associated catabolic state. Additional risk factors for incisional infection include obesity, inadequately controlled diabetes, and systemic corticosteroid use. Surgical variables include operative procedures in excess of 4 hours, breaks in surgical technique, capacious incision at the operative site, excessive cautery, passive drains, shaving of the area in which the incision is made immediately before surgery, and placement and types of sutures. Infections may range from a mild cellulitis to a devastating fasciitis, deep infection with myonecrosis, and mixed anaerobic–aerobic synergistic abdominopelvic gangrene (83).

Cellulitis

Etiology

Cellulitis is a relatively frequent occurrence. The presence of a foreign body in a wound is an unavoidable risk factor in many cases, but this variable should be removed or reduced as much as possible. Devitalized tissue, especially fat, can also act as a foreign body. Excess cautery causes thermal injury; the charred tissue may act as a foreign body. The presence of significant amounts of devitalized tissue usually produces a wound defect. A mechanical wound retractor can cause fat necrosis, and there appears to be only minimal ability to resorb these areas during wound healing. These areas should be carefully identified and excised before closing the wound. If drains are used, they should be closed, and drains should be vacuumed. Drains should not exit through the wound but rather through an adjacent puncture site, and they should be removed as early as possible. *S. aureus* is recovered from 50% or more of wound infections. If the operative procedure involves transection of the vagina, the

infections may harbor other species of normal flora of the lower reproductive tract, such as gram-positive and gram-negative anaerobes and *Enterobacteriaceae*. Cellulitis of the leg occurs with increased frequency in patients after vulvectomy (84). The affected leg is not always edematous. Group B beta-hemolytic streptococci are frequently recovered. Prophylactic therapy with oral penicillin may reduce recurrences in some patients (84). Increased prevalence of penicillinases among clinical streptococcal isolates cautions against penicillin preparation without beta-lactamase inhibitor.

Signs and Symptoms

Cellulitis is almost uniformly associated with pain and erythema in the incisional margins, with an increase in local skin and tissue temperature, and many times with fever. Incisions are usually tender at examination. Incisional cellulitis may not become evident until the fourth postoperative day or later.

Diagnosis

The infected surgical incision should be explored. This can frequently be performed at the bedside. Opposing skin edges in such incisions are usually separated without difficulty and may expose underlying purulent material, seromas, hematomas, or any combination of these. The wound should be explored thoroughly, and if the wound shows unusual features, aerobic and anaerobic cultures should be obtained. Foreign bodies such as sutures or drains should be removed, and obviously necrotic areas should adequately debrided. It is important to document deep fascial integrity. If this cannot be done at the bedside, it should be performed in the operating room.

Therapy

The wound should be packed open with fine-mesh gauze approximated to the incisional margins and changed with each dressing change. The dressing is changed 2 to 4 times daily; avoiding harsh chemical and repeat mechanical debridement in the absence of necrotic tissue. Commonly used solutions are hydrogen peroxide, acetic acid, and Dakin's solution (0.25% sodium hypochlorite). In general, these debriding solutions should be removed from the wound with sterile normal saline before packing because they may impede healing. Except in unusual instances, it is unnecessary to administer parenteral antimicrobials. These incisions may be left open to heal by secondary intent, or they may be closed before discharge from the hospital after the margins exhibit healthy viable granulation tissue. The optimal time for secondary closure is about the fourth day after institution of wound therapy. Studies have shown that normal wound healing occurs as long as the hematocrit exceeds 17%, but then a lower level will impede healing (85).

Necrotizing Fasciitis

Necrotizing fasciitis is a potentially life-threatening infection of the soft tissues above deep fascia that can involve the abdominal wall or vulva with extension to the proximal thighs and buttocks (85). There are several descriptive names for this infection, such as beta-hemolytic streptococcal gangrene, hospital gangrene, gram-negative anaerobic cutaneous gangrene, non-clostridial gas gangrene, gangrenous erysipelas, or synergistic necrotizing cellulitis, but the name used by most is that coined by Wilson in 1952, that is, necrotizing fasciitis (86). This significant infection has been reported in patients with endometrial cancer following irradiation and hysterectomy (87–89). It has also been found in endopelvic fascia, in a suprapubic catheter

site during chemotherapy, in the vulva in diabetes, and after diagnostic laparoscopy (90–95).

Etiology

Bacteria recovered from necrotizing fasciitis infected sites include anaerobes, particularly *Peptostreptococcus*, *Prevotella*, and *Bacteroides* species, as well as *E. faecalis*, *S. aureus*, and *Enterobacteriaceae*. These bacteria produce large quantities of proteolytic and other enzymes and toxins that allow rapid spread to contiguous tissues. Superficial vessels are occluded, depriving the affected areas of oxygen, other nutrients, and antibiotics. This deprivation interferes with bacterial eradication. Patients at particularly high risk of developing this infection include women older than 50 years of age and those with arteriosclerotic heart disease, diabetes, or other chronic diseases.

Signs and Symptoms

Early in the course of necrotizing fasciitis, the signs and symptoms are those of any wound cellulitis. Because there is no response to the usual methods of therapy, antibiotic therapy will frequently be initiated. The infection, however, seems to smolder initially, then rapidly progresses to involve the wound and to produce clinical sepsis. Mortality rates for this infection have been as high as 76%. The degree of disease evident on the skin is only a small fraction of the total amount of tissue that is involved because the skin is not the primary area of infection. Hallmarks of this infection include the presence of severe pain in contrast to scant physical findings, edema and superficial crepitance may be present. The skin overlying the affected area becomes blue or brown as the disease progresses, and there may be formation of bullae. Edema progresses, and there may be seepage of grayish fluid from the skin and does not bleed if cut. Lack of familiarity with this infection and failure to recognize its signs may delay diagnosis. Even when recognized and treated early, there is a high mortality rate.

Diagnosis

Diagnostic criteria as first outlined by Fisher et al. (96) include the following:

1. Extensive necrosis of the superficial fascia with widespread undermining of surrounding tissue
2. A moderate to severe systemic toxic reaction
3. Absence of muscle involvement
4. Failure to demonstrate *Clostridium* species in the wound or blood cultures
5. Absence of major vascular occlusion
6. Histologic demonstration of intense leukocytic infiltration, focal necrosis of the superficial fascia and surrounding tissues, and microvascular thrombosis

Early diagnosis followed as soon as possible by appropriate treatment produces the highest cure rate. Radiologic evaluation, particularly with MRI, may confirm the diagnosis rapidly, and should be ordered whenever the disease is suspected. The average interval between diagnosis and initiation of treatment is approximately 5 days. If the interval is 4 days or less, survival rates are high, but an interval of 7 days or more is more likely to result in patient death because even intense antimicrobial therapy is rarely successful at this late stage.

Therapy

Although the administration of broad-spectrum antimicrobials is important, wide and often disfiguring surgical debridement is the treatment required for preservation of life. The excision must extend to areas that bleed. Adjunctive therapy with whirlpool

baths and perhaps hyperbaric oxygen may be considered early in the course of the disease.

Clostridial Myonecrosis

Clostridial myonecrosis (gas gangrene) was described by Altmeier (97). It is an infection that occurs in muscle and adjacent tissues beneath the deep fascia and is seen most commonly after trauma. However, it can be seen after intra-abdominal surgery or surgery in an area that has been contaminated by feces. Mortality rates are about 25%, and poor-prognosis factors are leukopenia, advanced age, renal failure, and intravascular hemolysis.

Etiology

Clostridial myonecrosis is caused by *C. perfringens* (80% to 95%), *C. novyi* (10% to 40%), or *C. septicum* (5% to 20%). It is usually seen in association with gastrointestinal mucosal ulceration or perforation because *Clostridium* species are normal inhabitants of the gastrointestinal tract. *C. perfringens* may be isolated from as many as 20% of the women with upper genital tract infections not involving sexually transmitted diseases. The mere presence of *C. perfringens* in a wound does not mean that the patient will develop gas gangrene; it develops in only 1% to 2% of wounds in which that species can be isolated.

Signs and Symptoms

Early signs and symptoms of clostridial myonecrosis are tense edema in tissue that is extremely tender and pain that rapidly intensifies. If an incision is open, it is not uncommon to see a swollen, herniated muscle. There is frequently a serosanguinous, dirty discharge that has many gram-positive or gram-variable rods but few leukocytes. There may also be gas bubbles, and the secretions have a particularly sweet, offensive odor. The surrounding tissue frequently has crepitus. The skin becomes red to green-purple and then turns yellow before becoming a characteristic bronze color. The usual incubation period is about 2 to 3 days, but it can be as short as 6 hours. With progression of the infection, the patient becomes obviously ill, pale, and sweaty, with increased pulse rate and decreased blood pressure. Temperature is usually elevated, but hypothermia and shock may occur early in the course of the illness.

Diagnosis

A positive wound culture may accompany the characteristic signs and symptoms of clostridial myonecrosis. X-ray films of the affected area frequently show gas deep in the tissues. Blood cultures grow clostridia in approximately 15% of the cases. It is common to find a decrease in hemoglobin and an increase in circulating leukocytes. Involved muscle is pale and edematous, with loss of elasticity, and it does not bleed or contract with stimulation. Histologic findings demonstrate coagulation necrosis of muscle fibers.

Therapy

Clostridial myonecrosis is another infection that requires prompt and extensive debridement in the operating room. Cultures must be performed, and because clostridia may develop plasmid-mediated antibiotic resistance, repeated cultures with sensitivity testing may be required if a patient is slow to respond. In addition to wide debridement, the treatment of choice is penicillin G at a dose of 1 to 2 million units every 2 to 3 hours. Gram stain also may indicate the presence of gram-negative bacteria, in which case, coverage should be provided for those bacteria

as well. Chloramphenicol is as effective against *Clostridium* species as it is against many gram-negative species, although seldom used due to potentially life-threatening drug toxicity. Metronidazole, imipenem, or clindamycin, all of which having good *in vitro* activity against *C. perfringens*, may be considered. Other antibiotics with good *in vitro* activity include tetracycline, erythromycin, and rifampin. Hyperbaric oxygen may be adjunctive, but its efficacy is uncertain.

Intraperitoneal Catheter Infections

Etiology

Delivery of chemotherapeutic agents through an intraperitoneal catheter has enabled physicians to deliver high concentrations of drug locally while decreasing systemic side effects (42,98). However, intraperitoneal catheters can become infected at the exit site, along the catheter tunnel, or secondary peritonitis may occur in rare cases. *S. epidermidis* is the most common organism followed by *S. aureus* and *Streptococcus* species. Gram-negative bacilli and anaerobes, presumably from the bowel, are also found, especially in patients with polymicrobial infections. Patients who have been treated for bacterial peritonitis in the past may develop peritonitis due to *Candida* species.

Signs and Symptoms

With exit-site or tunnel infections, patients report discomfort at the site. Patients with peritonitis may complain of diffuse abdominal pain, with or without a change in bowel pattern. Fever may be absent in peritonitis, making the diagnosis more difficult because many patients with pelvic tumor have abdominal pain. On examination, patients with exit-site or tunnel infections have redness and sometimes have discharge where the catheter has been inserted. Patients with peritonitis have tenderness and frequently have abdominal rebound.

Diagnosis

Diagnosis of exit-site and tunnel infections is made clinically, with support from a Gram stain and culture of any discharge. Patients with suspected peritonitis should have withdrawal of peritoneal fluid for cell count and microbiologic evaluation. A rough guideline, derived from experience among patients receiving continuous ambulatory peritoneal dialysis, is that any leukocyte count in peritoneal fluid >100 cells/mm³ suggests infection. Gram stain and culture should reveal the specific organism. Chemical peritonitis after instillation of chemotherapy can mimic infectious peritonitis. Peritoneal fluid cultures are often not helpful in distinguishing between infectious versus chemical peritonitis, especially in infections due to a fastidious organism. Use of biomarkers such as C-reactive protein or procalcitonin remains uncertain.

Therapy

For patients with peritonitis, systemic therapy is advised according to the recovered organisms. Treatment should be continued for 10 days or longer, with serial peritoneal fluid cell counts guiding therapy. The peritoneum provides a large absorptive surface, and antibiotics delivered intraperitoneally readily enter the intravascular space; however, we suggest that intraperitoneal antibiotic therapy should be reserved for patients with serious, treatment-refractory infection. Treatment of fungal peritonitis is a unique problem. Amphotericin B can cause adhesions if delivered intraperitoneally. Echinocandins such as micafungin and caspofungin appear to be the treatment of choice for patients with intra-abdominal and peritoneal candidiasis (99). Fluconazole, which can be administered orally or intravenously, was shown in

one study of patients receiving continuous ambulatory peritoneal dialysis to effectively treat *C. albicans* peritonitis and should be avoided in patients with *Candida glabrata* and *Candida krusei* infection (100). Fluconazole may be used for long-term therapy in patients with *Candida* peritonitis who have responded to initial aggressive therapy with micafungin (100 mg IV daily) or caspofungin (70 mg $\times$ 1 IV followed by 50 mg IV daily).

Septic Pelvic Thrombophlebitis

Septic pelvic thrombophlebitis, also known as suppurative pelvic thrombophlebitis, is a disorder that has been diagnosed most frequently after antimicrobial therapy for pelvic infection after cesarean section or septic abortion, but it can be seen as a complication of infection after any type of pelvic surgery. The mortality rate observed in 1917 was 52% after surgical therapy (101). Fortunately, this complication of pelvic infection is now very rare. The use of antimicrobial prophylaxis and the enhanced antibacterial activity of current therapeutic regimens are presumed to be paramount in the disappearance of this potentially lethal infection.

Etiology

Septic pelvic thrombophlebitis is clot formation in the pelvic veins as a result of infection. It can be seen after hysterectomy, other pelvic operative procedures including brachytherapy, and in association with pelvic trauma or perirectal abscess. Classically, there is relative venous stasis before phlebitis that develops adjacent to pelvic infection. The intimal lining of the veins is invaded by bacteria, including *Enterobacteriaceae*, especially *E. coli*, aerobic and anaerobic streptococci, and *Bacteroides*. The veins involved may be the ovarian, hypogastric, or uterine, with essentially equal involvement in the right and left sides. If common iliac veins are involved, clot formation is more frequently seen on the left for unknown reasons. Infected clot may embolize to the lungs, kidneys, liver, brain, and spleen.

Signs and Symptoms

A clinical diagnosis may not be readily evident. Presentation is essentially that of a fever of unknown cause, and the physician must rule out infections such as pyelonephritis, pneumonia, and pelvic or abdominal abscess. The most frequent presentation currently seen is persistence of fever associated with tachycardia after clinical response to antimicrobial therapy for a pelvic infection. Physical examination is normal in most instances, but it may be possible to palpate tender cords in the vaginal fornices. In patients with bacteremia and septic emboli, chills are observed in as many as 67% of the patients, pyrexia may be elevated to 41°C, and the variations in temperature may be quite hectic. Dyspnea, tachypnea, pleuritic pain, cough, hemoptysis, restlessness, anxiety, and perhaps angina may all be seen with septic embolization.

Diagnosis

Compatible clinical presentation and CT or MRI scan are used for diagnosis (102). Criteria for diagnosis of venous thrombosis using CT studies include enlargement of the involved vein(s), sharply defined vessel walls enhanced by contrast media, and a low-density intraluminal mass (103). Diagnosis using MRI is based on intense intraluminal signals from clot in involved veins and a lack of signal with normal blood flow in uninvolved vessels; no contrast agent is needed. Blood culture should be performed if there is suspicion of septicemia. Tests for blood gases, a chest radiograph, and IV contrast enhanced chest CT scan or in patients with contraindication to IV contrast use, a

ventilation-perfusion scan may be performed to assess pulmonary embolization. A gallium scintiscan may be necessary to identify very small septic embolic foci in the lungs.

Therapy

Early treatment of venous thrombosis was surgical (101). The first to advocate the use of anticoagulants in addition to antibiotics were Schulman and Zatuchni (104). In some cases, antibiotics alone may be adequate and can be used in patients in whom anticoagulation can be detrimental (105). In the largest published study of heparin therapy, the mean time to become afebrile was 2.5 days, and the average duration of heparin therapy was 8 days (106,107). It is unnecessary to initiate warfarin sodium (Coumadin) therapy in patients without evidence of emboli. Thromboembolism during or after treatment with heparin has not been reported. Antibiotic therapy must be continued. If there is significant improvement in the pulse rate and temperature pattern within 12 to 48 hours after addition of heparin, reassessment is mandatory. Treatment with low-molecular-weight heparin has not been studied or standardized for this condition (108). Heparin therapy is not without complications. Between 2% and 5% of patients may have an allergic reaction; bleeding occurs in 7% to 10% of patients; and the most devastating effect is the development of the “white clot syndrome” (109). This occurs in <1% of patients, but it may be associated with major limb amputation in 20% of those suffering from it, and death has been reported in nearly half of these patients. This phenomenon is a paradoxical arterial platelet aggregation associated with thrombocytopenia, and it should be suspected in patients with decreasing platelet counts or an increasing requirement of heparin to maintain adequate anticoagulation. The only current indications for surgical intervention are embolization during heparin therapy or lack of response. The usual intervention is placement of a vena cava filter, which is a procedure usually performed by an interventional radiologist.

Neutropenia and Fever

Etiology

Patients with severe neutropenia are at particularly high risk for severe morbidity and mortality unless empiric intravenous antibiotic therapy is instituted at the first evidence of fever or clinical worsening. Most commonly, the febrile neutropenic patient does not have an obvious source of fever. Even in those with bacteremia, the source is rarely clinically evident. Bacteria often enter the bloodstream through the gastrointestinal tract because of the small chemotherapy-induced disruption of the intestinal mucosa and the accompanying neutropenia and thrombocytopenia. Neutropenic patients may also develop a clinically diagnosed group of infections, including pneumonia and cellulitis. Neutropenic patients with these clinically diagnosed infections may progress very rapidly, may have exceedingly subtle clinical signs and symptoms, and always require early, aggressive therapy of their infections to achieve a response.

Signs and Symptoms

Fever is often the only complaint of patients with neutropenia and bacteremia. Patients receiving chemotherapy should be instructed to take their own temperature at home twice a day (more frequently if a subjective feeling of fever develops) and to contact their treating physician for temperatures above 38.0°C, or 100.4°F.

Diagnosis

Diagnosis is made by blood culture. Of all febrile, neutropenic patients from whom blood cultures are obtained, only 10%

to 20% have an organism isolated. The others probably have enough organisms to cause fever and systemic illness, but an insufficient burden of microorganisms to be cultivated using current standard culture-based techniques. Coagulase-negative *Staphylococcus*, *S. aureus*, streptococci, *E. coli*, *Klebsiella* species, and *Pseudomonas* species are frequently isolated bacteria (110). In a recent report of 2,142 patients with febrile neutropenia, 499 (23%) patients developed bacteremia due to gram-positive bacteria (57%), gram-negative bacteria (34%) and polymicrobial infection was seen in 10% (111). Mortality rates were lowest (5%) in patients with gram-positive infection followed by 18% with gram-negative bacteremia, and they were 13% in patients in whom polymicrobial bloodstream infection was diagnosed (111). Polymicrobial infections are often underreported, and neutropenic patients with intestinal and genitourinary tract mucosal damage have a higher risk of systemic infection due to multiple microorganisms (7).

Therapy

The Infectious Disease Society of America (IDSA) updates guidelines for management of the patients with fever and neutropenia. Full consideration of this complex topic is beyond the scope of this chapter (112). In general, a febrile neutropenic patient should receive antibiotics with activity against *P. aeruginosa* pending results of blood cultures. Numerous regimens are effective, and their use should be determined according to sensitivity patterns for *P. aeruginosa* at a given hospital. In general, good results have been achieved with a beta-lactam antibiotic plus beta-lactamase inhibitor such as ticarcillin-clavulanic acid, piperacillin-tazobactam, or a third-generation cephalosporin such as ceftazidime or cefepime, or a carbapenem such as imipenem or meropenem with or without an aminoglycoside. Monitoring peak and trough levels of aminoglycosides is recommended to maintain drug levels in optimum therapeutic range and to mitigate drug-induced ototoxicity and nephrotoxicity. The choice of the specific aminoglycoside (e.g., tobramycin, amikacin) is dictated by the sensitivity patterns in a given hospital. Once-daily dosing of aminoglycosides is not recommended for the neutropenic patient but can be given in other settings. The length of therapy for neutropenic patients is determined by many factors and must be individualized. Patients with prolonged neutropenia and fever should be followed by an infectious disease specialist.

Fungal Infections

Etiology

Patients with pelvic cancer may be at risk for the development of fungal infections, particularly those caused by *Candida* species, including *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* (113). Infection may include fungemia, pelvic abscess, or infected urinary stents in patients with extensive pelvic disease and urinary outflow obstruction. Risk factors for the development of invasive candidiasis include prolonged courses (7 to 10 days) of intravenous broad-spectrum antibiotics; an intravenous catheter, particularly a central venous catheter; major abdominal surgery; treatment-induced severe neutropenia for longer than a week, and immunosuppressive therapy, especially with corticosteroids. Patient with enteric or colonic fistula or bowel perforation have an increased risk for tissue invasive candidiasis (114).

Signs and Symptoms

Patients with the appropriate risk factors who have unexplained fevers may be fungemic. Other than fevers, which can include rigors and hypotension and closely resemble bacteremia, there may be no other symptoms. Blood cultures are positive in only

50% of the patients with autopsy-proven disseminated candidiasis. Any blood culture positive for yeast should be considered to be significant. A full evaluation for a hidden source should be completed, including a thorough reevaluation with history and physical examination, and appropriate laboratory tests that include repeat blood cultures. It is imperative to perform an expert ophthalmoscopic examination for possible *Candida* vitritis, retinitis/retinal abscesses or endophthalmitis should be performed in all patients with presumed, probable or definite fungemia, since this complication may occur in up to 5% to 15% of patients with fungemia (115).

Presence of multiple body-site *Candida* species colonization proportionally increases the risk for invasive candidiasis including fungemia and acute disseminated candidiasis (116). *Candida* species may cause urinary tract infection in a patient with such indwelling devices as a Foley catheter, internal stents, or percutaneous nephrostomies. Rarely a “fungus ball,” consisting of a matted mass of yeast, may cause urinary tract obstruction. *Candida* species invasive lung disease is exceedingly rare and may occasionally be seen in critically ill and in high-risk patients at intensive care unit or patients with refractory relapsed acute leukemia and prolonged severe neutropenia. Thus, recovery of any yeast from a respiratory specimen should be considered to be most likely due to oropharyngeal contamination of lower respiratory tract culture. Unlike patients with leukemia and recipients of allogeneic hematopoietic stem cell transplantation, in patients with gynecologic malignancy invasive mold disease is exceedingly rare. Identification of filamentous fungi, such as *Aspergillus*, should be approached with caution and mold-active drug therapy reserved for highly immunosuppressed patients with clinical and radiographic features suggestive of invasive aspergillosis in this patient population (117).

Diagnosis

The diagnosis of a fungal infection is often difficult. The physician must differentiate between invasive disease, which must be treated, and colonization, which does not require systemic antifungal therapy. The recovery of fungi from a urine, sputum, or wound culture does not necessarily mean that the fungus is pathogenic, and clinical judgment must be used to determine if a patient requires therapy. In general, cultures from sterile sites (e.g., blood, cerebrospinal fluid, pleural or peritoneal fluid) should be considered to represent invasive infection until a full evaluation is done. Also, *Candida* recovered from the initial specimen of drainage from an obstructed biliary or urinary tract should be considered to be potentially associated with invasive fungal disease.

With most specimens, however, the distinction between colonization and infection is not so simple. For urine, the presence or absence of pyuria is the simplest and most reliable means of differentiation. Those without pyuria are very likely only colonized and need no therapy. In such patients, a repeat urinalysis and culture may clarify the situation. Recently approved fungal antigen assays including serum beta D glucan and galactomannan have provided much needed diagnostic sensitive and specificity in select group of patients with high risk for invasive fungal disease (118).

Therapy

Treatment options for invasive candidiasis have expanded in recent years. Amphotericin B has the longest record for treatment of invasive fungal infections (113). The optimal duration of therapy for candidemia is not well-defined and should be determined by individual responses. However, a 7- to 14-day course of therapy is probably adequate for most episodes (113).

Since the introduction of fluconazole in 1990, the option for invasive candidiasis, severe drug toxicity associated with amphotericin B is observed less and less (113,119). Echinocandins such as caspofungin (70-mg load and then 50 daily IV) showed

comparable response in patients with invasive candidiasis versus patients randomized to receive amphotericin B (99). In a large prospective trial, comparing first 2 available echinocandins showed 75% efficacy for micafungin compared with 70% in patients treated with caspofungin at the end of antifungal therapy; there were also nonsignificant higher responses among patients with *Candida* peritonitis (67% vs. 40%) and deep tissue abscesses (100% vs. 67%) in micafungin group versus caspofungin, respectively (120). These new class of drugs offer comparable effectiveness but have fewer side effects than the amphotericin B products.

Patients who have *Candida* species consistently cultured from urine but no evidence of systemic fungal infection may benefit from bladder irrigation with amphotericin B, which reduces or eradicates bladder yeast colonization, and may prevent invasive fungal infection. Fluconazole is increasingly being given for this indication and appears to be effective.

Pneumonia

Etiology

Postoperative pneumonia remains a common cause of fever in any surgical patient, including those with gynecologic cancer. Infection may occur from aspiration during intubation or extubation or from hypoventilation due to “splinting” in patients with severe postoperative pain. Postobstructive pneumonia may occur in patients with tumor metastatic to the lungs. In addition, pneumonia may occur in patients with chemotherapy-induced neutropenia.

Signs and Symptoms

The familiar signs and symptoms of pneumonia are cough, fever, chest discomfort, and dyspnea and evidence of pulmonary consolidation on lung examination.

Diagnosis

The diagnosis is usually suggested by the clinical situation and by the findings on physical examination. These are further supported by chest radiographs and sputum examination and culture. Chest radiography may show consolidation (Fig. 29.7). Gram-negative organisms predominate in the mouth flora of hospitalized patients, so an aspiration pneumonia occurring in a hospitalized patient is typically due to gram-negative rods. Although thought by many to be a substantial contributor, anaerobes seldom isolated in hospitalized patients with aspiration pneumonia.

Therapy

Empiric, rather than pathogen-directed, coverage of patient following major surgical procedure with clinical pneumonia is usually necessary and varies according to the setting (121). For a patient who has been hospitalized less than 3 days and has had no other recent hospitalizations or recent courses of oral or intravenous antibiotics, single-drug therapy with levofloxacin or moxifloxacin is adequate (121). For the patient who has been hospitalized for a longer period or who has recently received broad-spectrum antibiotics (increasing the likelihood of infection due to multi-drug resistant organisms), *P. aeruginosa* should be covered by the addition of an aminoglycoside such as gentamicin or tobramycin (3 to 5 mg/kg per day in 3 divided doses), and a beta-lactam should be selected to cover the usual isolates in that hospital. *S. maltophilia* is now increasingly seen in cancer patients without traditional risk factors such as severe neutropenia, prolonged stay in critical care units, or mechanical ventilation (122). Treatment includes high-dose trimethoprim-sulfamethoxazole (15 mg/kg in 3 to 4 divided doses) in combination with a second drug to which the bacteria are susceptible

(17). Patients with *S. aureus* pulmonary infection may present with rapid clinical deterioration and necrotizing pneumonia due to MRSA is often seen as complication following a recent influenza virus like illness; the postviral bacterial infections are especially serious superinfections and require urgent, appropriate antibiotic therapy. Vancomycin (1 g twice daily) or linezolid (600 mg every 12 hours) may be given in patients with lobar or multifocal pneumonia and history of recent influenza-like illness. Therapy for patients with pneumonia should extend up to 10 to 14 days depending on (a) clinical response, (b) concurrent bacteremia, (c) presence of empyema or complicated parapneumonic effusion, or (d) secondary hematogenous foci of infection dissemination. Various professional societies have codified recommendations for pneumonia management (123).

GASTROENTEROLOGIC SOURCES OF INFECTION

Diarrhea Associated with Antibiotics or Chemotherapy

Etiology

Diarrhea is a common finding in patients undergoing treatment of gynecologic malignancy. In a study of 351 hospitalized women with gynecologic cancer in 1980s, 12% developed diarrhea during the course of their hospital stay (Fig. 29.11); 10% had diarrhea due to *Clostridium difficile* (124). In cancer patients, *C. difficile* associated diarrhea (CDAD) is most commonly as a result following exposure to broad-spectrum antibiotics or in some cases chemotherapy alone (124,125).

Signs and Symptoms

Antibiotic-associated diarrhea can occur at any time during an antibiotic course and for at least a month after discontinuation. Patients typically develop abdominal pain, fever, and frequent watery diarrhea defined as ≥ 3 unformed bowel movements in 24 hours lasting for ≥ 2 days; however, CDAD may sometimes cause abdominal pain and fever without diarrhea.

Diagnosis

Any patient with antibiotic-, radiation-, or chemotherapy-associated diarrhea should have a full evaluation of stool, including routine cultures and antitoxin immunoassays or nucleic acid amplification tests (126). CT scans may be helpful in localizing areas of bowel inflammation, especially in the prior radiation field (Fig. 29.10). In patients with a highly suspicious clinical and radiographic presentation but no evidence of *C. difficile* toxin in stool, sigmoidoscopy or colonoscopy may reveal intense mucosal ulceration and inflammation, and the pathognomonic pseudomembranes are observed in small number of cases with advanced disease. CT scan may not be able to differentiate between chemotherapy associated versus diffuse bowel edema in patients with CDAD (Figs. 29.11 and 29.12). One study has suggested that evaluation of stool for *C. difficile* toxin is the only cost-effective test (124). A markedly elevated white blood cell count may also be a clue to diagnosis (127). In a recent retrospective study from a tertiary care cancer center, PCR increased the yield of *C. difficile* cases by twofold compared to that of the standard cytotoxic assay (128). Currently, in most secondary and tertiary care medical centers, nucleic acid amplification assay have largely replaced the less sensitive immunoassays.

Therapy

Oral therapy with metronidazole (250 mg to 500 mg 4 times daily for 2 to 4 weeks) is adequate to treat most cases of



FIGURE 29.10. A 56-year-old woman with cervical cancer being treated with radiation therapy presented with pelvic pain. Axial CT performed with enteric and IV contrast demonstrates mural thickening of small bowel loop in the lower pelvis (arrow) secondary to radiation enteritis.



FIGURE 29.11. A 57-year-old woman with recurrent ovarian cancer treated with chemotherapy. Coronal CT imaged performed with enteric and IV contrast demonstrates abnormal small bowel loops in the right lower quadrant (arrows). The bowel wall is thickened with submucosal edema and mucosal hyperenhancement compatible with enteritis.

antibiotic-associated diarrhea (125–127). Because of continued reports of vancomycin-resistant bacteria (129), the use of oral vancomycin is restricted in many hospitals. However, response to metronidazole has been compromised in part with the emergence and spread of hypervirulent North American Pulsed Field type 1 (NAP1) *C. difficile* strains in the United States and Europe (130). Most institutions are currently following IDSA guidelines for moderate and severe CDAD, oral vancomycin should be given to only patients with strong suspicion or proven CDAD and those who have not responded to metronidazole mild *C. difficile* associated illness. Some patients may require repeated or prolonged courses of metronidazole or oral vancomycin particularly if their clinical course necessitates continuation of the provocative agent (i.e., continued antibiotics or chemotherapy). Antidiarrheal compounds such as Lomotil® or Imodium® should not be

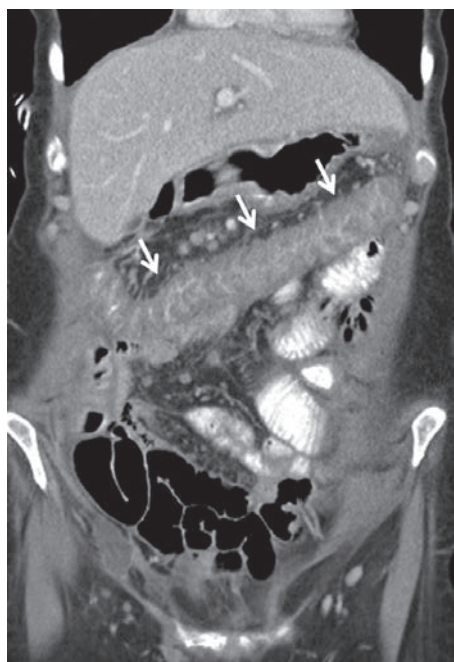


FIGURE 29.12. A 67-year-old woman with *Clostridium difficile* colitis. The patient had a history of recurrent ovarian cancer with associated sigmoid colon obstruction. She underwent sigmoid resection and diverting colostomy and a long course of antibiotics and developed abdominal pain, fever and diarrhea. Coronal CT performed with enteric and IV contrast demonstrates mural thickening of the colon with mucosal hyperenhancement, compatible with colitis. *C. difficile* titers were positive.

given routinely. If, however, diarrhea persists after appropriate tests and cultures, symptomatic therapy should be considered. Nitazoxanide is a nitrothiazolide and effectively treats intestinal infestation of *Cryptosporidium* and *Giardia* species; at low concentrations, nitazoxanide also inhibits *C. difficile*. A recent trial showed that nitazoxanide 500 mg twice daily was as effective in eradicating *C. difficile* as metronidazole given 250 mg 4 times daily (131). Nitazoxanide may be used for patients with metronidazole-refractory or recurrent *C. difficile* colitis although in our experience clinical efficacy of nitazoxanide in patient who had failed first-line anti CDI drugs remains less favorable. In a recent trial fidaxomicin (200 mg twice daily) or vancomycin (125 mg 4 times daily) orally for 10 days was assessed for clinical response and early relapses (132). The overall response was comparable for both treatment groups; patients treated with fidaxomicin had significantly lower rate of recurrence of *C. difficile* infection associated with non-NAP1 (nonvirulent) strains (132). Currently, this option is being used in patient with relapsed CDAD or those with high risk for relapsed infection.

Noninfectious Causes of Fever

Not all patients with gynecologic malignancy and fever have an infection. Pulmonary embolus, drug-related fever, and

tumor-related fever represent the main noninfectious sources of fever, but others, such as factitious fever and underlying collagen vascular disorder, autoimmune disorders and foreign-body type hypersensitivity reaction must also be considered. The use of biologic markers such as procalcitonin (PCT) and neopterin levels has been suggested to help distinguish between infectious versus noninfectious causes of fever, although further studies are needed to validate these tests prior to routine clinical use (133). Similarly, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) along with PCT have been suggested to improve recognition of patients with true infection and may facilitate decisions of whether or not to start empiric antimicrobial therapy (134). Unfortunately, neither PCT nor sTREM-1 by itself has shown consistent in differentiating infectious conditions versus tumor or treatment related febrile response. However, it is postulated that combination of systemic PCT and local and/or systemic sTREM-1 or CRP and/or neopterin may provide distinguishing patients with infection from those with noninfectious illness. Results from several randomized intervention studies on PCT-guided antimicrobial therapy in sepsis or pneumonia show PCT may aid in clinical decision making (134,135). At present, randomized trial to assess role of select biomarker panel including PCT, neopterin, and sTREM-1 are lacking.

Pulmonary embolus should be considered in a bed-bound or postoperative patient with any combination of fever, chest pain, dyspnea, or an abnormal chest radiograph. Patients with bulky pelvic tumors are also at risk. A high level of suspicion is important, and spiral intravenous contrast-enhanced chest CT scans or ventilation-perfusion scans may establish the diagnosis; in rare instances, a more definite pulmonary angiogram may be performed. Therapy remains anticoagulation with low-molecular-weight heparin. For patients who are unable to tolerate these drugs or who continue to have pulmonary emboli despite therapy, inferior vena caval filters are required.

Many drugs including antibiotics may cause fever (136). Patients typically develop fever and a diffuse maculopapular rash after several days of therapy. Eosinophilia, although a helpful sign, is usually lacking. Mild elevations in liver function tests may be present though nonspecific. Atypical presentations of drug fever, including patients without rash or those who develop fever weeks into therapy or after completion of therapy, can also occur. The diagnosis is usually made by discontinuing the antibiotic and observing the patient. It is important to remember that some drug fevers may take as long as a week to resolve. Supportive measures, such as antipyretics and antipruritics, may decrease symptoms.

The diagnosis of tumor fever can be made only after systematic exclusion of all other potential causes of fever. Most patients with tumor fever have metastatic disease involving the liver or lung. In these patients, the fever may be as high as 40°C, and chills may be absent; when not febrile, these patients often feel relatively well. In patients suspected of having tumor fever, a clinical trial of broad-spectrum antibiotics is given. If the fever does not abate and no other clear infection source is evident, the likelihood of tumor fever increases. Nonsteroidal anti-inflammatory agents such as naprosyn often produce an immediate and sustained response when administered to patients with tumor fever. This should only be done after infectious causes of fever have essentially been excluded, and a trial of broad spectrum antibiotic therapy has not resulted in defervescence.

REFERENCES

1. Safdar A, Armstrong D. Infections in patients with neoplastic diseases. In: Grenvik M, Ayers SM, Holbrook PR, et al. eds. *Textbook of Critical Care*. 4th ed. Philadelphia, PA: WB Saunders; 2000:715–726.
2. Safdar A, Armstrong D. Infectious morbidity in critically ill patients with cancer. *Crit Care Clin*. 2001;17:531–570.
3. Gilstrap LC, Gibbs RS, Michel TJ, et al. Genital aerobic bacterial flora of women receiving radiotherapy for gynecologic malignancy. *Gynecol Oncol*. 1986;23:35–39.
4. Gordon AN, Martens M, LaPread Y, et al. Response of lower genital tract flora to external pelvic irradiation. *Gynecol Oncol*. 1989;35:233–235.

5. Talwar P, Chakrabarti A, Patel F, et al. Yeasts at different mucosal sites in patients with carcinoma cervix before and following radiotherapy. *J Hyg Epidemiol Microbiol Immunol.* 1992;36:311–316.
6. Evaldson G, Heimdahl A, Kager L, et al. The normal human anaerobic microflora. *Scand J Infect Dis.* 1982;35:9–15.
7. Rolston KVI, Bodey GP, Safdar A. Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. *Clin Infect Dis.* 2007;45:228–233.
8. Barton DPJ, Fiorica JV, Hoffman MS, et al. Cervical cancer and tubo-ovarian abscesses: a report of three cases. *J Reprod Med.* 1993;38:561–564.
9. Imachi M, Tanaka S, Ishikawa S, et al. Spontaneous perforation of pyometra presenting as generalized peritonitis in a patient with cervical cancer. *Gynecol Oncol.* 1993;50:384–388.
10. Protopappas AG, Diakomanolis ES, Milingos SD, et al. Tubo-ovarian abscess in postmenopausal women: gynecologic malignancy until proven otherwise. *Eur J Obstet Gynecol Reprod Biol.* 2004;114:203–209.
11. Inagaki J, Rodriguez V, Bodey GP. Causes of death in cancer patients. *Cancer.* 1974;33:568–573.
12. Iatrakis G, Sakellaropoulos G, Georgoulas N, et al. Gynecologic cancer and surgical infectious morbidity. *Clin Exp Obstet Gynecol.* 1998;25:36–37.
13. Chang HK, Lo KY, Chiang HS. Complications of urinary diversion after pelvic exenteration for gynecologic malignancy. *Int Urogynecol J.* 2000;11:358–360.
14. Wydra D, Emerich J, Sawicki S, et al. Major complications following exenteration in cases of pelvic malignancies: a 10-year experience. *World J Gastroenterol.* 2006;12:1115–1119.
15. Matar MJ, Safdar A, Rolston KV. Relationship of colonization with vancomycin-resistant enterococci and risk of systemic infection in patients with cancer. *Clin Infect Dis.* 2006;42:1506–1507.
16. Gould N, Kamelle S, Tillmanns T, et al. Predictors of complications after inguinal lymphadenopathy. *Gynecol Oncol.* 2001;82:329–332.
17. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis.* 2007;45:1602–1609.
18. Safdar A, Rodriguez GH, Balakrishnan M, et al. Changing trends in etiology of bacteremia in patients with cancer. *Eur J Clin Microbiol Infect Dis.* 2006;25:522–526.
19. Han XY, Kamana M, Rolston KV. Viridans streptococci isolated by culture from blood of cancer patients: clinical and microbiologic analysis of 50 cases. *J Clin Microbiol.* 2006;44:160–165.
20. Green JA, Kirwan JM, Tierney JF. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix. *Lancet.* 2001;385:781–786.
21. Yessaian A, Magistris A, Burger RA, et al. Radical hysterectomy followed by tailored postoperative therapy in the treatment of stage 1B2 cervical cancer: feasibility and indications for adjuvant therapy. *Gynecol Oncol.* 2004;94:61–66.
22. Jurado M, Martinez-Monge R, Garcia-Foncillas J, et al. Pilot study of concurrent cisplatin, 5-fluorouracil, and external beam radiotherapy prior to radical surgery ± intraoperative electron beam radiotherapy in locally advanced cervical cancer. *Gynecol Oncol.* 1999;74:30–37.
23. Micha JP, Goldstein BH, Rettenmaier MA, et al. Pelvic radiation necrosis and osteomyelitis following chemoradiation for advanced stage vulvar and cervical carcinoma. *Gynecol Oncol.* 2006;101:349–352.
24. Wisplinghoff H, Cornely OA, Moser S, et al. Outcomes of nosocomial bloodstream infections in adult neutropenic patients: a prospective cohort and matched case-control study. *Infect Control Hosp Epidemiol.* 2003;24:905–911.
25. Anadoliotaki A, Valatas V, Mantadakis E, et al. Bloodstream infections in patients with solid tumors: associated factors, microbial spectrum and outcome. *Infection.* 2004;32:65–71.
26. Elting LS, Rubenstein EB, Rolston KV, et al. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis.* 1997;25:247–259.
27. Zahar JR, Farhat H, Chachaty E, et al. Incidence and clinical significance of anaerobic bacteremia in cancer patients: a 6-year retrospective study. *Clin Microbiol Infect.* 2005;11:724–729.
28. Fainstein V, Elting LS, Bodey GP. Bacteremia caused by non-sporulating anaerobes in cancer patients—a 12-year experience. *Medicine (Baltimore).* 1989;68:151–162.
29. Bodey GP, Rodriguez S, Fainstein V, et al. Clostridial bacteremia in cancer patients—a 12-year experience. *Cancer.* 1991;67:1928–1942.
30. Pelletier JP, Plumbley JA, Rouse EA, et al. The role of *Clostridium septicum* in paraneoplastic sepsis. *Arch Pathol Lab Med.* 2000;124:353–356.
31. Safdar A. Strategies to enhance immune function in hematopoietic transplantation recipients who have fungal infections. *Bone Marrow Transplant.* 2006;38:327–337.
32. Safdar A, Singhal S, Mehta J. Clinical significance of non-*Candida* fungal blood isolation in patients undergoing high-risk allogeneic hematopoietic stem cell transplantation (1993–2001). *Cancer.* 2004;100:2456–2461.
33. Raad I, Hachem R, Hanna H, et al. Sources and outcome of bloodstream infections in cancer patients: the role of central venous catheters. *Eur J Clin Microbiol Infect Dis.* 2007;26:549–556.
34. Raad I, Hanna H, Jiang Y, et al. Comparative activities of daptomycin, Linezolid, and tigecycline against catheter-related methicillin-resistant *Staphylococcus* bacteremic isolates embedded in biofilm. *Antimicrob Agents Chemother.* 2007;51:1656–1660.
35. Ghanem GA, Boktour M, Warneke C, et al. Catheter-related *Staphylococcus aureus* bacteremia in cancer patients: high rate of complications with therapeutic implications. *Medicine (Baltimore).* 2007;86:54–60.
36. Estes JM, Rocconi R, Straughn JM, et al. Complications of indwelling venous access devices in patients with gynecologic malignancies. *Gynecol Oncol.* 2003;91:591–595.
37. Silver DF, Hempling RE, Recio FO, et al. Complications related to indwelling caval catheters on a gynecologic oncology service. *Gynecol Oncol.* 1998;70:329–333.
38. Minassian VA, Sood AK, Lowe P, et al. Long-term central venous access in gynecologic cancer patients. *J Am Coll Surg.* 2000;191:403–409.
39. Roybal JJ, Feliberti EC, Rouse L, et al. Pump removal in infected patients with hepatic chemotherapy pumps: when is it necessary? *Am Surg.* 2006;72:880–884.
40. Strecker EP, Heber R, Boos I, et al. Preliminary experience with locoregional intraarterial chemotherapy of uterine cervical or endometrial cancer using the peripheral implantable port system (PIPS): a feasibility study. *Cardiovasc Intervent Radiol.* 2003;26:118–122.
41. Shoji T, Tanaka F, Yanagihara K, et al. Phase II study of repeated intrapleural chemotherapy using implantable access system for management of malignant pleural effusion. *Chest.* 2002;121:821–824.
42. Sakuragi N, Nakajima A, Nomura E, et al. Complications related to intraperitoneal administration of cisplatin or carboplatin for ovarian carcinoma. *Gynecol Oncol.* 2000;79:420–423.
43. Driesen P, Boutin C, Viallat JR, et al. Implantable access system for prolonged intrapleural immunotherapy. *Eur Respir J.* 1994;7:1889–1892.
44. Adachi S, Noda T, Ito K, et al. Complications associated with CDDP intraperitoneal chemotherapy. *Asia Oceania J Obstet Gynaecol.* 1994;20:7–12.
45. Prasad KN, Pradhan S, Datta NR. Urinary tract infection in patients of gynecologic malignancies undergoing external pelvic radiotherapy. *Gynecol Oncol.* 1995;57:380–382.
46. Roos EJ, Van Eijkeren MA, Boon TA, et al. Pelvic exenteration as treatment of recurrent or advanced gynecologic and urologic cancer. *Int J Gynecol Cancer.* 2005;15:624–629.
47. Ledger WJ, Gee C, Lewis WP. Guidelines for antibiotic prophylaxis in gynecology. *Am J Obstet Gynecol.* 1975;121:1038–1045.
48. Hemsell DL, Johnson ER, Hemsell PG, et al. Cefazolin is inferior to cefotetan as single-dose prophylaxis for women undergoing elective total abdominal hysterectomy. *Clin Infect Dis.* 1995;20:677–684.
49. Hemsell DL, Bernstein SG, Bawdon RE, et al. Preventing major operative site infection after radical abdominal hysterectomy and pelvic lymphadenectomy. *Gynecol Oncol.* 1989;35:55–60.
50. Velasco E, Thuler LC, Martins CA, et al. Risk factors for infectious complications after abdominal surgery for malignant disease. *Am J Infect Control.* 1996;24:1–6.
51. Brooker DC, Savage JE, Twigg LB, et al. Infectious morbidity in gynecologic cancer. *Am J Obstet Gynecol.* 1987;156:513–520.
52. Morgan LS, Daly JW, Monif GR. Infectious morbidity associated with pelvic exenteration. *Gynecol Oncol.* 1980;10:318–328.
53. Orr JW Jr, Shingleton HM, Hatch KD, et al. Correlation of perioperative morbidity and colonization to radical hysterectomy interval. *Obstet Gynecol.* 1982;59:726–731.
54. Berkeley AS, Orr JW, Cavanagh D, et al. Comparative effectiveness and safety of cefotetan and cefoxitin as prophylactic agents in patients undergoing abdominal or vaginal hysterectomy. *Am J Surg.* 1988;155:81–85.
55. Mann WJ Jr, Orr JW, Shingleton HM, et al. Perioperative influences on infectious morbidity in radical hysterectomy. *Gynecol Oncol.* 1981;11:207–212.
56. Gussman D, Riva J, Carlson JA Jr. Prophylaxis for radical hysterectomy. *Infect Surg.* 1987;6:55.
57. Rosenshein NB, Ruth JC, Villar J, et al. A prospective randomized study of doxycycline as a prophylactic antibiotic in patients undergoing radical hysterectomy. *Gynecol Oncol.* 1983;15:201–206.
58. Marsden DE, Cavanagh D, Wisniewski BJ, et al. Factors affecting the incidence of infectious morbidity after radical hysterectomy. *Am J Obstet Gynecol.* 1985;152:817–821.
59. Sevin BU, Ramos R, Lichtinger M, et al. Antibiotic prevention of infections complicating radical abdominal hysterectomy. *Obstet Gynecol.* 1984;64:539–545.
60. Micha JP, Kucera PR, Birkett JP, et al. Prophylactic mezlocillin in radical hysterectomy. *Obstet Gynecol.* 1987;69:251–254.
61. Sevin BU, Ramos R, Gerhardt RT, et al. Comparative efficacy of short-term versus long-term

- cefoxitin prophylaxis against postoperative infection after radical hysterectomy: a prospective study. *Obstet Gynecol.* 1991;77:729–734.
62. Shapiro M, Schoenbaum SC, Tager IB, et al. Benefit-cost analysis of antimicrobial prophylaxis in abdominal and vaginal hysterectomy. *JAMA.* 1983;249:1290–1294.
63. van Lindert AC, Giltaij AR, Derksen MD, et al. Single-dose prophylaxis with broad-spectrum penicillins (piperacillin and mezlocillin) in gynecologic oncological surgery, with observation on serum and tissue concentrations. *Eur J Obstet Gynecol Reprod Biol.* 1990;36:137–145.
64. Van Eyk N, van Schalkwyk J. Infectious Diseases Committee. Antibiotic prophylaxis in gynecologic procedures. *J Obstet Gynaecol Can.* 2012;34:382–391.
65. Turner S. The effect of penicillin vaginal suppositories on morbidity in vaginal hysterectomy and on the vaginal flora. *Am J Obstet Gynecol.* 1950;60:806–812.
66. Wright VC, Lanning MN, Natale R. Use of a topical antibiotic spray in vaginal surgery. *Can Med Assoc J.* 1978;118:1395–1398.
67. Shapiro M, Munoz A, Tager IB, et al. Risk factors for infection at the operative site after abdominal or vaginal hysterectomy. *N Engl J Med.* 1982;307:1661–1666.
68. Hemsell DL, Heard MC, Hemsell PG, et al. Alterations in lower reproductive tract flora after single-dose piperacillin and triple-dose cefoxitin at vaginal and abdominal hysterectomy. *Obstet Gynecol.* 1988;72:875–880.
69. Hemsell DL, Bawdon RE, Hemsell PG, et al. Single-dose cephalosporin for prevention of major pelvic infection after vaginal hysterectomy: cefazolin versus cefoxitin versus cefotaxime. *Am J Obstet Gynecol.* 1987;156:1201–1205.
70. Hemsell DL, Johnson ER, Hemsell PG, et al. Cefazolin inferior to cefotetan for single-dose prophylaxis in women undergoing hysterectomy. *Clin Infect Dis.* 1995;20:677–684.
71. Kobamatsu Y, Makinoda S, Yamada T, et al. Evaluation of the improvement of cepheps on the prophylaxis of pelvic infection after radical hysterectomy. *Gynecol Obstet Invest.* 1991;32:102–106.
72. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis.* 2006;43:322–330.
73. Contant CM, Hop WC, van't Sant HP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicenter randomized trial. *Lancet.* 2008;370:2112–2117.
74. Nichols RL, Condon RE. Preoperative preparation of the colon. *Surg Gynecol Obstet.* 1971;132:323–337.
75. Lichtenstein GR, Cohen LB, Uribarri J. Review article: bowel preparation for colonoscopy—the importance of adequate hydration. *Aliment Pharmacol Ther.* 2007;26:633–641.
76. Braverman J, Adachi A, Lev-Gur M, et al. Spontaneous clostridia gas gangrene of uterus associated with endometrial malignancy. *Am J Obstet Gynecol.* 1987;156:1205–1207.
77. Douvier S, Nabholz JM, Friedman S, et al. Infectious pneumoperitoneum as an uncommon presentation of endometrial carcinoma: report of two cases. *Gynecol Oncol.* 1989;33:392–394.
78. Weinstein WM, Onderdonk AB, Bartlett JG, et al. Experimental intra-abdominal abscesses in rats: development of an experimental model. *Infect Immun.* 1974;10:1250–1255.
79. Safdar A, Rolston KV. Vancomycin tolerance, a potential mechanism for refractory gram-positive bacteremia observational study in patients with cancer. *Cancer.* 2006;106:1815–1820.
80. Ohmagari N, Hanna H, Graviss L, et al. Risk factors for infections with multidrug-resistant *Pseudomonas aeruginosa* in patients with cancer. *Cancer.* 2005;104:205–212.
81. Roy S, Higuera I, Angel-Muller E, et al. Ertapenem once a day versus piperacillin-tazobactam every 6 hours for treatment of acute pelvic infections: a prospective, multicenter, randomized, double-blind study. *Infect Dis Obstet Gynecol.* 2003;11:27–37.
82. McNeeley SG Jr, Hopkins MP, Ehlerova B, et al. Infection on a gynecologic oncology service. *Gynecol Oncol.* 1990;37:183–187.
83. Henderson W. Synergistic bacterial gangrene abdominal hysterectomy. *Obstet Gynecol.* 1977;49(suppl. 1):24–27.
84. Bouma J, Dankert J. Recurrent acute leg cellulitis in patients after radical vulvectomy. *Gynecol Oncol.* 1988;29:50–57.
85. Hunt TK, Rabkin J, von Smitten K. Effects of edema and anemia on wound healing and infection. *Curr Stud Hematol Blood Transfus.* 1986;53:101–113.
86. Bahary CM, Joel-Cohen SJ, Neri A. Necrotizing fasciitis. *Obstet Gynecol.* 1977;50:633–637.
87. Wilson B. Necrotizing fasciitis. *Am Surg.* 1952;18:416–431.
88. Daly JW, King CR, Monif GR. Progressive necrotizing wound infections in postirradiated patients. *Obstet Gynecol.* 1978;52(Suppl.):5S–8S.
89. Husseinadeh N, Nahhas WA, Manders EK, et al. Spontaneous occurrence of synergistic bacterial gangrene following external pelvic irradiation. *Obstet Gynecol.* 1984;63:859–862.
90. Bearman DM, Livengood CH 3rd, Addison WA. Necrotizing fasciitis arising from a suprapubic catheter site. A case report. *J Reprod Med.* 1988;33:411–413.
91. Hoffman MS, Turnquist D. Necrotizing fasciitis of the vulva during chemotherapy. *Obstet Gynecol.* 1989;74:483–484.
92. Roberts DB. Necrotizing fasciitis of the vulva. *Am J Obstet Gynecol.* 1987;157:568–571.
93. Prun SC. Acute necrotizing fasciitis of the endopelvic fascia. *Obstet Gynecol.* 1978;52(suppl.):25–45.
94. Sotrel G, Hirsch E, Edelin KC. Necrotizing fasciitis following diagnostic laparoscopy. *Obstet Gynecol.* 1983;62(suppl. 3):67S–69S.
95. McNeeley SG Jr, Hendrix SL, Bennett SM, et al. Synthetic graft placement in the treatment of fascial dehiscence with necrosis and infection. *Am J Obstet Gynecol.* 1998;179:1430–1434.
96. Fisher JR, Conway MJ, Takeshita RT, et al. Necrotizing fasciitis. Importance of roentgenographic studies for soft-tissue gas. *JAMA.* 1979;241:803–806.
97. Altmeier WA. Gas gangrene. *Surg Gynecol Obstet.* 1947;84:504.
98. Fujiwara K, Sakuragi N, Suzuki S, et al. First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up. *Gynecol Oncol.* 2003;90:637–643.
99. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med.* 2002;347:2020–2029.
100. Blot SI, Vandewoude KH, Waele JJ. *Candida* peritonitis. *Curr Opin Crit Care.* 2007;13:195–199.
101. Miller C. Ligation or excision of the pelvic veins in the treatment of puerperal pyaemia. *Surg Gynecol Obstet.* 1917;25:431.
102. Twickler DM, et al. Imaging of puerperal septic thrombophlebitis: prospective comparison of MR imaging, CT, and sonography. *AJR Am J Roentgenol.* 1997;169:1039–1043.
103. Zerhouni EA, Barth KH, Siegelman SS. Demonstration of venous thrombosis by computed tomography. *AJR Am J Roentgenol.* 1980;134:753–758.
104. Schulman H, Zatuchni G. Pelvic thrombophlebitis in the puerperal and postoperative gynecology patient. Obscure fever as an indication for anticoagulant therapy. *Am J Obstet Gynecol.* 1964;90:1293–1296.
105. Twickler DM, Senaiwan AT, Evans RS, et al. Imaging of puerperal septic thrombophlebitis: prospective comparison of MR imaging, CT, and sonography. *AJR Am J Roentgenol.* 1997;169:1039–1043.
106. Josey WE, Staggers SR Jr. Heparin therapy in septic pelvic thrombophlebitis: a study of 46 cases. *Am J Obstet Gynecol.* 1974;120:228–233.
107. Brown CE, Stettler RW, Twickler D, et al. Puerperal septic pelvic thrombophlebitis: incidence and response to heparin therapy. *Am J Obstet Gynecol.* 1999;181:143–148.
108. Lee AY, et al. Low-molecular-weight heparin versus a coumadin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349:146–153.
109. Stanton PE Jr, Evans JR, Lefemine AA, et al. White clot syndrome. *South Med J.* 1988;81:616–620.
110. Raad II, Escalante C, Hachem RY, et al. Treatment of febrile neutropenic patients with cancer who require hospitalization. A prospective randomized study comparing imipenem and cefepime. *Cancer.* 2003;98:1039–1047.
111. Klastersky J, Ameye L, Maertens J, et al. Bacteremia in febrile neutropenic cancer patients. *Int J Antimicrob Agents.* 2007;30(suppl. 1):51–59.
112. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52:427–431.
113. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. *Clin Infect Dis.* 2000;30:662–678.
114. Marsh PK, Tally FP, Kellum J, et al. Candida infections in surgical patients. *Ann Surg.* 1983;198:42–47.
115. Lamas GA, Esmaeli B, Chamilos G, et al. Fungal endophthalmitis in a tertiary care cancer center: a review of 23 cases. *Eur J Clin Microbiol Infect Dis.* 2008;27:343–347.
116. Laverdière M, Rotstein C, Bow EJ, et al. Impact of fluconazole prophylaxis on fungal colonization and infection rates in neutropenic patients. The Canadian Fluconazole Study. *J Antimicrob Chemother.* 2000;46:1001–1008.
117. Scott H, Griffin D. Ovarian cancer complicated by invasive pulmonary aspergillus. *Gynecol Oncol.* 2006;100(1):216–217.
118. Eggimann P, Marchetti O. Is (1→3)- β -D-glucan the missing link from bedside assessment to pre-emptive therapy of invasive candidiasis? *Crit Care.* 2011;15:1017.
119. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia

- and its consequences in nonneutropenic subjects. *Clin Infect Dis*. 2003;36:1221–1228.
120. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis*. 2007;45:883–893.
 121. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. 2001;344:665–671.
 122. Aisenberg G, Rolston KV, Dickey BF, et al. *Stenotrophomonas maltophilia* pneumonia in cancer patients without traditional risk factors for infection, 1997–2004. *Eur J Clin Microbiol Infect Dis*. 2007;26:13–20.
 123. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl. 2):S27–S72.
 124. Cirisano FD, Greenspoon JS, Stenson R, et al. The etiology and management of diarrhea in the gynecologic oncology patient. *Gynecol Oncol*. 1993;50:45–48.
 125. Satin AJ, Harrison CR, Hancock KC, et al. Relapsing *Clostridium difficile* toxin-associated colitis in ovarian cancer patients treated with chemotherapy. *Obstet Gynecol*. 1989;74:487–489.
 126. Turgeon DK, Novicki TJ, Quick J, et al. Six rapid tests for direct detection of *Clostridium difficile* and its toxins in fecal samples compared with the fibroblast cytotoxicity assay. *J Clin Microbiol*. 2003;41:667–670.
 127. Wanaitha A, Goldsmith EA, Marino BJ, et al. *Clostridium difficile* infection in patients with unexplained leukocytosis. *Am J Med*. 2003;115:543–546.
 128. Kaltsas A, Simon M, Unruh LH, et al. Clinical and laboratory characteristics of *Clostridium difficile* infection in patients with discordant diagnostic test results. *J Clin Microbiol*. 2012;50:1303–1307.
 129. Low DE, Keller N, Barth A, et al. Clinical prevalence, antimicrobial susceptibility, and geographic resistance patterns of enterococci: results from the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin Infect Dis*. 2001;32(suppl. 2):S133–S145.
 130. Drekonja DM, Butler M, MacDonald R, et al. Comparative effectiveness of *Clostridium difficile* treatments: a systematic review. *Ann Intern Med*. 2011;155:839–847.
 131. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of *Clostridium difficile* colitis. *Clin Infect Dis*. 2006;43:421–427.
 132. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364:422–431.
 133. Ruokonen E, Ilkka L, Niskanen M, et al. Procalcitonin and neopterin as indicators of infection in critically ill patients. *Acta Anaesthesiol Scand*. 2002;46:398–404.
 134. Schultz MJ, Determann RM. PCT and sTREM-1: the markers of infection in critically ill patients? *Med Sci Monit*. 2008;14:RA241–247.
 135. Gibot S, Cravoisy A. Soluble form of the triggering receptor expressed on myeloid cells-1 as a marker of microbial infection. *Clin Med Res*. 2004;2:181–187.
 136. Hirschmann JV. Fever of unknown origin in adults. *Clin Infect Dis*. 1997;24:291–300; Quiz 301–302.

Management of Acute and Chronic Complications of Gynecologic Cancer Treatment

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GENERAL COMPLICATIONS OF GYNECOLOGIC CANCER SURGERY

Stroke

Stroke is estimated to occur following gynecologic oncology surgery in less than 1% of patients. Risk factors reflect those in the general population: history of previous stroke or transient ischemic attack (TIA), atherosclerosis, hypertension, diabetes, and advanced age (1). The etiology of stroke is attributed to hypoperfusion injury, hemorrhage, or embolism. In contrast to cardiac surgery, the majority of noncardiac stroke is due to cerebrovascular thrombosis, rather than embolic events (2). Hypotension (relative to the patient's baseline blood pressure) increases the risk of stroke in patients undergoing noncardiac, nonneurological surgery (3,4). Despite this, no evidence is available that intraoperative monitoring or regulation of blood pressure reduces the incidence of stroke. Avoidance of severe hyperglycemia and hypoglycemia is recommended, though there is a lack of consensus regarding glucose targets (2).

Cardiac events

Major noncardiac surgery is associated with major cardiac events (cardiac arrest, myocardial infarction, heart failure, arrhythmias) in 0.5% to 3.0% (3,5). Postoperative myocardial infarction is associated with 50% to 70% mortality rate and carries a high risk for future cardiac events. More than half of perioperative myocardial infarctions are unrecognized (asymptomatic non-ST elevation), and the incidence peaks during the first 24 hours postoperatively. Recent myocardial infarction, heart failure, ischemic heart disease, diabetes, renal insufficiency, cerebrovascular disease, obesity, sleep apnea, and poor functional status constitute high-risk factors.

Prevention of perioperative cardiac events should focus on evaluation of risk factors, risk stratification, and maximization of patient function. Good evidence supports the continuation of β -blockers and HMG-CoA reductase inhibitors ("statins") throughout the perioperative period for patients already treated with β -blockers. Perioperative measures should focus on maintenance of normothermia and postoperative monitoring of serum troponin levels.

Deep Vein Thrombosis and Pulmonary Embolism

Deep vein thrombosis (DVT) and/or pulmonary embolism (PE) comprise the spectrum of complications known as venous

thromboembolism (VTE). VTE following surgery is the most common cause of peri- and postoperative death (6). DVT affects 0.1% of patients each year, but the incidence is significantly higher among patients undergoing surgical treatment for gynecological cancer, occurring in up to 20% of cases (7).

Patients with gynecologic cancer are at high risk for VTE because of their underlying malignancy, increased age, and extensive nature of treatment. The underlying mechanism of disease includes increased release of procoagulant factors, cytokine imbalance, and activation of the antifibrinolytic pathways. Clinical risk factors include a history of VTE, obesity, immobility, trauma, prolonged surgical time, radiation therapy, and increasing complexity of surgery. Patients with the highest risk for developing postoperative VTE have 2 or more of the following: age greater than 60 years, malignancy, and history of VTE (8). Early ambulation, heparin, low-molecular-weight heparin, and sequential compression devices (graduated compression stockings or intermittent pneumatic compression) are effective in reducing the incidence of VTE (9). The incidence of VTE in patients undergoing major gynecologic cancer surgery is decreased with dual, prolonged (4-week) prophylaxis without increasing bleeding complications (10). Current guidelines recommend VTE prophylaxis for at least 4 weeks following surgery in the absence of bleeding or other contraindications.

Bladder and Ureteral Injury

Injuries to the lower urinary tract (laceration, transection, crush injury, ligation, thermal injury, injury through devascularization) are uncommonly diagnosed intraoperatively; the outcomes of patients who are diagnosed late (urinomas, peritonitis, sepsis, fistula) are worse (11). The risk of bladder/ureter injury ranges between 1.1% and 5.3% in patients requiring a radical hysterectomy and is approximately 1% for standard hysterectomy for uterine cancer (11–14). Bladder injuries recognized at the time of the initial surgical procedure should be repaired immediately using a standard 2-layered closure of delayed absorbable suture. Bladder injuries diagnosed postoperatively (e.g., fistula) may be treated with an indwelling catheter for a period of several weeks. If spontaneous closure does not occur with prolonged drainage, surgical repair is indicated. Ureteral injuries recognized intraoperatively should be repaired by excising the injured segment of ureter, placement of a ureteral stent, and reapproximating the distal urinary tract (ureteroureterostomy, ureteroneocystostomy with psoas hitch, and possibly a Boari flap). Ureteral injuries detected remote from the incident surgical procedure can be managed by attempted placement of a ureteral stent, which can be accomplished either retrograde via cystoscopy or antegrade via a percutaneous nephrostomy tube.

If spontaneous closure does not occur after an observation period of 4 to 6 weeks, or if stent placement is not feasible, surgical repair is indicated. Long-term outcomes are generally excellent.

Injury to Small and Large Bowel

Bowel injuries occur in approximately 1% of patients undergoing surgery for gynecologic cancer. Risk factors include previous surgery, adhesions, and previous radiotherapy. Most bowel injuries are recognized at the time of surgery. The general principles of management include that any bowel anastomosis (hand-sewn or stapled) needs to be patent, tension-free, and well-vascularized. If any of these 3 conditions is unmet, the risk of leakage is very high. Small or large bowel injuries require primary bowel resection if the blood supply to the bowel is compromised or if injuries occurred at multiple levels.

Nerve Injury

Poor patient position, improper placement of retractor blades, and radical surgical dissection increase the risk of nerve injury (11). *Neurapraxia* is caused by compression leading to changes in intraneural microcirculation and is fully reversible. *Axonotmesis* (crush injury) will sever axons and function will resolve with gradual regeneration of nerve fibers. Transection of nerve fibers causes aberrant regeneration of the axons (misalignment), resulting in permanent functional losses.

The lumbosacral plexus is at risk for injury during gynecologic surgery. The use of short retractor blades or flexible blades with packs placed under the blades instead of self-retainers may reduce the risk of nerve injury intraoperatively (11). Additionally, avoidance of long-term hip extension (femoral nerve) or if flexion (sciatic nerve) in lithotomy position will decrease the risk of nerve injuries.

Hemorrhage

Intraoperative hemorrhage is defined as blood loss greater than 1,000 mL or if there is a requirement for intraoperative blood transfusion. Significant hemorrhage can be expected in 4% to 7.5% of patients undergoing surgery for advanced ovarian cancer (15). Risk factors include anemia prior to surgery, history of prolonged bleeding, blood-thinning medication and herbs/supplements, and intraoperative hypothermia. The principles of management of intraoperative hemorrhage include tamponade (packs) or atraumatic grasping and control of all feeding vessels; identification of sensitive structures (ureters, nerves); dissection of bleeding sources; correction of coagulopathy; the selective use of sutures, clips, diathermy, patches; and the use of topical hemostatic agents. Internal iliac artery ligation and hysterectomy should be considered if other measures fail. Finally, “damage-control” surgery, with placement of pelvic packing, transfer to the intensive care unit for stabilization, and return to the operating room for pack removal after 24 to 48 hours, may be a last resort.

Postoperative Ileus

Postoperative adynamic ileus is delayed gastrointestinal tract recovery; it may impair wound healing and lower the threshold for infections. Gastrointestinal motility is controlled by the enteric autonomous nervous system and influenced by neural reflexes (interfered by regional anesthesia), inflammation/trauma (tissue handling) and neuro-humoral substances (systemic analgesia). Medical illnesses (e.g., diabetes mellitus) or medications may increase the risk of ileus.

Differentiating postoperative ileus from a mechanical small bowel obstruction (SBO) is critical. Rapidly progressive systemic (septicemia) and abdominal symptoms (peritonitis, feculent vomiting) point to the likelihood of SBO. Bowel sounds are an unreliable indicator and are usually quiet or absent with ileus, but may be high-pitched or absent with SBO. Computed tomography (with oral gastrografin) is recommended to help differentiate ileus from SBO. The treatment of ileus is conservative and nonsurgical, and includes restriction of oral intake, nasogastric tube suction, intravenous fluid and electrolyte replacement, and discontinuing systemic opioids if possible. Total parenteral nutrition (TPN) should be considered after 7 to 10 days without satisfactory oral nutrient intake.

Postoperative Small Bowel Obstruction

Postoperative SBO results from a mechanical blockage of intestinal motility. Possible causes include herniation of bowel (port sites, internal herniation), early adhesions, intussusceptions, and small bowel tumors. The characteristic presentation of SBO is that patients initially recover well (pass flatus, tolerate oral intake), but then develop nausea, vomiting, abdominal discomfort, and pain. Computed tomography will show a site of bowel obstruction (transition point), gaseous distension of small bowel, and paucity of air in the rectum. Effective management requires an expedited diagnosis followed by a short (72 to 96 hours) conservative trial of nasogastric suction and fluid resuscitation. If there is no improvement after this period, surgical intervention is warranted. Protracted delays may cause secondary problems, such as bowel ischemia and necrosis.

Surgical Site Infection

Surgical site infections (SSI) lead to delayed wound healing, revision surgery, increased use of antibiotics, and increased length of hospital stay (16). On average, a patient with SSI spends 7 days longer in the hospital, is 60% more likely to spend time in the ICU, is 5 times more likely to be readmitted within 30 days of discharge, and is twice as likely to die (17). The incidence rates vary depending on patient factors and type of surgery, and range from 2% to 10% after laparotomy, while the rate is lower with minimally invasive surgery. Risk factors for SSI include concomitant systemic disease (diabetes, anemia, immunosuppression, immunosuppressive therapy with radiotherapy, chemotherapy, or steroids), obesity, advanced age, preexisting infection, hematoma, damaged tissue, extensive surgery, hypothermia, hemorrhage, and use of drains or catheters (18). Infection control programs reduce the rates of SSI by 35% to 41%, to 35% (19). Prophylactic antibiotics are most effective when administered 30 to 60 minutes preoperatively. A preoperative Chlorhexidine shower is as effective as bar soap or detergents. Trials on antibacterial sutures are ongoing.

DISEASE SITE-SPECIFIC SURGICAL COMPLICATIONS

Surgery for Ovarian Cancer—Cytoreductive Surgery

Acute Complications

Ovarian cancer cytoreductive surgery has evolved to a contemporary approach designed to achieve complete cytoreduction, with an accepted increase in morbidity balanced against the maximal benefit on long-term survival. A comprehensive approach

to advanced-stage ovarian cancer must address disease not only in the pelvis, but also frequently involves surgery on the large and small bowel, diaphragm, liver, spleen, and distal pancreas. Recognition and management of associated perioperative complications is critical. The morbidity of extensive surgical debulking is increased with age, poor nutritional status, and poor functional status (20–24).

The *en bloc* resection of locally advanced ovarian cancer (radical oophorectomy or modified posterior exenteration) carries an operative mortality of 0% to 8%, with more contemporary series reporting rates of 4% or lower (25–27). Wound complications are seen in 6% to 34% of patients, particularly with severe hypoalbuminemia (<3.0 ng/dL) and large-volume ascites (28). The estimated blood loss with radical oophorectomy ranges from 800 to 2900 mL, with as many as 87% of patients receiving blood product transfusion.

Intestinal complications with radical debulking are among the most commonly encountered, with prolonged ileus reported in up to 40% of patients. A large series of 587 patients recently reported an average incidence of postoperative ileus of 30.3% (25.9% without bowel resection, 38.5% with bowel resection) (29). The pattern of spread of ovarian cancer results in the need for bowel resection in 19% to 54% of cases (30,31). Colorectal anastomotic leak occurs in fewer than 4% of cases and can lead to abscess, fistula formation, sepsis, and reoperation; the mean time to diagnosis is 19 days (range, 4 to 32 days) (25,26,31,32–34). Anastomoses below the peritoneal reflection and less than 7 cm from the anal verge are at the highest risk for failure (35). While there are limited data in gynecologic oncology patient populations, randomized studies on the management of colorectal disorders suggest that mechanical bowel preparation does not lower the risk of anastomotic leak. A recent meta-analysis of 18 randomized controlled trials with over 5,800 patients confirmed that administration of mechanical bowel preparation yielded no difference in anastomotic leak rates (4.4% vs. 4.5%; odds ratio [OR], 0.99 [0.74, 1.13]) or wound complications (9.6% vs. 8.5%; OR, 1.16 [0.95, 1.42]) (36). Studies of intraperitoneal pelvic drain placement in the setting of a rectal anastomosis similarly suggest no benefit to lowering the risk of anastomotic leak (37). While the value of pelvic drainage in reducing anastomotic leak has not been demonstrated, drainage may still be useful in the prevention of pelvic fluid collections, abdominal compartment syndrome from re-accumulation of large-volume ascites, infected hematomas, and urinomas following urinary tract resection. Finally, intestinal diversion has historically been utilized for protection of a rectal anastomosis during primary cytoreductive surgery. Older data suggest that up to 59% of patients requiring rectal anastomosis also underwent protective intestinal diversion with colostomy or ileostomy. Based on more contemporary data, intestinal diversion to “protect” a colorectal anastomosis is not routinely required but may be advisable in patients with very low anastomoses, technically suboptimal anastomoses, or severe hypoalbuminemia (21% leak rate with albumin <3.0 g/dL vs. 3.4% leak rate with albumin >3.0 g/dL) (26,33). Initial management of anastomotic leak includes antibiotic therapy and percutaneous drainage under image guidance. If conservative management is unsuccessful, surgical exploration and diversion are required.

Upper abdominal procedures including splenectomy, distal pancreatectomy, partial hepatectomy, and diaphragmatic peritonectomy or full-thickness resection may be required to render a patient completely free of visible disease. Development of pleural effusions following diaphragmatic peritonectomy or resection occurs in 9% to 64% of patients, although these can be managed with thoracentesis alone in the majority of symptomatic patients. When full-thickness resections are required, perioperative morbidity has been reported in as many as 20% of patients (38,39). A small postoperative pneumothorax will frequently resolve spontaneously and can be monitored with daily chest radiographs.

Chest tube placement is occasionally required for major resections of the right hemidiaphragm, large pleural effusions, or worsening pneumothorax.

Acute complications associated with splenectomy include hemorrhage, left lower lobe atelectasis, splenic vein thrombosis, arteriovenous fistula between the splenic artery and vein, and infectious morbidity (40,41). Overwhelming postsplenectomy infection, most commonly due to *Streptococcus pneumoniae*, is a serious complication with a prevalence of 3.2% and a mortality rate as high as 70% (42). Vaccinations for pneumococcus, meningococcus, and *Haemophilus influenza* type B are the cornerstones of prevention.

Distal pancreatectomy is occasionally indicated to achieve complete disease resection and can result in pancreatic fistula (leak) and pancreatic pseudocyst formation (30,43). Intraoperative placement of a closed suction drain in the left upper quadrant can be useful to monitor for signs of early fistula formation as well as prevent pseudocyst formation. Mild enzyme leakage has little clinical impact and can be managed with prolonged drainage and standard oral feeding. Enzyme leakage greater than 3-fold the upper limit of normal or the presence of pain, fever, or leukocytosis requires delay of oral nutrition, administration of antibiotics, somatostatin analogues, and parenteral nutrition.

Chronic Complications

Ovarian cancer patients may experience long-term sequelae related to prior cytoreductive surgery, often exacerbated by the presence of disease recurrence or carcinomatosis. More commonly encountered complications requiring operative intervention are mechanical bowel obstruction or anastomotic stricture. SBO in ovarian cancer patients is best approached with an extended trial of bowel rest and decompression with nutritional supplementation unless bowel dilation is greater than 5 cm, at which point the risk of perforation increases. Carcinomatous ileus can be confused with mechanical bowel obstruction; however, this condition is unlikely to be surgically correctable. If mechanical SBO is refractory to conservative measures, surgical options include resection with reanastomosis, diverting ileostomy, enterocolonic bypass, or palliative percutaneous gastrostomy. Associated complications may include anastomotic failure, blind loop syndrome, or short gut syndrome. Finally, late complications may follow extensive resection of the ileum or a right hemicolectomy; these late complications include chronic diarrhea from impaired absorption of water, fat, and bile salts, and problems related to poor absorption of nutrients, including the fat-soluble vitamins and vitamin B₁₂.

Surgery for Uterine Cancer

Acute Complications

Until recently, total abdominal hysterectomy (TAH) was considered the standard surgical approach to hysterectomy for uterine cancer. However, minimally invasive surgical techniques have become increasingly popular due to their favorable outcomes in treatment. To date, three prospective randomized controlled clinical trials are available to compare outcomes from open and laparoscopic surgery for uterine cancer (12–14). The Gynecologic Oncology Group (GOG) LAP2 Trial (GOG 222) recruited a total of 2,616 women (12). Patients were eligible if they had clinical stage I to IIA uterine cancer; all histological cell types were allowed and all patients had to have pelvic and aortic lymph node dissection. The Australian LACE Trial enrolled 760 patients. Patients were eligible if they had endometrioid cell type, clinical stage I disease. Patients were not eligible if they had a uterine size larger than 10 weeks gestation, had evidence of extrauterine spread (ovarian masses, enlarged lymph nodes), or were unfit for surgery

due to medical comorbidities (14). The Dutch TLH Trial aimed to compare outcomes in early-stage endometrial cancer treated by laparoscopy or laparotomy. Patients with early-stage endometrial cancer (endometrioid cell type, FIGO grade 1 or 2, clinically stage I disease, negative endocervical curettage) or complex endometrial hyperplasia with atypia were eligible (13). Intraoperative surgical complications were comparable in all 3 trials.

In the LAP2 trial, postoperative surgical complications were significantly more common in patients who had a laparotomy than in patients who had a laparoscopic procedure (21% vs. 14%). Postoperative ileus (8% vs. 4%) and cardiac arrhythmia (2% vs. 1%) were significantly more common in patients in the open/laparotomy group. In the LACE trial, the open/laparotomy group had a 44% higher incidence of postoperative complications (18.6% in open, 12.9% in laparoscopic) compared to patients in the laparoscopy arm. The incidence of serious adverse events was 74% higher in the open group compared to the laparoscopy group (14.3% for open, 8.2% for laparoscopy). Wound infections or dehiscence were the main contributors to the difference in postoperative complications between laparoscopic (2.0%) and open (8.9%) groups. An open surgical approach (laparotomy), higher Charlson's medical comorbidities score, moderately or poorly differentiated tumors on curetting, lower performance status prior to surgery, obesity, and anemia were independently associated with an increased risk for surgical adverse events (44). Patient's age at surgery was not a risk factor for surgical complications. The Dutch TLH trial recorded comparable postoperative surgical complications in the open and the laparoscopic group (10.6% open/laparotomy; 11.9% laparoscopy). Interestingly, the incidence of postoperative complications was similar among all 3 trials for patients randomized to the laparoscopic arm (ranging from 11.9% to 14%). In contrast, the incidence of postoperative complications in the open/laparotomy arm was significantly lower in the Dutch TLH trial (10.6%) compared to LACE (18.6%) or LAP2 (21%). In the Dutch TLH trial, no patient required a retroperitoneal node dissection, whereas in the U.S. LAP2 trial, all patients had to have a pelvic and aortic lymph node dissection. In the Australian LACE trial, approximately half of patients had a retroperitoneal node dissection; however, no differences in the incidence of acute surgical complications were observed between the treatment arms when stratified by nodal dissection status.

Chronic Complications

Lymphedema and lymphocele are the main chronic complications following surgery for uterine cancer, and the incidence varies depending on the type of surgery and extent of lymph node removal. Overall, lymphedema occurs in 20% of patients following hysterectomy with lymphadenectomy (45). Obesity, number of lymph nodes removed, extent of surgery, postoperative infection, radiation therapy, and postoperative DVT increase the risk of developing lymphedema. Lymphoceles are an accumulation of lymphatic fluid in dead space due to postoperative leakage of lymphatic fluid coupled with incomplete lymphatic reabsorption. Most lymphoceles are asymptomatic and found incidentally. Its true incidence is therefore unknown (range, 0% to 58.5%) (46–48).

Surgery for Cervical Cancer:Radical Hysterectomy and Pelvic Exenteration

Acute Complications

Radical hysterectomy for early-stage cervical cancer is associated with a major complication rate (excessive blood loss, urinary/gastrointestinal tract injury, nerve injury) of 5% to 10%. Ureterovaginal fistula occurs in 2% to 3% of cases and typically presents within 14 days of surgery with watery leakage

per vagina commonly associated with pain or fever (49). A computed tomography urogram is usually diagnostic. Instillation of methylene blue dye intravenously or via retrograde instillation into the bladder can also help to distinguish a vesicovaginal from ureterovaginal fistula by observing for extravasated dye onto a vaginal tampon. Ureterovaginal fistulas can be managed in most cases with ureteral stenting or percutaneous nephrostomy. Vesicovaginal fistulas occur in 1% to 3% of cases, and can often be managed with prolonged catheterization and continuous decompression of the bladder for 4 to 6 weeks. For nonhealing fistulas, larger fistulas (>1 cm), or complex fistulas involving both ureter and bladder, surgical management with closure is indicated. This can be approached vaginally with a Latzko partial colpocleisis if the defect is small, apical, and not in proximity to the ureter. Bulbocavernosus or Martius fat pad grafts can also be used (50). Trigone involvement or larger complex fistulas are best approached abdominally with a layered closure and an omental flap. Urinary retention due to sensory loss and voiding dysfunction are well-recognized complications of radical hysterectomy and result from the denervation of the bladder during the parametrial dissection. Most patients are managed with prolonged bladder decompression for 3 to 7 days with a transurethral or suprapubic catheter. A retrograde voiding trial is recommended to assess for bladder function prior to removal of the catheter, and postvoid residual values of 40 to 50 mL are generally acceptable. Minimally invasive approaches to radical hysterectomy, including both traditional laparoscopic and robotically-assisted techniques, may offer several health-related benefits including less pain, shorter hospital stay, and more rapid return to full activity than the abdominal approach. However, the incidence of vaginal cuff complications/dehiscence (1.6% to 4.1%) may be higher than that observed with laparotomy (<0.5%) (56–60); there is also a potential higher risk for nerve injuries (51,52).

Total pelvic exenteration (TPE) is primarily indicated as salvage therapy for cervical cancer patients who have failed radiation therapy or require combined treatment of recurrence in the central pelvis. Acute perioperative morbidity related to TPE is high, with up to 75% of patients experiencing a major complication; mortality rates of 1% to 5% are typical. Furthermore, reoperation rates to address major complications are high, with rates of 16% to 25.6% reported in the literature (53,54). Morbidity of TPE is attributable to long operative times, compromised healing of the irradiated field, and the complexity of the surgical reconstruction. Significant blood loss, infectious morbidity primarily involving the urinary tract, sepsis, wound complications, fistulas, ileus, and anastomotic leaks of the intestinal or urinary anastomosis are some of the more commonly reported complications. Sepsis, adult respiratory distress syndrome, heart failure, pulmonary embolus, and multiorgan system failure are typical terminal events. The acute complication rate for both urinary continent and incontinent and urinary diversion ranges from 17% to 20%; these complications include urinary leak, fistula, or anastomotic failure (55). Such problems can be managed conservatively in many cases with prolonged conduit drainage and diversion with percutaneous nephrostomy. Refractory leaks may require surgical revision of the reservoir. Despite the high risk of complications, 5-year survival is in the range of 50% (54,56,57).

Chronic Complications

Urinary retention following radical hysterectomy is usually self-limited; however, long-standing bladder dysfunction may require patient intermittent self-catheterization. Long-term rectal dysfunction is similarly encountered and manifests as constipation or urgency. Nerve-sparing radical hysterectomy, which preserves autonomic and splanchnic innervation to the bladder and rectum, has been reported to decrease bladder and rectal morbidity (49,58). Ureteral strictures are encountered in 1% to 3% of patients and may present with fever and pain, but may be

asymptomatic and can lead to loss of renal function. Management is with ureteral stent placement, if possible, or percutaneous nephrostomy placement. Occasionally reoperation with ureteral reimplantation can be required. Colonic stomas may be prone to prolapse, hernia, or stricture. However, the most commonly reported intestinal complication is bowel obstruction. Unlike early postoperative bowel obstruction, late obstructions are more likely due to adhesive disease or disease recurrence. Sexual dysfunction is an underreported long-term side effect following radical hysterectomy (59).

Patients undergoing pelvic exenteration are at risk for a number of long-term complications. Urinary diversions are prone to stomal stricture, chronic urinary tract infection, renal dysfunction, nephrolithiasis, metabolic alterations, and difficulty with accessing the reservoir (56,57). Reestablishing intestinal continuity after exenteration has been advocated to minimize the long-term psychosocial and quality-of-life issues surrounding 2 permanent abdominal stomas but has been associated with a higher risk of reoperation (50% to 60%) and disease recurrence (57). Sexual dysfunction and distorted body image are common problems associated with pelvic exenteration.

Surgery for Vulvar Cancer

Acute Complications

Surgical innovation in vulva cancer evolved as a response to minimize the risk of surgical complications associated with the *en bloc* radical vulvectomy and bilateral inguinal lymphadenectomy popularized by Stanley Way in the 1950s, rather than from a concern about poor survival outcomes. Vulvar or groin wound breakdown occurs in as many as 50% of patients following radical vulvectomy (60–62). Development of a wound infection is predictive of future wound breakdown and lymphedema (61). Risk factors include increased patient's age, obesity, diabetes mellitus, smoking, and prior radiation to the groin. The use of myocutaneous flaps can reduce tension on suture lines, prevent wound breakdown, infection, and improve cosmetic and functional outcome. A nonrandomized, prospective study showed a reduction in wound breakdown for patients undergoing radical vulvectomy with lymph node dissection and hyperbaric oxygen therapy (63).

Contemporary management of vulvar cancer is tailored to the size and location of the primary tumor and generally consists of radical partial vulvectomy or wide radical excision combined with ipsilateral or bilateral inguinal lymphadenectomy through separate groin incisions (64). The incidence rates of wound infection, cellulitis, and wound breakdown are 21% to 39%, 21% to 57%, and 17% to 39%, respectively. Optimizing glucose control in patients with diabetes mellitus, using appropriate antibiotic prophylaxis, and sparing the saphenous vein are important prevention strategies (65). Sentinel lymph node biopsy (SLNB) is an emerging technique that has been associated with a reduction in groin wound breakdown (11.7% vs. 34%) and cellulitis (4.5% vs. 21.3%) compared to systematic groin node dissection (66).

Chronic Complications

Chronic complications from vulvar cancer surgery are often a result of groin node dissection. As many as 50% of patients requiring a groin dissection will experience a long-term complication related to the procedure. Lymphedema occurs in 14% to 48% of patients and presents as leg swelling or heaviness of the lower limbs (67). It results in an inability to perform daily activities, impacts on psychological and social well-being, and represents a significant financial burden associated with the treatment (68). Obesity, the number of lymph nodes removed, extent of surgery, postoperative infection, radiation therapy to the groins, and postoperative DVT increase the risk of developing

lymphedema after groin dissection (69). SLNB has been associated with a 1.9% incidence rate of lymphedema, compared with 25.2% in patients undergoing systematic groin dissection (66). Lymphocele formation develops in 7% to 19% of patients after inguinal-femoral lymphadenectomy (60).

Over half of women who undergo vulvectomy report sexual dysfunction and psychological issues resulting in dyspareunia, problems with micturition, negative feelings about body image, decreased desire, and inability to orgasm (68). Providing information before and after surgery that details how the treatment may affect sexuality and change anatomy, as well as the provision of methods for how to cope with feelings regarding the illness; may decrease anxiety. The FACT-V questionnaire is a valid and reliable tool that can measure the impact of treatment on QOL and improve standardization or quality of life research efforts.

Surgery in the Irradiated Field

Radiation induces a complex series of tissue changes including vascular sclerosis and tissue ischemia, the end result of which is fibrosis. Tissue planes are obliterated and healing is compromised. It is estimated that approximately 5% to 7% of patients who undergo radiation therapy for cervical cancer will experience major treatment complications that require surgery (70). The most common sites of intestinal injury in patients who undergo pelvic irradiation are areas that typically lie in the pelvic field. The ileum is the most frequent site of injury, because of the greater radiosensitivity of the small intestine compared with the colon. The most common indications for reoperative surgery in patients irradiated for cervical or endometrial cancer are intestinal obstruction (44%) and intestinal fistula or perforation (32%). Radiation damage frequently leads to matted loops of distal ileum densely fixed in the pelvis associated with obstruction or fistula. In the setting of intestinal necrosis, perforation, or abscess formation, resection should be attempted if it can be done without undue risk of damage to adjacent structures. Alternative more conservative approaches such as intestinal bypass procedures are less morbid but may lead to the development of blind-loop syndrome or result in subsequent spontaneous perforation or fistula formation. In a series of 77 patients who underwent surgery for radiation injury to the small intestine, no difference in short-term complications was noted whether patients underwent resection or bypass (71).

Urinary tract complications that may lead to surgery in a previously radiated patient include radiation-induced nonhealing or complex ureterovaginal or vesicovaginal fistulas and ureteral strictures, which compromise renal function. Asymptomatic stricture is likely more common and underreported in the literature and may lead to a silent loss of renal function. Many cases of radiation injury to the lower urinary tract can be managed conservatively with ureteral stent placement, percutaneous nephrostomy, or attempts at endoureteral dilation. Recurrent cancer must always be considered and the appropriate diagnostic biopsies and imaging obtained prior to consideration for surgical correction or urinary diversion (72).

ACUTE AND CHRONIC COMPLICATIONS OF RADIATION THERAPY FOR GYNECOLOGIC CANCERS

Radiation therapy plays a major role as a primary, adjuvant, and palliative treatment of cancers of the cervix, vulva, vagina, and endometrium. Notable progress has been made in the treatment of locally advanced cervical cancers, with the addition of radio-sensitizing chemotherapy based on

demonstrated improved patient outcomes in multiple studies (73–75). Vaginal brachytherapy is also increasingly being delivered using high-dose-rate (HDR) application. Unfortunately, external beam pelvic radiation therapy and brachytherapy are associated with effects on normal tissues, with subsequent acute and chronic manifestations that may adversely affect patients' quality of life, and pose limitations to treatment.

Acute effects usually develop beyond a radiation dose of 2000 Gy, and symptoms present within 4 weeks of starting treatment, while chronic effects are usually diagnosed after 1 month of completion of therapy. Normal tissue tolerance, volume of tissue irradiated, total dose received, dose fractions, as well as the arrangement of radiation treatment fields; are treatment-related factors that determine the severity of radiation effects in normal tissues. In addition, age, tobacco use, and chronic diseases such as diabetes, hypertension, peripheral vascular disease, and prior inflammation can influence the onset and severity of postradiation symptoms. The most common acute and chronic complications of radiation therapy in gynecologic cancers occur in the gastrointestinal tract, lower urinary tract, and reproductive tract (76). The GOG and Radiation Therapy Oncology Group (RTOG) use the National Cancer Institute Common Terminology Criteria for Adverse Events and the Common Toxicity Criteria for reporting the tissue effects and complications of radiation therapy. Table 30.1 shows the RTOG Morbidity Grading System. Normal tissue tolerance to therapeutic radiation varies by organ site (Table 30.2).

GASTROINTESTINAL TRACT AND URINARY BLADDER

Gastrointestinal symptoms and side effects are among the most common complications of radiation therapy. Intestinal cells have a fast doubling time of approximately 12 to 15 hours. Radiation induces acute gastrointestinal injury by causing acute mucosal inflammation and death of superficial intestinal cells with accompanying cytokine activation and release in the intestinal submucosa. These changes manifest as deepithelialization and ulceration, edema, erythema, and mucosal hemorrhage. Subsequently, there is mucosal ischemia with fibrosis and tissue hypoxia. In the chronic state, the intestinal mucosa appears pale and flat with multiple telangiectasias, and the bowel demonstrates decreased compliance and luminal capacity (77).

Table 30.1 Radiation Therapy Oncology Group Morbidity Grading System

Grade	Morbidity
1	Minor symptoms requiring no treatment
2	Symptoms responding to simple outpatient management; lifestyle (performance status) not affected
3	Distressing symptoms altering patient's lifestyle (performance status); hospitalization for diagnosis or minor surgical intervention (e.g., urethral dilatation) may be required
4	Major surgical intervention (e.g., laparotomy, colostomy, cystectomy) or prolonged hospitalization is required
5	Fatal complications

Source: Reprinted with permission from Pilepich MV, Pajak T, George FW, et al. Preliminary report on phase III RTOG studies of extended-field irradiation in carcinoma of the prostate. *Am J Clin Oncol* 1983;6:485–491.

Small Bowel

Acute Complications

The normal tissue tolerance of the small bowel is 45 Gy. Acute symptoms begin above 20 Gy depending on the volume of bowel segment involved (78). Due to its mobility, the small bowel is typically spared during external beam pelvic radiation. In patients with relatively fixed bowel segments due to prior adhesions from surgery, the potential for small bowel injury is increased. Acute and subacute symptoms of radiation-induced small bowel injury usually manifest within 1 month of commencement of therapy. Common presentations include abdominal cramps and diarrhea, which may be bloody. Nausea and vomiting, anorexia, and abdominal cramps may dominate the clinical picture in patients with acute SBO. Disruption of the mucosal integrity and immunity can lead to bacterial overgrowth, malabsorption, and enteritis. Diarrhea can usually be managed successfully with antimotility agents such as loperamide, diphenoxylate, and kaopectate (77). Patients with serious electrolyte derangements and dehydration require more aggressive resuscitation. It is important to exclude *Clostridium difficile* colitis as a cause of symptoms prior to initiating antimotility therapy. Dietary adjustments in the form of a low-residue diet and low-fat diet can help in patients with malabsorption. Acute obstruction should be managed initially with bowel rest, nasogastric suction, hydration, electrolyte repletion, and nutritional support. Radiologic studies may identify areas of stricture or narrowing. Surgery is indicated in patients who do not respond to medical management, and those who develop peritonitis.

Chronic Complications

Chronic small bowel injury results in diarrhea, bleeding, malabsorption with nutritional deficiencies, pain, fistula formation, and radiation-induced SBO (Figure 30.1). Symptoms can appear years after therapy (78). Severe bleeding may require invasive therapy for control, in the form of endoscopic coagulation or segmental resection. Long-term nutritional adjustments may be necessary in order to combat vitamin deficiencies, bile acid malabsorption, dumping syndrome, and chronic caloric deficiency. In patients with satisfactory performance status and reasonable life expectancy, surgery may be undertaken to address chronic small bowel strictures. Enteric fistulas present a challenge to the patient and physician, and require a multidisciplinary management approach with nutritional and surgical teams experienced in the care of this complication. Radiation-induced fistulas are less likely to heal, and may require bowel diversion for symptom control.

Large Bowel

Acute Complications

The tissue tolerance of the rectum is 70 to 75 Gy. The relatively fixed position of the rectum and close relationship to the vaginal tube are major factors in rectal injury during pelvic radiation therapy, specifically vaginal brachytherapy. Radiation-induced proctitis occurs in 2% to 20% of patients following pelvic radiation (79,80). Similar to the small bowel, acute effects are caused by intestinal epithelial inflammation and cell loss, with mucosal edema, ulceration, and bleeding. Acute symptoms of diarrhea with mucus, bleeding, tenesmus, cramping, fecal urgency, and incontinence may be severe enough to interrupt treatment. Acute symptoms are usually self-limiting, but may require the use of antimotility agents, dietary adjustment (fiber), and hygiene measures for control. Typically, these symptoms subside significantly or stop within 3 months of onset.

Table 30.2 Normal Tissue Tolerance to Therapeutic Irradiation

Organ	TD 5/5 Volume			TD 5/50 Volume			Selected Endpoints
	1/3	2/3	3/3	1/3	2/3	3/3	
Kidney	5,000	3,000 ^a	2,300	—	4,000 ^a	2,800	Clinical nephritis
Bladder	N/A	8,000	6,500	N/A	8,500	8,000	Symptomatic bladder contracture and volume loss
Bone: femoral head	—	—	5,200	—	—	6,500	Necrosis
Skin	10 cm ²	30 cm ²	100 cm ²	10 cm ²	30 cm ²	100 cm ²	Telangiectasia, necrosis, ulceration
	—	—	5,000	—	—	6,500	—
	7,000	6,000	5,500	—	—	7,000	—
Stomach	6,000	5,500	5,000	7,000	6,700	6,500	Ulceration/perforation
Small intestine	5,000	—	4,000 ^a	6,000	—	5,500	Obstruction, perforation/fistula
Colon	5,500	—	4,500	6,500	—	5,500	Obstruction/perforation
Rectum	Volume 100 cm ²	No volume effect	6,000	Volume 100 cm ²	No volume effect	8,000	Severe proctitis/necrosis/fistula, stenosis
Liver	5,000	3,500	3,000	5,500	4,500	4,000	Liver failure
Bone marrow	4,000	1,000	400	4,500	1,000	650	—
Spinal cord	5,000	5,000	4,700	7,000	7,000	—	—

N/A, not available; TD, total dose.

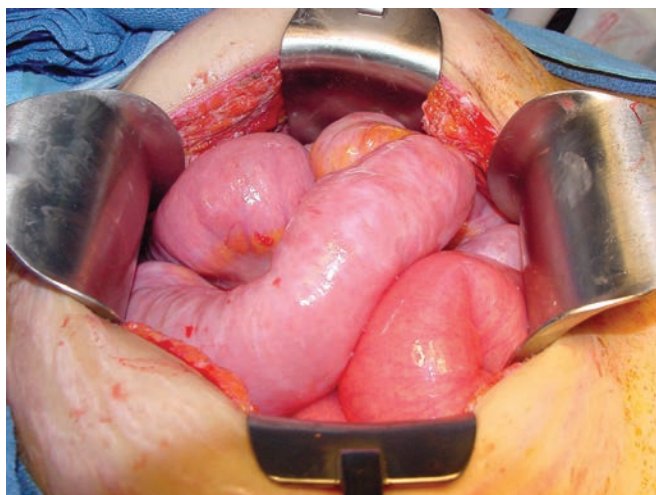
^a <50% of volume does not make a significant change.Source: Reprinted with permission from Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21:109–113.

Chronic Complications

Chronic large bowel changes are due to obliterative endarteritis, mucosal ischemia, and fibrosis; with pale mucosa, telangiectasias, and ulcerations. Stricture and fistula formation are also potential sequelae. Rectal bleeding is a common presentation of chronic radiation proctitis, and can be severe in up to 6% of patients. Chronic proctitis may not be preceded by a history of acute proctitis, and is generally diagnosed in patients who develop symptoms at least 3 months after completion of radiation therapy. The anterior rectal mucosa is the usual site of bleeding from telangiectasias. Unlike in acute proctitis, lower gastrointestinal endoscopy (flexible sigmoidoscopy) is indicated in the evaluation of chronic proctitis. The most effective medical treatments for chronic radiation proctitis are sucralfate enema, metronidazole enema, and hyperbaric oxygen (77,81). Invasive

treatments for chronic proctitis involve the endoscopically assisted use of topical and ablative therapies. Surgery for radiation-induced proctitis carries high morbidity rates, and should be approached by surgeons experienced in performing technically complex bowel surgery in previously irradiated fields.

Fecal incontinence after radiation injury is a psychologically debilitating symptom that is underreported and also underassessed by treating physicians. A large population study from Sweden reported a 12% rate among patients treated with pelvic radiation and brachytherapy for gynecologic cancers (82). Self-reported rates of fecal incontinence and fecal urgency among patients treated with pelvic radiation and brachytherapy for gynecologic cancers are as high as 34% and 58%, respectively (83). Increasing dietary fiber can alter stool consistency and increase stool bulk. Patients can also use hygiene pads or diapers, and undergo pelvic floor therapy and toilet training. Rectal mucus discharge or seepage can similarly be addressed with toilet training and hygiene.

**FIGURE 30.1.** Radiation-induced small bowel obstruction.

Urinary Bladder

Acute Complications

Tissue effects in the urinary bladder are commonly observed following pelvic radiation. Due to difficulties associated with changes in volume and shape during treatment, calculations of dose tolerance have been imprecise; however, the quoted tolerance of the urinary bladder is between 65 to 80 Gy. Patients with acute radiation cystitis have irritative lower urinary tract symptoms, and bleeding. Mucosal inflammation is the hallmark feature (84). Before instituting a treatment regimen for presumed acute radiation cystitis, it is a good practice to exclude a lower urinary tract infection.

Chronic Complications

Radiation-induced ischemia and fibrosis can lead to chronic cystitis, with hematuria, decreased bladder capacity, urinary

urgency, frequency, and incontinence. Chronic severe urinary complications are relatively uncommon (1% at 5 years and 2% at 20 years) but can adversely impact patients' quality of life. Cystoscopic evaluation is appropriate prior to treatment; however, biopsies are not necessary unless atypical or unexpected findings are encountered (85,86). Medical management should suffice for most patients. Generally, antispasmodics like pyridium, as well as anticholinergics, and muscarinic receptor inhibitors can be used for irritative bladder symptoms. Patients with severely diminished bladder capacity can be managed with long-term indwelling catheters, or considered for urinary diversion if they are fit for surgery and have reasonable life expectancy. Formalin instillations into the bladder, cystoscopic fulguration, and hyperbaric oxygen therapy have been described for problematic bleeding and chronic cystitis respectively (87). Less commonly, urinary tract fistulas can occur between the bladder and colon, rectum, or vagina. Conservative management is usually not successful in the management of radiation fistulas, and urinary diversion may offer the only reasonable chance of symptom control. Prior surgery, inflammatory bowel disease, and smoking can adversely impact on treatment outcomes following surgical treatment.

REPRODUCTIVE TRACT

Vagina and Sexual Side Effects

Acute Complications

The vagina is a relatively radio-resistant structure, with a tolerance of up to 140 Gy. Radiation effects on the vaginal mucosa have traditionally been assessed in the proximal vagina, which has a lower dose limit of 120 Gy following external beam and brachytherapy (88). Acute manifestations of radiation injury include epithelial desquamation, redness, and dryness. The incidence of grade 1 and 2 vaginal toxicity is 10% among patients receiving external beam pelvic irradiation and vaginal brachytherapy for gynecologic cancers, while grade 4 toxicity occurs in 3.6% of patients (89).

Chronic Complications

Late radiation effects on the vagina lead to mucosal pallor, telangiectasias, loss of elasticity, and diminished lubrication. Agglutination of the vaginal apex can lead to vaginal narrowing and shortening. Problems with vaginal lubrication, decreased capacity, and mucosal thinning impact on sexual functioning; they account for a significant amount of morbidity and loss of quality of life in patients with cervical and vaginal cancers who are irradiated. Sexual intercourse should be encouraged in patients who are able to resume intercourse. Vaginal dilators have also been shown to help vaginal patency in patients who are not sexually active. Vaginal dilators may be traumatic in the acute phase radiation injury, and are probably better used to address chronic vaginal problems of narrowing and shortening after inflammation has subsided (90,91). Factors such as age, smoking, hormonal status, and radiation dose influence the severity of vaginal effects, and the development of ulceration and vaginal fistulas (92). Microscopic examination of vaginal smears and vulvar/vaginal biopsies after radiation may show atypical cells that are due to radiation-induced changes. Expert pathology consultations are helpful in such instances. Care should be taken to avoid unnecessary biopsies because of the risk of ulceration.

Vulva

Acute Complications

The vulva and distal vagina are less tolerant to radiation than the proximal vagina. Maximum radiation dose to the vulva

should be limited to 70 Gy. Acute vulva changes after radiation may be observed within a month of commencing therapy. Initial effects are due to tissue injury, leading to dry desquamation. This is followed by a moist desquamation reaction that involves denudation of vulvar skin, with edema and surface vesicles due to continued acute inflammatory response (92). Daily use of sitz baths followed by drying of the vulva should be used initially for acute symptoms. Avoidance of chemical washes and friction against the vulvar skin are important.

Chronic Complications

In chronic radiation vulvitis, areas of skin may appear hypopigmented or depigmented due to loss of melanocytes. There is also loss of sebaceous glands, dermal atrophy, loss of hair, and fragility. Patients who smoke, and have chronic microvascular disease are at risk of nonhealing ulcers (92). Water-based emollients, perineal hygiene, and the avoidance of friction help to reduce dryness and sores, and prevent infection.

Ovary

Clinical effects of radiation on ovarian function are more pronounced in premenopausal patients. Acute ovarian failure occurs as a result of injury to the granulosa cells, with subsequent inability of follicle maturation. Total (fractionated) radiation dose of 24 Gy will produce permanent loss of ovarian function (93). Typical doses to the ovaries are less than this; the dose of radiation that produces lethal toxicity to 50% of ovarian follicles (LD50) has been quoted to be between 4 and 6 Gy. Wallace et al. using a model for follicle decline applied to age-related estimations of ovarian volume suggested a LD50 value of 2 Gy (Table 30.3) (94). The severity of radiation-induced ovarian failure is dependent on the age of the patient, total dose received, and concomitant use of alkylating chemotherapy. Vasomotor symptoms, as well as vaginal dryness, mood changes, diminished libido, breast atrophy, subfertility, and osteoporosis, are some of the many problems related to ovarian failure in these patients. Management is usually in accordance with established guidelines for postmenopausal symptom therapy.

Fetal Effects

Definite thresholds for fetal effects of radiation have been difficult to define in humans partly because of the species-specific nature of

Table 30.3 Predicted Mean Age of Ovarian Failure after Radiation

	3 Gy	6 Gy	9 Gy	12 Gy
Age at Treatment (years)	Ovarian Failure (years)	Ovarian Failure (years)	Ovarian Failure (years)	Ovarian Failure (years)
Birth	35.1	22.6	13.7	7.9
1	35.2	22.9	14.3	8.7
9	36.5	26.0	19.7	14.5
15	37.8	28.8	23.0	19.0
20	39.0	31.4	26.4	22.8
25	40.6	34.2	29.8	26.5
30	42.2	37.0	33.2	30.1

Source: Used with permission from: Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiation Oncol Biol Phys* 2005;62(3):738-744.

radiation damage. *In utero* effects of radiation are dependent on the dose received, the gestational age, the cell type, and the stage of development affected. Up to 2 weeks of gestation, radiation effects follow an “all or none” pattern (95). Therefore, either a lethal abnormality is induced in the embryonic cells, or the entire cell population of undamaged cells continues to replicate without consequences. Between 2 and 8 weeks, the most radiosensitive cells are neural cells, which undergo a process of mitosis and migration into the cerebral cortex, prior to terminal differentiation. Radiation-induced cell kill produces clinical effects of microcephaly and mental retardation in fetuses exposed to greater than 0.3 to 0.5 Gy between 8 to 15 weeks gestation. Growth retardation and microcephaly are the main effects seen between 16 and 25 weeks of high doses of radiation exposure. Severe fetal anomalies are rarely seen beyond 30 weeks gestation.

Pelvic Bone Effects

Insufficiency fractures result from diminished bone elasticity under physiologic stress conditions. External beam pelvic radiation affects bone tissue directly by reducing osteoblast number and function leading to demineralization and osteopenia. Indirect radiation effects occurs through microvascular occlusion and impaired ability of bone marrow to undergo repopulation of stem cell depleted areas. The tolerance dose of healthy bone tissue is between 65 and 70 Gy, but it is suggested that toxicity actually begins above a total dose of 45 Gy (96). Preexisting osteoporosis is the main predisposing risk factor for developing postradiation insufficiency fractures. Other factors are age and postmenopausal status, radiation dose, low body weight, smoking, chronic steroid use, diabetes, and rheumatoid arthritis. The majority of patients will develop fractures within one year of completion of treatment. Estimates of the exact incidence vary (10% to 45%) based on small retrospective studies (97). The median time to presentation is 14 months, and the sacrum may be involved in as many as 83% of patients with fractures (97). The most prevalent symptom of insufficiency fractures is pain in the sacral area of the back, and in the pubic area. The characteristic finding on radionuclide bone scans is a butterfly or H-shaped area of abnormal uptake in the sacral area (96). Most patients with insufficiency fractures respond to pelvic rest, physiotherapy rehabilitation with pelvic exercises, and nonsteroidal or opiate analgesics. Patients who receive pelvic radiation should periodically be assessed for pelvic fractures with pelvic imaging, especially when pelvic pain is reported.

Radiation osteitis results from radiation-induced microvascular injury with inflammation and ischemia. Areas of sclerosis may develop in conjunction with demineralization (96). Diagnostic confusion can occur when fractures also appear. Severe microvascular injury and osteocyte killing can lead to ischemia and an acellular bone matrix. Disruption or occlusion of the nutrient vessels and periosteal and endosteal anastomoses lead to avascular necrosis. This lesion may be seen less commonly in the femoral head.

Hematopoietic Effects

External beam pelvic radiation, especially when given with chemotherapy, commonly produces hematologic toxicity (98,99). Radiation affects hematopoietic stem cells, stromal cells, and other cells that secrete colony-stimulating factors. Acute toxicity manifests as neutropenia, anemia, and thrombocytopenia; and may be dose limiting, pending recovery of cell counts. At doses typically utilized for external beam pelvic radiation, the drop in neutrophil, platelet, and red blood cell counts reflects the kinetics and half-lives of these cells, similar to that observed with chemotherapy. Chronic radiation injury results from stromal cell damage and bone marrow fibrosis, with diminished ability of the bone marrow to support hematopoiesis.

Lymphatic Effects

Surgery or radiation alone in the pelvis or groin can lead to lymphedema, but when combined, the incidence of lymphedema increases. The prevalence of lymphedema is quoted from 11% to 18% and is greater in those treated for vulvar carcinoma with inguinofemoral lymphadenectomy and adjuvant radiation. Symptoms may be unilateral or bilateral and range from mild, soft, pitting edema to severe, indurated, brawny edema placing the woman at risk for cellulitis. Treatment includes compression stockings, massage, elevation, and good skin and nail care to avoid infection.

Neural Effects

Radiation neuropathy and plexopathy is seen most commonly between 1 and 5 years following pelvic radiation for cervical cancer. Dose threshold for this condition is not exactly known. Leg weakness, numbness, sensory changes, and leg edema are all presenting features. Loss of perineal sensation and incontinence suggest bilateral plexopathy (100). Pain is a late symptom, an important differentiating feature from tumor recurrence, which is a key differential diagnosis. Clinical evaluation helps to exclude obvious evidence of tumor. MRI is the best imaging modality for diagnosis of plexopathy. PET scan is also useful in differentiating radiation-induced plexopathy from tumor-associated plexopathy when the diagnosis is unclear. Treatment is usually supportive care with pain control.

Skin

Acute Complications

Severe skin toxicity is seen less frequently today due to the use of skin-sparing photon energy with megavoltage radiation therapy. In doses typically used for primary radiation of vulvar cancers and groin nodes, the severity of skin effects is influenced by radiation dose and type, age, preexisting medical disease, prior surgery in the radiation site, smoking, as well as overall nutritional status (101). Acute skin effects occur during treatment, and are seen for several weeks after. Direct effects on the epithelial cells of the basal epidermis, dermal capillaries, and lymphatics set up an inflammatory reaction characterized by erythema, vascular permeability, acute inflammatory cell infiltration, and release of proinflammatory molecules. Hair follicle loss and dry desquamation occur in 2 weeks, followed by plasma exudation, edema, and moist desquamation. The vulva is normally prone to moisture and friction, which can interfere with healing.

Chronic Complications

Delayed skin effects occur within 6 months. The hallmark feature is tissue hypoxia leading to atrophy of skin elements, notably sebaceous glands, sweat glands, and hair follicles (101). Compared to normal skin, there is irregular organization of elastic tissues and collagen. The skin is thin and delicate, with telangiectasias and areas of abnormal pigmentation. Doses beyond 70 Gy can lead to fibrotic, inelastic skin. Ulcers or chronic sinuses are slow or unable to heal, especially when the skin is subsequently stressed from surgery, infection, or trauma. Radiation to skin can seriously impede wound healing if surgery is required any time afterwards. Radiation is associated with decreased wound strength, with the greatest risk of breakdown during the inflammatory and proliferative phases of wound healing when fibroblasts are most active (102). The wound remodeling stage is least sensitive to the acute effects of radiation. Perineal hygiene with nonchemical washes, followed by gentle blow-drying are recommended for radiation vulvitis. Avoidance of friction and

use of cotton undergarments are helpful. The management of chronic radiation skin ulcers and fistulas is beyond the scope of this section.

MINIMIZING RADIATION-RELATED TOXICITY

A better understanding of the radiation dose and toxicity relationship over the years has led to the adoption of several measures to reduce acute and chronic effects of radiation treatments for gynecologic cancers. Strategies to help minimize normal tissue damage include treatment of all fields each day, use of a 4-field technique, 3-D conformal therapy with blocking of normal structures, shrinking-field techniques, prone position, and the use of belly boards to exclude bowel. Newer techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy (IGRT) hold promise to decrease acute and long-term toxicity. IMRT uses highly sophisticated computer software and hardware to shape the form and intensity of the radiation beam to conform more precisely to a patient's tumor and to avoid the normal tissues and is associated with a decrease in hematologic, gastrointestinal, and genitourinary side effects (103).

Over the years, many therapies have been studied as radioprotectors and sensitizers. One of the most promising is amifostine (WR-2721; Ethiol), which has noted protective effects on the salivary glands, bone marrow, oral mucosa, esophagus, intestinal mucosa, and bladder mucosa (104). The compound is an organic thiophosphate diphosphorylated to the active metabolite (WR-1065) in the tissue. The differential protection of normal versus tumor tissue is due to a differential concentration of tissue alkaline phosphatase and pH differences that allow variable metabolite uptake. After cellular uptake, WR-1065 scavenges oxygen free radicals and by this mechanism affords normal tissue radioprotection. Two randomized trials in pelvic radiation demonstrated a significant decrease in bladder and gastrointestinal toxicity without compromising median survival or therapeutic response (105,106).

COMPLICATIONS OF CHEMOTHERAPY AND BIOLOGICAL AGENTS

Chemotherapy drugs are toxins that are used to kill cancer cells. However, none of the currently available chemotherapeutic agents have toxicities that affect only the cancer cell. Most have some toxic effects on normal cells. The toxicities of chemotherapy can be categorized as acute (with onset early in treatment), or chronic (delayed or cumulative toxicities that may not appear until late in treatment or after treatment is completed).

Myelosuppression

Hematologic effects of chemotherapy affect all 3 myeloid lineages. The fall in white blood cells (WBC) starts a few days after chemotherapy and will usually nadir 10 to 14 days after chemotherapy. Severe or grade 4 neutropenia is defined as an absolute neutrophil count (ANC) less than 500/mm³; febrile neutropenia (FN) is defined as an ANC <1000/mm³ and oral temperature >38.3°C (107). FN is a major complication of chemotherapy that can require hospitalization and intravenous antibiotic treatment and may result in treatment compromise by dose reduction or delay in therapy (108). The prophylactic use of WBC colony-stimulating factors (CSFs) can reduce the

incidence and severity of FN but adds significantly to treatment cost. Most guidelines recommend prophylactic CSF use for chemotherapy regimens with a greater than 20% risk of FN (109). Gynecologic cancer regimens with a > 20% risk of FN include topotecan (daily × 5 regimen), single agent full dose docetaxel, BEP (bleomycin, etoposide, and cisplatin), MAID (mesna, doxorubicin [Adriamycin], and ifosfamide with or without dacarbazine), and gemcitabine and docetaxel (109). Of note, the taxane/carboplatin combination regimens have a lower risk of FN and routine prophylactic CSF use is not recommended for these regimens (110). In addition to the specific chemotherapy regimen used, age over 60, prior FN, and prior exposure to multiagent chemotherapy increase risk of FN and may be indications for prophylactic CSF.

The effects of chemotherapy on platelets may manifest later with nadirs as late as days 14 to 18 of a 21-day cycle. Carboplatin in particular has a potent effect on the platelets. Carboplatin-related thrombocytopenia is frequently cumulative such that nadir platelets decline with continued treatment. The gradual onset of thrombocytopenia allows for dose and schedule modification; as a result, severe thrombocytopenia is rare (111).

Red blood cells have a much longer half-life than platelets or WBCs so anemia may manifest much later in treatment. Patients who have significant blood loss with initial surgery are clearly at greater risk for chemotherapy-related anemia. Erythropoietin-stimulating agents (ESAs) have been associated with decreased survival and should be used only during chemotherapy for symptomatic patients with hemoglobin less than 11 g/dL or asymptomatic patients with hemoglobin less than 10 g/dL who are at risk for symptomatic anemia (112).

Emesis

Chemotherapy-related nausea and vomiting is largely a central nervous system effect related to stimulation of the chemoreceptor trigger zone. Poorly controlled nausea leads to metabolic abnormalities, poor treatment compliance, and anticipatory nausea. The incidence of emesis is affected by the agent, the dose, and the schedule. Acute nausea peaks 4 to 6 hours after chemotherapy and usually resolves within 24 hours of treatment. Delayed nausea, occurring more than 24 hours after chemotherapy, is most commonly seen with cisplatin and adriamycin. Cisplatin-associated emesis peaks 2 to 3 days after chemotherapy, but can last up to 7 days. Prophylactic treatment is based on the emetogenic potential of the treatment regimen and should be initiated before chemotherapy. 5-HT₃-receptor antagonists have provided a significant advance in control of nausea and emesis. Dexamethasone improves the efficacy of 5-HT₃-receptor antagonists. Neurokinin-1 receptor antagonist therapy blocks the binding of substance P to NK-1 receptors and adds additionally to 5-HT₃-receptor antagonists and dexamethasone. Multiday regimens such as BEP or MAID are particular challenges and require close monitoring of nausea and emesis (113).

Nephrotoxicity

Cisplatin is the chemotherapeutic agent most commonly associated with renal compromise. Cisplatin produces its nephrotoxic effects by damaging the renal tubules, resulting in a decrease in the glomerular filtration rate (114). Vigorous isotonic saline hydration to maintain a urine output of at least 100 mL/hour decreases the concentration of cisplatin at the tubules and significantly reduces the risk of renal toxicity from cisplatin. A common regimen will be 1 L of normal saline supplemented with potassium and magnesium over 2 to 3 hours before cisplatin and 500 mL of the same solution over 2 hours after cisplatin. Forced diuresis with mannitol to maintain urine output can lead to transient intravascular dehydration and exacerbate cisplatin

nephrotoxicity (115). Likewise, furosemide should not be used unless there is evidence of volume overload. Cisplatin nephrotoxicity is cumulative; thus, close monitoring of creatinine is mandatory. Even rises that remain within normal limits can indicate a significant decrease in creatinine clearance. In addition, the use of other nephrotoxic agents, such as IV contrast, should be avoided near the time of cisplatin administration.

In addition to abnormalities in renal function tests, electrolyte abnormalities such as hypomagnesemia, hypocalcemia, and hypokalemia resulting from defective distal tubular reabsorption can be seen after cisplatin administration. This can be a long lasting effect and some patients require electrolyte monitoring for years after cisplatin use.

Neurotoxicity

A major dose-limiting side effect of cisplatin is neurotoxicity. The common neurologic effects of cisplatin include peripheral sensory neuropathy and ototoxicity; however, retinal toxicity, encephalopathy, seizures, and autonomic dysfunction can also occur. Cisplatin predominantly affects large sensory fibers. Typical symptoms are numbness, paresthesias, and pain beginning in the fingers and toes. This can progress proximally in a “stocking glove” distribution and can ultimately result in difficulty in walking and impaired fine motor functions such as writing, typing, and buttoning. Physical exam findings will include loss of deep tendon reflexes, decreased vibratory sensation, and diminished proprioception (116). Although cisplatin-induced neurotoxicity may occur after a single dose, it more commonly increases with higher cumulative doses.

Cisplatin may also cause tinnitus and hearing loss in the high frequency range in a dose-dependent fashion (117). High-dose cisplatin regimens of 100 mg/m² per dose or higher achieve very high peak plasma levels that appear to result in a greater incidence of ototoxicity than lower-dose regimens.

The antitumor effect of paclitaxel (Taxol) results from promoting microtubule assembly. As a consequence, neuropathy is one of its toxic side effects. Some patients treated with paclitaxel report an acute painful musculoskeletal toxicity with arthralgias and myalgias that usually peak in the first 5 days after treatment. It is not clear whether this is a neurologic toxicity, but it is frequently classified as such. This can usually be managed with nonsteroidal medications, but sometimes requires the use of narcotic analgesics. A cumulative peripheral sensory neuropathy is the most commonly reported neurotoxic effect of paclitaxel. Symptoms include symmetrical numbness, paresthesias, and burning pain in a glove-and-stocking distribution.

The combination of paclitaxel and cisplatin has been shown to have the potential to produce a higher incidence of peripheral neuropathy than either agent used alone. Of particular concern is the combination of cisplatin (75 mg/m²) and short duration, 3-hour infusion of paclitaxel (175 mg/m²) administered on the same day. Studies demonstrate a 20% to 25% incidence of severe (grade 3) peripheral neuropathy using cisplatin with short infusion paclitaxel (118). For this reason, IV cisplatin is commonly given after a prolonged, 24-hour infusion of paclitaxel. An alternative is to administer cisplatin on day 2, one day after 3-hour paclitaxel; however, the incidence of neurotoxicity with this approach has not yet been well documented.

Although less neurotoxic than cisplatin plus paclitaxel, combination chemotherapy with carboplatin and paclitaxel, a commonly employed regimen in several gynecologic malignancies, also has the potential to produce peripheral neuropathy (119).

Pulmonary Toxicity

Bleomycin, an antitumor antibiotic, is a component of the BEP treatment regimen used for malignant germ cell tumors.

The most serious toxic effect of bleomycin is a potentially life-threatening interstitial pulmonary fibrosis that can occur in up to 10% of patients (120). The mechanism of bleomycin-induced lung injury is not entirely clear but oxidative damage to the lung appears important. The toxicity is rare (0% to 2%) in patients who have received a total cumulative bleomycin dose <270 mg but increase to 6% to 18% when dose reaches 360 mg (121). However, it should be noted that severe pulmonary toxicity has been observed at total bleomycin doses <100 mg. In addition to the cumulative dose received, other risk factors for bleomycin-induced pulmonary dysfunction include age >40 years and prior or concurrent thoracic irradiation.

Patients who are to receive bleomycin should have screening pulmonary function testing, including carbon monoxide-diffusing capacity (DLCO). These should be repeated if the patient develops cough, dyspnea, crackles on lung exam, or abnormal chest imaging. Mild worsening of DLCO (15% to 20%) is common in bleomycin-treated patients. A more substantial worsening, particularly in combination with new symptoms, should lead to discontinuation of bleomycin. Corticosteroid therapy is the mainstay of treatment, but has little or no impact on established fibrotic lesions.

Cardiac

Doxorubicin has demonstrated activity in several gynecologic malignancies and is a component of a number of commonly used treatment regimens. Doxorubicin has a serious potential side effect of cumulative cardiac toxicity when given as a bolus administration (122). Cardiac abnormalities are rarely observed with a total doxorubicin dose <350 mg. With a cumulative dose of >550 mg/m², the incidence of cardiac dysfunction is 1% to 10%. Doxorubicin-induced heart injury is unique, and specific histologic features, best seen on electron microscopy, can be observed in tissue obtained through an endomyocardial biopsy during a right-heart catheterization (123).

Risk factors for cardiac toxicity include a history of significant hypertension, preexisting cardiac disease, prior cardiac or mediastinal irradiation, and age >70 years (124). Evaluation of left ventricular ejection fraction (LVEF) with MUGA or ECHO is recommended before initiating doxorubicin treatment for anyone with any of the above risk factors. Most clinicians additionally evaluate LVEF in patients over age 50 to rule out occult, unexpected cardiac function abnormalities. Some advocate LVEF evaluation in any patient who will receive doxorubicin. LVEF should be reevaluated after a cumulative doxorubicin dose of 250 to 300 mg/kg. In most patients, a major drop in the cardiac ejection fraction is observed *before* the onset of clinical symptoms, allowing for discontinuation of doxorubicin before more serious damage results.

It should be noted that administration of doxorubicin by continuous infusion (as in the MAID regimen) or by sustained release (if liposomal form) does not have the same cardiac toxicity as bolus administration (125).

The rate of doxorubicin cardiac toxicity is increased when it is administered with paclitaxel or with the anti-HER2/ neu monoclonal antibody trastuzumab (Herceptin). In the TAP regimen (paclitaxel [taxol], doxorubicin [Adriamycin], and cisplatin) used for treatment of endometrial cancer paclitaxel and cisplatin are given on day 1 and doxorubicin is given on day 2. The incidence of grade 3 or greater congestive heart failure was 2% with that regimen (126).

Infertility

Improvements in early diagnosis and treatment have resulted in improved survival rates of women with cancer. However, chemotherapy has clear gonadal toxicity resulting in premature

amenorrhea and frank ovarian failure. When premenopausal women are diagnosed with cancer, concerns about preserving fertility may seem secondary to optimizing treatment outcomes. But for many women, optimizing fertility preservation represents hope for the future and a desire to reclaim their “normal” life. Women who have deferred childbearing until late in life often see maintaining fertility as a means of not allowing cancer to derail their life goals (127).

The ovary is especially susceptible to chemotherapy because of the normal decline in the number of primordial follicles after birth and the inability of follicles to replicate. The overall risk of infertility depends on several factors, including the chemotherapy drugs used, the intensity of the drugs, the duration of treatment, the age of the patient, and her existing ovarian reserve. Chemotherapy primarily affects the replicating, hormone-producing granulosa and theca cells but has little direct effects on the quiescent oocytes (128). The chemotherapy drugs most strongly associated with ovarian damage are the alkylating agents, such as cyclophosphamide, and anthracycline doxorubicin. Cisplatin and etoposide are less toxic to the ovary, while the gonadal toxicity of bleomycin and taxanes are unknown. Follicular damage leads to decreased ovarian hormone production, elevated gonadotropins, and greater follicular recruitment. This positive feedback loop results in an accelerated rate of damage with more prolonged therapy. Thus, duration of treatment impacts ovarian reserve and the fewer ovulatory cycles of exposure, and there is less ensuing follicular damage (128).

Chemotherapy-associated amenorrhea should not necessarily be equated with loss of fertility. Amenorrhea may be transient and many women will have return of menses and maintain fertility.

The risk of infertility and possible pretreatment interventions should be discussed with women who desire fertility preservation before chemotherapy is started. Embryo cryopreservation is the best-established technique for preserving reproductive capacity (129). This requires ovarian stimulation and oocyte retrieval, which can take 2 to 6 weeks. Thus, embryo cryopreservation should be attempted only when there is no contraindication to use of the hormones required for ovarian stimulation and when chemotherapy can be safely deferred. This also requires an available partner or donor as a sperm source. Cryopreservation of oocytes or ovarian tissue remains investigational at this time (130). Women who have stored embryos but who develop amenorrhea during chemotherapy will require exogenous estrogen and progesterone to prepare the endometrium for implantation. This hormonal therapy will need to continue at least through the first trimester until the placenta is able to provide the necessary hormonal support.

The use of GnRH agonists to protect ovarian function during chemotherapy remains controversial. While some studies have demonstrated improved rates of resumption of menstruation after GnRH use, improved pregnancy outcomes have not yet been demonstrated (131).

Secondary Hematologic Malignancies

The administration of DNA-damaging chemotherapy has been associated with an increase in the risk of developing acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). Alkylating agents in particular have been most strongly associated with secondary leukemias, but topoisomerase inhibitors and platinum agents are also implicated. The peak incidence of secondary leukemia occurs 4 to 5 years after alkylating agent administration, while the latency for topoisomerase-inhibitor associated leukemia is shorter, approximately 18 months. Secondary hematologic malignancies have an especially poor prognosis with survival that is significantly inferior to *de novo* AML (132).

Current chemotherapy for EOC has changed significantly over the past 2 decades. In particular, the alkylating agents have been largely replaced with taxanes. Vay and colleagues recently reported on changing patterns of AML after a diagnosis of EOC using the NCI Surveillance, Epidemiology, and End Results (SEER) database from 1973 through 2006 (133). They identified 199 AML cases among 63,359 patients with a prior diagnosis of EOC, an overall incidence of 0.17%, and found that the median latency to development of leukemia was 4 years after diagnosis, a time consistent with prior observations of alkylating agent-associated secondary leukemias (134). They found that secondary leukemia rates have significantly decreased with more recent EOC diagnosis. The incidence of secondary leukemia was 6/1000 in those diagnosed before 1982, 2/1000 for patients diagnosed between 1982 and 1996, and 0.4/1000 for EOC diagnosed after 1996. These time periods reflect major shifts in EOC treatment. In 1982, platinum-based chemotherapy became the standard of care, and in 1996, paclitaxel replaced cyclophosphamide in EOC treatment regimens. This is an overall 15-fold lowering of the secondary leukemia incidence during the time period under study. It is, however, recognized that some aspects of contemporary EOC treatments have the potential to increase DNA damage and contribute to second malignancies including more prolonged therapy with maintenance and consolidation, the use of targeted therapies, particularly PARP inhibitors, the use of colony stimulating WBC growth factors, and radiographic imaging used to follow disease (134–136).

REFERENCES

1. Szeder V, Torbey M. Prevention and treatment of perioperative stroke. *Neurologist*. 2008; 14(1):30–36.
2. Ng J, Chan MTV, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology*. 2011;115(4):879–890.
3. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008; 371(9627):1839–1847.
4. Bijker JB, Wilton A, Van Klei Y, et al. Intraoperative Hypotension and 1-Year Mortality After Noncardiac Surgery. *Surv Anesthesiol*. 2011; 55(1):40.
5. Poldermans D, Bax J, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and peri-operative cardiac management in non-cardiac surgery: the Task Force for Pre-operative Cardiac Risk Assessment and Peri-operative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J*. 2009;30:2769–2812.
6. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery. *Ann Surg*. 2006;243(1):89–95.
7. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585–593.
8. Clarke-Pearson DL, Dodge RK, Synan I, et al. Venous thromboembolism prophylaxis: patients at high risk to fail intermittent pneumatic compression. *Obstet Gynecol*. 2003;101(1):157–163.
9. Einstein MH, Pritts EA, Hartenbach EM. Venous thromboembolism prevention in gynecologic cancer surgery: a systematic review. *Gynecol Oncol*. 2007;105(3):813–819.
10. Einstein MH, Kushner DM, Connor JP, et al. A protocol of dual prophylaxis for venous thromboembolism prevention in gynecologic cancer patients. *Obstet Gynecol*. 2008;112(5):1091.
11. Mendez LE. Iatrogenic injuries in gynecologic cancer surgery. *Surg Clin North Am*. 2001;81(4):897–923.
12. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy Compared With Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol*. 2009;27:5331–5336.

13. Mourits MJE, Bijen CB, Arts HtJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. *Lancet Oncol.* 2010;11(8):763–771.
14. Obermair A, Janda M, Baker J, et al. Improved surgical safety after laparoscopic compared to open surgery for apparent early stage endometrial cancer: Results from a randomised controlled trial. *Eur J Cancer.* 2012;48(8):1147–1153.
15. Vergote I, Tropé CG, Amant F. European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group; NCIC Clinical Trials Group. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363(10):943–953.
16. Kleven RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep.* 2007;122(2):160–166.
17. Perencevich EN, Sands KE, Cosgrove SE, et al. Health and economic impact of surgical site infections diagnosed after hospital discharge. *Emerg Infect Dis.* 2003;9(2):196–203.
18. Malone DL, Genuit T, Tracy JK, et al. Surgical Site Infections: Reanalysis of Risk Factors. *J Surg Res.* 2002;103(1):89–95.
19. Stulberg JJ, Delaney CP, Neuhauser DV, et al. Adherence to Surgical Care Improvement Project Measures and the Association With Postoperative Infections. *JAMA.* 2010;303(24):2479–2485.
20. Winter WE 3rd, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2007;25:3621–3627.
21. Winter WE 3rd, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2008;26:83–89.
22. Aletri GD, Eisenhauer EL, Santillan A, et al. Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. *Gynecol Oncol.* 2011;120:23–28.
23. Langstraat C, Aletri GD, Cliby WA. Morbidity, mortality and overall survival in elderly women undergoing primary surgical debulking for ovarian cancer: a delicate balance requiring individualization. *Gynecol Oncol.* 2011;123:187–191.
24. Thrall MM, Goff BA, Symons RG, et al. Thirty-day mortality after primary cytoreductive surgery for advanced ovarian cancer in the elderly. *Obstet Gynecol.* 2011;118:537–547.
25. Obermair A, Hagenauer S, Tamandl D, et al. Safety and efficacy of low anterior en bloc resection as part of cytoreductive surgery for patients with ovarian cancer. *Gynecol Oncol.* 2001;83:115–120.
26. Mourtoun SM, Temple LK, Abu-Rustum NR, et al. Morbidity of rectosigmoid resection and primary anastomosis in patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. *Gynecol Oncol.* 2005;99:608–614.
27. Park JY, Seo SS, Kang S, et al. The benefits of low anterior en bloc resection as part of cytoreductive surgery for advanced primary and recurrent epithelial ovarian cancer patients outweigh morbidity concerns. *Gynecol Oncol.* 2006;103:977–984.
28. Nugent EK, Hoff JT, Gao F, et al. Wound complications after gynecologic cancer surgery. *Gynecol Oncol.* 2011;121:347–352.
29. Bakkum-Gamez JN, Langstraat CL, Martin JR, et al. Incidence of and risk factors for postoperative ileus in women undergoing primary staging and debulking for epithelial ovarian carcinoma. *Gynecol Oncol.* 2012;125:614–620.
30. Chi DS, Zivanovic O, Levinson KL, et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. *Gynecol Oncol.* 2010;119:38–42.
31. Hoffman MS, Griffin D, Tebes S, et al. Sites of bowel resected to achieve optimal ovarian cancer cytoreduction: implications regarding surgical management. *Am J Obstet Gynecol.* 2005;193:582–586.
32. Bristow RE, del Carmen MG, Kaufman HS, et al. Radical oophorectomy with primary stapled colorectal anastomosis for resection of locally advanced epithelial ovarian cancer. *J Am Coll Surg.* 2003;197:565–574.
33. Richardson DL, Mariani A, Cliby WA. Risk factors for anastomotic leak after recto-sigmoid resection for ovarian cancer. *Gynecol Oncol.* 2006;103:667–672.
34. Peiretti M, Bristow RE, Zapardiel I, et al. Rectosigmoid resection at the time of primary cytoreduction for advanced ovarian cancer. A multi-center analysis of surgical and oncological outcomes. *Gynecol Oncol.* 2012;126:220–223.
35. Vignali A, Fazio VW, Lavery IC, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. *J Am Coll Surg.* 1997;185:105–113.
36. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev.* 2011;9:CD001544.
37. Jesus EC, Karliczek A, Matos D, et al. Prophylactic anastomotic drainage for colorectal surgery. *Cochrane Database Syst Rev.* 2004;4:CD002100.
38. Cliby W, Dowdy S, Feitoza SS, et al. Diaphragm resection for ovarian cancer: technique and short-term complications. *Gynecol Oncol.* 2004;94:655–60.
39. Zapardiel I, Peiretti M, Zanagnolo V, et al. Diaphragmatic surgery during primary cytoreduction for advanced ovarian cancer: peritoneal stripping versus diaphragmatic resection. *Int J Gynecol Cancer.* 2012;21:1698–1703.
40. Magtibay PM, Adams PB, Silverman MB, et al. Splenectomy as part of cytoreductive surgery in ovarian cancer. *Gynecol Oncol.* 2006;102:369–374.
41. Eisenkop SM, Spirtos NM, Lin WC. Splenectomy in the context of primary cytoreductive operations for advanced epithelial ovarian cancer. *Gynecol Oncol.* 2006;100:344–348.
42. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet.* 2011;378:86–97.
43. Kehoe SM, Eisenhauer EL, Abu-Rustum NR, et al. Incidence and management of pancreatic leaks after splenectomy with distal pancreatectomy performed during primary cytoreductive surgery for advanced ovarian, peritoneal and fallopian tube cancer. *Gynecol Oncol.* 2009;112:496–500.
44. Kondalsamy-Chennakesavan S, Janda M, Gebiski V, et al. Risk factors to predict the incidence of surgical adverse events following open or laparoscopic surgery for apparent early stage endometrial cancer: Results from a randomised controlled trial. *Eur J Cancer.* 2012 Apr 12. PMID: 22503396.
45. Ryan M, Stainton MC, Jaconelli C, et al. The experience of lower limb lymphedema for women after treatment for gynecologic cancer. *Oncol Nurs Forum.* 2003;30(3):417–423.
46. Logmans A, Kruijthof RH, de Bruin HG, et al. Lymphedema and lymphocysts following lymphadenectomy may be prevented by omentoplasty: a pilot study. *Gynecol Oncol.* 1999;75:323–327.
47. Benedetti-Panici P, Maneschi F, Cuttito G, et al. A randomized study comparing retroperitoneal drainage with no drainage after lymphadenectomy in gynecologic malignancies. *Gynecol Oncol.* 1997;65:478–482.
48. Achouri A, Huchon C, Bats A-S, et al. Postoperative lymphocysts after lymphadenectomy for gynaecological malignancies: preventive techniques and prospects. *Eur J Obstet Gynecol Reprod Biol.* 2012;161(2):125–129.
49. Likic IS, Kadija S, Ladjjevic NG, et al. Analysis of urologic complications after radical hysterectomy. *Am J Obstet Gynecol.* 2008;199:644 e1–3.
50. Pushkar DY, Dyakov VV, Kasyan GR. Management of radiation-induced vesicovaginal fistula. *Eur Urol.* 2009;55:131–137.
51. Cronin B, Sung VW, Matteson KA. Vaginal cuff dehiscence: risk factors and management. *Am J Obstet Gynecol.* 2012;206:284–288.
52. Kho RM, Akl MN, Cornella JL, et al. Incidence and characteristics of patients with vaginal cuff dehiscence after robotic procedures. *Obstet Gynecol.* 2009;114:231–235.
53. De Wever I. Pelvic exenteration: surgical aspects and analysis of early and late morbidity in a series of 106 patients. *Acta Chir Belg.* 2011;111:273–281.
54. Khoury-Collado F, Einstein MH, Bochner BH, et al. Pelvic exenteration with curative intent for recurrent uterine malignancies. *Gynecol Oncol.* 2012;124:42–47.
55. Hockel M, Dornhofer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. *Lancet Oncol.* 2006;7:837–847.
56. Berek JS, Howe C, Lagasse LD, et al. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. *Gynecol Oncol.* 2005;99:153–159.
57. Goldberg GL, Sukumvanich P, Einstein MH, et al. Total pelvic exenteration: the Albert Einstein College of Medicine/Montefiore Medical Center Experience (1987 to 2003). *Gynecol Oncol.* 2006;101:261–268.
58. Jackson KS, Naik R. Pelvic floor dysfunction and radical hysterectomy. *Int J Gynecol Cancer.* 2006;16:354–363.
59. Vrzackova P, Weiss P, Cibula D. Sexual morbidity following radical hysterectomy for cervical cancer. *Expert Rev Anticancer Ther.* 2010;10:1037–1042.
60. Hopkins MP, Reid GC, GW. M. Radical vulvectomy: the decision for the incision. *Cancer.* 1993;72(3):799–803.
61. Leminen A, Forss M, Paavonen J. Wound complications in patients with carcinoma of the vulva: Comparison between radical and modified vulvectomy. *Eur J Obstet Gynecol Reprod Biol.* 2000;93(2):193–197.
62. Cavanagh D, Fioria JV, Hoffman MS, et al. Invasive Carcinoma of the Vulva - Changing Trends in Surgical Management. *Am J Obstet Gynecol.* 1990;163(3):1007–1015.
63. Reedy MB, Capen CV, Baker DP, et al. Hyperbaric oxygen therapy following radical vulvectomy: An adjunctive therapy to improve wound healing. *Gynecol Oncol.* 1994;53:13–16.
64. Stehman FB, Bundy BN, Dvoretzky PM, et al. Early Stage-I Carcinoma of the Vulva Treated with Ipsilateral Superficial Inguinal Lymphadenectomy and Modified Radical Hemivulvectomy - A Prospective Study of the Gynecologic Oncology Group. *Obstet Gynecol.* 1992;79(4):490–497.
65. Zhang X, Sheng X, Niu J, et al. Sparing of saphenous vein during inguinal lymphadenectomy for vulvar malignancies. *Gynecologic Oncology.* 2007;105(3):722–726.
66. Van der Zee AGJ, Oonk MH, De Hullu JA, et al. Sentinel Node Dissection Is Safe in the Treatment of Early-Stage Vulvar Cancer. *J Clin Oncol.* 2008;26(6):884–889.
67. Gould N, Kamelle S, Tillmanns T, et al. Predictors of complications after inguinal lymphadenectomy. *Gynecol Oncol.* 2001;82(2):329–332.

68. Janda M, Obermair A, Cella D, et al. Vulvar cancer patients' quality of life: a qualitative assessment. *Int J Gynecol Cancer*. 2004;14:875–881.
69. Cormier JN, Rourke L, Crosby M, et al. The Surgical Treatment of Lymphedema: A Systematic Review of the Contemporary Literature (2004–2010). *Ann Surg Oncol*. 2012;19:642–651.
70. Perez CA, Breaux S, Bedwinek JM, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix.II. Analysis of complications. *Cancer*. 1984;54:235–246.
71. Smith ST, Seski JC, Copeland LJ, et al. Surgical management of irradiation-induced small bowel damage. *Obstet Gynecol*. 1985;65:563–567.
72. Gellrich J, Hakenberg OW, Oehlschlager S, et al. Manifestation, latency and management of late urological complications after curative radiotherapy for cervical carcinoma. *Onkologie*. 2003;26:334–340.
73. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy versus pelvic and para-aortic radiation for high-risk cervical cancer: a randomized Radiation Therapy Oncology Group clinical trial. *N Engl J Med*. 1999;340:1137.
74. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340:1144–1153.
75. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340:1154–1161.
76. Lind H, A Waldenström, Dunberger G, et al. Late symptoms in long-term gynaecological cancer survivors after radiation therapy: a population-based cohort study. *Br J Cancer*. 2011;105:737–745.
77. Andreyev H, Davidson S, Gillespie C, et al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. *Gut*. 2012;61:179–192.
78. Martin E, Pointreau Y, Roche-Forestier S, et al. Normal tissue tolerance to external beam radiation therapy: small bowel. *Cancer Radiother*. 2010;14:350–353.
79. Chun M, Kang S, Kil H, et al. Rectal bleeding and its management after irradiation for uterine cervical cancer. *Int J Radiation Oncol Biol Phys*. 2004;58:98–105.
80. Do N, Nagle D, Poylin V. Radiation proctitis: Current strategies in management. *Gastroenterol Res Pract*. 2011;1–9.
81. Craighead P, Shea-Budgell M, Nation J, et al. Hyperbaric oxygen therapy for late radiation tissue injury in gynecologic malignancies. *Curr Oncol*. 2011;18:220–227.
82. Dunberger G, Lind H, Steineck G, et al. Self-reported symptoms of fecal incontinence among long-term gynaecological cancer survivors and population-based controls. *Eur J Cancer*. 2010;46:606–615.
83. Dunberger G, Lind H, Steineck G, et al. Fecal incontinence affecting quality of life and social functioning among long-term gynecological cancer survivors. *Int J Gynecol Cancer*. 2010;20:449–460.
84. Pointreau Y, Atean I, Durdax C. Normal tissue tolerance to external beam radiation therapy: Bladder. *Cancer Radiother*. 2010;14:363–368.
85. Maier U, Ehrenbock P, Hofbauer J. Late urological complications and malignancies after curative radiotherapy for gynecological carcinomas: A retrospective analysis of 10, 709 patients. *J Urol*. 1997;158:814–817.
86. Levenback C, Eifel P, Burke T, et al. Hemorrhagic cystitis following radiotherapy for stage 1b cancer of the cervix. *Gynecol Oncol*. 1994;55:206–210.
87. Chong KT, Hampson NB, Corman JM. Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. *Urology*. 2005;65:649–653.
88. Magne N, Chargari C, Pointreau Y, et al. Normal tissue tolerance to external beam radiation therapy: the vagina. *Cancer Radiother*. 2010;14:369–372.
89. Au S, Grigsby P. The irradiation tolerance dose of the proximal vagina. *Radiat Oncol*. 2003;67:77–85.
90. Vaz A, Pinto-Neto A, Conde D, et al. Quality of Life and menopausal and sexual symptoms in gynecologic cancer survivors: a cohort study. *Menopause*. 2011;18:662–669.
91. Johnson N, Miles T, Cornes P. Dilating the vagina to prevent damage from radiotherapy: systematic review of the literature. *Br J Obstet Gynecol*. 2010;117:522–531.
92. Grigsby P, Russell A, Bruner D, et al. Late injury of cancer therapy on the female reproductive tract. *Int J Radiat Oncol Biol Phys*. 1995;31:1281–1299.
93. Stroud J, Mutch D, Rader J, et al. Effects of cancer treatment on ovarian function. *Fertil Steril*. 2009;9:417–427.
94. Wallace W, Thomson A, Kelsey T. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys*. 2005;62:738–744.
95. De Santis, M. Ionizing radiations in pregnancy and teratogenesis. A review of the literature. *Reprod Toxicol*. 2005;20:323–329.
96. Kwon J, Huh S, Yoon Y, et al. Pelvic bone complications after radiation therapy of uterine cervical cancer: evaluation with MRI. *Am J Radiol*. 2008;191:987–994.
97. Schmeler K, Jhingran A, Iyer R, et al. Pelvic fractures after radiotherapy for cervical cancer. *Cancer*. 2010;116:625–630.
98. Mauch P, Constine L, Greenberger J, et al. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31:1319–1339.
99. Banfi A, Bianchi G, Galotto M, et al. Bone marrow stromal damage after chemo/radiotherapy: occurrence, consequences and possibilities of treatment. *Leukemia and Lymphoma*. 2001;42:863–870.
100. Jaeckle K. Neurologic manifestations of neoplastic and radiation-induced plexopathies. *Semin Neurol*. 2010;30:254–262.
101. Wang J, Boerma M, Fu Q, Hauer-jensen M. Radiation responses in skin and connective tissues: effect on wound healing and surgical outcome. *Hernia*. 2006;10:502–506.
102. Gieringer M, Goespath J, Naim R. Radiotherapy and wound healing: principles, management and prospects. *Oncol Rep*. 2011;26:299–307.
103. Salama JK, Mundt AJ, Roeske J, et al. Preliminary outcome and toxicity report of extended field, intensity-modulated radiation therapy for gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2006;65:1170.
104. Yuhas JM, Spellman JM, Culo F. The role of WR-2721 in radiotherapy and/or chemotherapy. *Cancer Clin Trials*. 1980;3:211.
105. Athanassiou H, Antonadou D, Coliarakis N, et al. Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. *Int J Radiat Oncol Biol Phys*. 2003;56:1154.
106. Liu T, Liu Y, He S, et al. Use of radiation with or without WR-2721 in advanced rectal cancer. *Cancer*. 1992;69:2820.
107. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).
108. Fauci JM, Whitworth JM, Schneider KE, et al. Prognostic significance of the relative dose intensity of chemotherapy in primary treatment of epithelial ovarian cancer. *Gynecol Oncol*. 2011;122(3):532–535.
109. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2012. Myeloid growth factors.
110. Laskey RA, Poniewierski MS, Lopez MA, et al. Predictors of severe and febrile neutropenia during primary chemotherapy for ovarian cancer. *Gynecol Oncol*. 2012;125(3):625–630.
111. Markman M, Markman J, Webster K, et al. Thrombocytopenia associated with second-line carboplatin-based chemotherapy for ovarian, fallopian tube, and primary peritoneal cavity cancers. *J Cancer Res Clin Oncol*. 2004;130(12):741–744.
112. Rizzo JD, Brouwers M, Hurley P. American Society of Clinical Oncology, American Society of Hematology, et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol*. 2010;28(33):4996–5010.
113. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2012. Antiemesis.
114. Dobyan DC, Levi J, Jacobs C, et al. Mechanism of cis-platinum nephrotoxicity: II. Morphologic observations. *J Pharmacol Exp Ther*. 1980;213(3):551.
115. Santoso JT, Lucci JA 3rd, Coleman RL, et al. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. *Cancer Chemother Pharmacol*. 2003;52(1):13–18.
116. von Schlippe M, Fowler CJ, Harland SJ. Cisplatin neurotoxicity in the treatment of metastatic germ cell tumour: time course and prognosis. *Br J Cancer*. 2001;85(6):823.
117. Rademaker-Lakhai JM, Crul M, Zuur L, et al. Relationship between cisplatin administration and the development of ototoxicity. *J Clin Oncol*. 2006;24(6):918.
118. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. *J Natl Cancer Inst*. 2000;92:669.
119. Ozols RF, Bundy BN, Greer BE, et al. Gynecologic Oncology Group. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21(17):3194–3200.
120. O'Sullivan JM, Huddart RA, Norman AR, et al. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol*. 2003;14(1):91.
121. Culine S, Kramar A, Théodore C. Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP, et al. Randomized trial comparing bleomycin/etoposide/cisplatin with alternating cisplatin/cyclophosphamide/doxorubicin and vinblastine/bleomycin regimens of chemotherapy for patients with intermediate- and poor-risk metastatic nonseminomatous germ cell tumors: Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP. *J Clin Oncol*. 2008;26(3):421.
122. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer*. 2010;10:337.

123. Cooper LT, Baughman KL, Feldman AM, et al. American Heart Association, American College of Cardiology, European Society of Cardiology. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation*. 2007;116(19):2216.
124. Hershman DL, McBride RB, Eisenberger A, et al. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(19):3159.
125. Andreopoulou E, Gaiotti D, Kim E, et al. Pegylated liposomal doxorubicin HCL (PLD; Caelyx/Doxil): experience with long-term maintenance in responding patients with recurrent epithelial ovarian cancer. *Ann Oncol*. 2007;18(4):716.
126. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *Clin Oncol*. 2004;22(11):2159–2166.
127. Schover LR, Rybicki LA, Martin BA, et al. Having children after cancer: A pilot survey of survivors' attitudes and experiences. *Cancer*. 1999;86(4):697.
128. Falcone T, Attaran M, Bedaiwy MA, et al. Ovarian function preservation in the cancer patient. *Fertil Steril*. 2004;81(2):243.
129. Das M, Shehata F, Son WY, et al. Ovarian reserve and response to IVF and in vitro maturation treatment following chemotherapy. *Hum Reprod*. 2012;27(8):2509–2514. Epub 2012 May 22.
130. Gosden RG. Prospects for oocyte banking and in vitro maturation. *J Natl Cancer Inst Monogr*. 2005.
131. Bedaiwy MA, Abou-Setta AM, Desai N, et al. Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis. *Fertil Steril*. 2011;95(3):906.
132. Godley LA, Larson RA. Therapy-related Myeloid Leukemia. *Semin Oncol*. 355 2008;35(4):418–429.
133. Vay A, Kumar S, Seward S, et al. Therapy-related myeloid leukemia after treatment for epithelial ovarian carcinoma: an epidemiological analysis. *Gynecol Oncol*. 2011;123(3):456–460.
134. Hershman D, Neugut AI, Jacobson JS, et al. Acute Myeloid Leukemia or Myelodysplastic Syndrome Following Use of Granulocyte Colony-Stimulating Factors During Breast Cancer Adjuvant Chemotherapy. *JNCI*. 2007;99:196–205.
135. Rouleau M, Patel A, Hendzel MJ, et al. PARP inhibition: PARP1 and beyond. *Nature Reviews Cancer*. 2010;10:293–301.
136. Sodickson A, Baeyens PF, Andriole KP, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. *Radiology*. 2009;251:175–184.

RUSSELL K. PORTENYO ■ BROOKE SQUILLACE
■ PAULINE LESAGE

The heterogeneous patient population managed by gynecologic oncologists presents a broad range of problems in pain management. The incidence of cancer pain varies, depending on the type of neoplasm, stage, and extent of spread. Acute pains are highly prevalent, including the rather straightforward incisional pain that follows surgical procedures. Chronic pain occurs in the context of numerous other physical and psychosocial symptoms, often in the population with advanced disease. Effective relief of pain may improve mood, coping, function, and other aspects of quality of life. Gynecologic oncologists have the opportunity and obligation to effectively treat pain.

SCOPE OF THE PROBLEM

Pain is highly prevalent in the cancer population. Overall, 30% to 50% of patients undergoing active antineoplastic therapy and 75% to 90% of those with advanced disease experience chronic pain severe enough to warrant therapy (1–3). Although data specific to gynecologic tumors are meager, those extant suggest that the overall prevalence rates mirror these averages (1,4–6).

A survey of patients with ovarian cancer illustrates the prevalence and characteristics of chronic pain in this population (6). The sample included 111 inpatients and 40 outpatients. The median age was 55 years (range, 23 to 86 years), and most patients (82%) had stage III or IV disease at presentation and active disease (69%) at the time of the survey. Forty-two percent (n = 63) reported “persistent or frequent pain” during the preceding 2 weeks. This pain had a median duration of 2 weeks (range, <1 to 756 weeks) and was usually abdominal/pelvic (80%), frequent or almost constant (66%), and moderate to severe. Most patients reported that pain caused moderate or greater interference with various aspects of function, particularly activity (68%), mood (62%), work (62%), and overall enjoyment of life (61%). In a study of 97 outpatients with breast cancer (54% metastatic disease), 47% of patients experienced cancer-related pain substantially interfering with their mood, quality of life, and functional status. The most prevalent underlying pathology was postmastectomy syndrome (56%), followed by pain from bone metastasis (26%).

Tissue injury related to the neoplasm itself is the most common cause of chronic cancer pain. Pain prevalence increases with the extent of disease and can be as high as 90% among populations with advanced illness (7). Chronic pain also may be related to an antineoplastic treatment, such as surgery (8–10), and in a small minority of patients, pain is unrelated to either the malignancy or its treatment.

Observational studies suggest that satisfactory relief of chronic pain is possible in 70% to 90% of patients with cancer

(11–14). However, undertreatment remains a serious problem, however (15–19), despite the availability of well-accepted guidelines for pain management (20). It has been suggested that an average of 43% of cancer patients receive inappropriate care for pain (21). Many concerns may undermine optimal treatment, among which are the underreporting of symptoms or nonadherence of patients, and the inadequate assessment, knowledge, or communication of health professionals (22).

Although the prevalence of severe acute pain in patients with gynecologic cancers has not been determined, and is likely changing with the increasing use of minimally invasive procedures, it is nonetheless presumed to be common and potentially controllable in a very large majority of cases. As more cancer surgeries are performed in the ambulatory setting, the ability to provide adequate treatment in unmonitored settings has become a greater challenge.

Patients with cancer, particularly those with advanced disease, also experience numerous symptoms other than pain. The most common of these symptoms are fatigue and anxiety or depression. Acute treatment-related symptoms, such as chemotherapy-induced nausea and vomiting, also are prevalent. In the aforementioned survey of patients with ovarian cancer, the median number of symptoms per patient was 9 (range, 0 to 25) (Table 31.1) (6). In addition to pain, the most prevalent symptoms were fatigue (“lack of energy”), psychologic distress (“worrying,” “feeling sad,” and “feeling nervous”), and insomnia (“difficulty sleeping”). All of these symptoms had a prevalence of greater than 50%. Compared to norms, approximately one-third of the patients in this survey recorded heightened psychologic distress. The most important predictor of heightened distress was progressive impairment in physical functioning. Distress also can be worsened by psychological or social factors, or by spiritual or existential challenges (21).

Fatigue is one of the most common complications of cancer and its treatment, and exemplifies the problem of concurrent symptoms in the patient with significant pain. In a recent analysis, patients perceived fatigue to be the most distressing symptom adversely affecting quality of life (23). A definition proposed for the International Classification of Diseases 10th Revision–Clinical Modification (ICD-10-CM) stresses the multidimensional nature of the phenomenon (24) and the National Comprehensive Cancer Network 2011 guidelines identified 8 factors that should be assessed as potential causes of prolonged fatigue, one of which is pain (others include medications/side effects, emotional distress, sleep disturbance, anemia, nutrition, decreased functional status, and other comorbidities) (25). Patients with pain should be evaluated for meaningful concomitant symptoms, and the assessment of other symptoms should prompt an assessment of pain.

Table 31.1 Prevalence and Characteristics of Symptoms Associated with Ovarian Cancer (n = 151)

Symptom	Overall Prevalence (%)	Intensity ^a (%)	Frequency ^b (%)	Distress ^c (%)
Worrying	71.7	55.4	33.5	25.0
Lack of energy	68.6	52.6	37.3	28.0
Feeling sad	63.8	46.4	22.8	22.2
Pain	61.8	50.4	32.9	24.1
Feeling nervous	61.5	39.9	25.0	19.6
Difficulty sleeping	57.3	44.0	30.7	20.7
Dry mouth	45.6	30.2	18.8	8.7
Feeling drowsy	45.3	32.7	15.9	9.3
Feeling irritable	45.9	33.8	12.2	10.8
Numbness/tingling in hands/feet	42.7	24.0	26.0	9.3
“I don’t look like myself”	35.8	25.0	—	12.8
Nausea	35.6	18.8	9.4	8.1
Difficulty concentrating	34.7	16.0	7.3	11.3
Feeling bloated	34.7	26.0	17.3	8.7
Constipation	28.6	20.4	—	11.6
Lack of appetite	28.4	20.4	14.2	8.2
Change in the way food tastes	25.7	16.2	—	8.1
Hair loss	26.4	15.0	—	9.5
Cough	25.3	11.3	6.0	4.0
Itching	22.3	11.5	8.1	3.4
Diarrhea	20.8	10.1	6.0	4.0
Swelling of arms or legs	18.9	12.2	—	8.8
Shortness of breath	18.7	10.0	7.3	6.0
Weight loss	18.5	4.8	—	3.4
Problems with sexual interest or activity	17.6	14.9	10.9	6.8
Dizziness	16.2	5.4	2.7	2.7
Vomiting	13.3	8.7	3.3	6.0
Mouth sores	8.1	4.7	1.4	2.0
Nightmares	8.0	5.3	2.0	2.0
Problems with urination	7.3	5.3	4.0	3.3
Urinary accidents	7.4	4.1	0.7	1.4
Difficulty swallowing	5.4	3.4	2.7	2.0

^aPercentage of sample describing the symptom as “moderate,” “severe,” or “very severe.”

^bPercentage of sample describing the frequency of the symptom as “frequently” or “almost constantly.”

^cPercentage of sample describing the distress associated with the symptom as “quite a bit” or “very much.”

Source: Reprinted with permission from Portenoy RK, Kornblith AB, Wong G, et al. Pain in ovarian cancer: prevalence, characteristics, and associated symptoms. *Cancer*.1994;74:907–915.

ASSESSMENT OF CANCER PAIN

The assessment of chronic pain in patients with gynecologic cancer requires an understanding of its phenomenology, pathophysiology, and syndromes. Optimally, this assessment must also consider the broad range of physical, psychologic, and social disturbances concurrently experienced by these patients. Patients with acute pain, particularly acute postoperative pain, pose less complex management problems, but could still potentially benefit from an ongoing comprehensive assessment. The patient's description of the pain, findings on physical examination, objective data from imaging and other tests, and information about the extent of the malignant disease and its treatment are all utilized to assess the likely etiology and underlying pathophysiology of the pain, and if possible, identify a specific cancer syndrome (26).

National medical organizations have developed guidelines in an effort to more effectively detect and monitor pain. The Joint Commission on Accreditation of Healthcare Organizations developed a standard requiring that pain be assessed initially and periodically in all hospitalized patients. The National Comprehensive Cancer Network 2011 Adult Cancer Pain Guidelines require a formal pain assessment, measurement of pain intensity, reassessment of pain intensity at specific intervals, psychosocial support, and specific educational material (25).

Definition of Pain

According to the International Association for the Study of Pain, pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (27). Reported pain may be perceived by the clinician to be greater than or less than the observable degree of tissue injury. In the cancer population, a physical process capable of explaining the pain can usually be identified, but this does not obviate the need for a careful assessment of other factors, including psychologic disturbances, that could be influencing the intensity of the pain or contributing to pain-related distress.

The definition of pain can be further clarified by the distinctions among nociception, pain, and suffering (Fig. 31.1) (28). Nociception is the activity produced in the afferent nervous system by potentially tissue-damaging stimuli. Clinically, nociception is inferred to exist whenever tissue damage is identified. Pain is the perception of nociception and, like other perceptions, can be determined by more than the activity in the sensorineural apparatus alone. Although tissue damage related to the tumor or its treatment is common in those with cancer pain, a careful assessment is needed to infer the degree to which the pain report is consistent with the nociception presumed by the clinician on

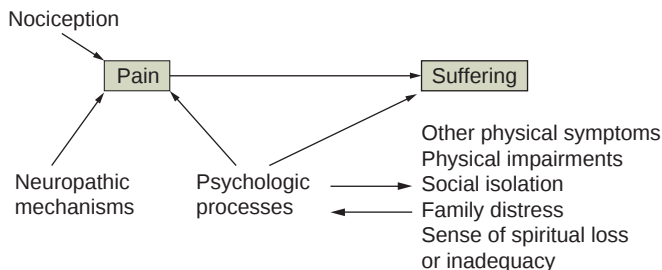


FIGURE 31.1. Distinctions and interactions between nociception, pain, and suffering.

Source: Reproduced with permission from Portenoy RK. Cancer pain: pathophysiology and syndromes. *Lancet*. 1992;339:1026–1031.

the basis of the physical findings. In all cases, factors other than nociception, including neuropathic processes that can sustain pain in the absence of ongoing tissue injury (see below) and psychologic disturbances, must be evaluated as other potential determinants of the pain. The failure to address these other factors while targeting therapy at the sources of nociception can lead to a poor outcome in which the focus of tissue damage is ameliorated but the pain continues.

Suffering, or "total pain," can be defined as a more global aversive experience determined by numerous perceptions, one of which may be pain (see below). Among the many other factors that may contribute to suffering are the perception of physical deterioration, the experience of symptoms other than pain, psychologic disturbances (e.g., depression or anxiety), disruption in the family, social isolation, and fear of death. Just as an inordinate focus on nociception, rather than pain, can lead to interventions that reduce tissue damage without alleviating symptoms, an emphasis on pain management alone in patients with profound suffering determined by other factors can fail to influence favorably the overall quality of life even if physical comfort is enhanced (29,30).

Evaluation of the Pain Complaint

The comprehensive assessment of pain should include information about temporal characteristics (onset and duration), course (stable or changing since onset, relatively constant or widely fluctuating), severity (both average and worst), location, quality, and provocative and palliative factors. This evaluation is complemented by information about the patient's extent of disease, related medical and psychosocial conditions, present and past pain management strategies and their outcomes, the impact of the pain on the patient's daily life and functioning, as well as the patient's and family's knowledge of, expectations about, and goals for pain management. Risk factors for the undertreatment of the patient's cancer pain and risk factors for serious physical or psychiatric comorbidities (such as drug abuse) should also be examined.

Characteristics of Pain

Intensity. The measurement and recording of pain intensity is an essential element in the comprehensive assessment of pain. Although more information than intensity alone is needed to understand and manage cancer pain, a systematic method for assessing intensity is foundational. The most common approaches are a verbal rating scale (none, mild, moderate, severe, excruciating) and/or an 11-point numeric scale (where 0 is no pain and 10 is the worst pain imaginable). A visual analog scale (VAS) that uses a 10-cm line anchored at one end by the words "no pain" or "least possible pain" and at the other end by "worst possible pain" is another simple and valid approach to pain measurement. The choice of scale is less important than consistency in its use over time. Brief assessment tools modeled on this approach also can be applied to the intensity measurement of nonpain symptoms, such as depression and fatigue.

Multidimensional scales are available, but usually are utilized in research settings. These scales provide a more comprehensive measure of the pain experience, often encompassing such factors as function and quality of life.

Temporal. Acute pain usually has a well-defined onset and a readily identifiable cause (e.g., surgical incision). It may be associated with anxiety, overt pain behaviors (moaning or grunting), and signs of sympathetic hyperactivity (including tachycardia, hypertension, and diaphoresis). In contrast, chronic pain is characterized by an ill-defined onset and a prolonged, fluctuating course. Overt pain behaviors and sympathetic

hyperactivity are typically absent, and vegetative signs, including lassitude, sleep disturbance, and anorexia, may be present. A clinical depression evolves in some patients. Most patients with chronic cancer pain also experience periodic flares of pain, or “breakthrough pain,” an observation with important therapeutic implications (see below).

Topographic. The distinctions among focal, multifocal, and generalized pains may influence both the assessment and treatment of the patient. Some therapies, such as nerve blocks and cordotomy, depend on the specific location and extent of the pain.

The distinction between focal and referred pain is similarly important. Focal pains are experienced superficial to the underlying nociceptive lesion, whereas referred pains are experienced at a site distant from the nociceptive lesion.

Pain may be referred from a lesion involving any of a large group of structures, including nerve, bone, muscle, or other soft tissue, and viscera (31–33). Various subtypes can be distinguished: (a) pain referred anywhere along the course of an injured peripheral nerve (such as pain in the thigh or knee from a lumbar plexus lesion); (b) pain referred along a course of the nerve supplied by a damaged nerve root (known as radicular pain); (c) pain referred to the lower part of the body, usually the feet and legs, from a lesion involving the spinal cord (called funicular pain); and (d) pain referred to a site remote from the nociceptive lesion and outside the dermatome affected by the lesion (e.g., shoulder pain from diaphragmatic irritation). Knowledge of pain referral patterns is needed in order to target appropriate assessment procedures. For example, a patient with recurrent cervical cancer who reports progressive pain in the inguinal region may require evaluation of numerous structures to identify the underlying nociceptive lesion, including the subjacent pelvic bones and hip joint, pelvic sidewall, paraspinal gutter at an upper lumbar spinal level, and intraspinal region at the upper lumbar level.

Etiology

The etiology of acute pain is usually clear-cut. Further evaluation to determine the underlying lesion or pathophysiology of the pain is not indicated unless the course varies from the expected. In contrast, the etiology of chronic cancer-related pain may be more difficult to characterize. In most cases, pain is due to direct invasion of pain-sensitive structures by the neoplasm (27,28,34). The structures most often involved are bone and neural tissue, but pain can also occur when there is an obstruction of hollow viscus, distention of organ capsules, distortion, or occlusion of blood vessels, and infiltration of soft tissues. The etiology of pain in less than a quarter of patients relates to an antineoplastic treatment, and less than 10% have pain unrelated to the neoplasm or its treatment (34).

These data suggest that a careful evaluation of cancer patients with pain is likely to identify an underlying nociceptive lesion, which will usually be neoplastic. A survey of patients referred to a pain service in a major cancer hospital noted that previously unsuspected lesions were identified in 63% of patients (35). This outcome altered the known extent of disease in virtually all patients, changed the prognosis for some, and provided an opportunity for a primary antineoplastic therapy in approximately 15%.

Pathophysiology

Pain is labeled nociceptive if it is inferred that the sustaining mechanisms involve ongoing tissue injury. This injury can involve either somatic or visceral structures. The quality of somatic nociceptive pain is typically described as aching, stabbing,

throbbing, or pressure-like. The quality of visceral nociceptive pain is largely determined by the structures involved. Obstruction of hollow viscus is usually associated with complaints of gnawing or crampy pain, whereas injury to organ capsules or mesentery is associated with an aching or stabbing discomfort.

Pain is labeled neuropathic if the evaluation suggests that it is sustained by abnormal somatosensory processing in the peripheral or the central nervous system (CNS) and there is some identifiable neurologic injury. Neuropathic mechanisms are involved in approximately 40% of cancer pain syndromes and can be disease-related (e.g., tumor invasion of nerve plexus) or treatment-related (e.g., postmastectomy syndrome, chemotherapy-induced painful polyneuropathy) (34). Among those with metastatic disease, neuropathic pain usually results from neoplastic injury to peripheral nerves. Other, less common subtypes include (a) those in which the focus of activity is in the CNS (sometimes generically termed deafferentation pain); and (b) those in which the pain is believed to be maintained by efferent activity in the sympathetic nervous system (so-called sympathetically maintained pain). Identification of a neuropathic mechanism is extremely important in clinical management because specific therapies may be useful for these conditions (see below).

Neuropathic pain is diagnosed on the basis of the patient's verbal description of the pain and evidence of injury to neural tissue. Patients may use any of a variety of verbal descriptors but some, such as “burning,” “shock-like,” or “electrical,” are particularly suggestive of neuropathic pain (36,37). Areas of abnormal sensations are often found on physical examination. These may include hypesthesia (a numbness or lessening of feeling), paresthesias (abnormal nonpainful sensations such as tingling, cold, or itching), hyperalgesia (increased perception of painful stimuli), hyperpathia (exaggerated pain response), and allodynia (pain induced by nonpainful stimuli such as a light touch or cool air).

Although pain can occur as a primary outcome of psychologic processes, labeled in psychiatric parlance as one of the somatoform disorders, this appears to be rare in the cancer population. Nonetheless, psychologic factors may augment or alter the pain complaint, and not surprisingly, pain may be associated with fluctuations in psychologic distress. In one series of 203 inpatients with cancer, for example, depression was independently associated with pain intensity after controlling for performance status, disease status, and perceived treatment effect (38).

To assess the complex relationship between pain and psychiatric disease, it is useful to have familiarity with the common disorders that are present in gynecologic malignancies. One study observed major depression in nearly one quarter of women hospitalized with cervical, endometrial, and vaginal cancer (39), and another reported more severe depression and poorer body image among gynecologic patients than those with breast cancer undergoing mastectomy (40).

If the assessment of the pain does not provide enough information to categorize it as primarily nociceptive or neuropathic, or mixed, or yield a sufficient understanding of the psychologic factors that may be influencing the pain, it is important to acknowledge this lack of certainty and avoid labeling the patient with a term that may inappropriately direct care. The greatest concern in this regard is the labeling of pain as psychogenic when the assessment does not yield positive evidence of a psychiatric disorder, but an alternative answer is lacking. In this case, it is better to label the pain idiopathic than to speculate about underlying factors that are not clearly demonstrable from the evaluation.

Pain Syndromes

Efforts to improve the assessment of cancer pain have been greatly encouraged by the description of numerous pain

syndromes, each of which is defined by a cluster of symptoms and signs (Table 31.2) (27,28,34,41,42). Syndrome identification can help direct the diagnostic evaluation, clarify the prognosis, and target therapeutic interventions. Recognition of pain syndromes that occur commonly among patients with gynecologic cancers (Table 31.3) can also facilitate the assessment of these patients.

Table 31.2 Cancer Pain Syndromes

- I. Pain associated with direct tumor involvement
 - A. Due to invasion of bone
 1. Base of skull
 2. Vertebral body
 3. Generalized bone pain
 - B. Due to invasion of nerves
 1. Peripheral nerve syndromes
 2. Painful polyneuropathy
 3. Brachial, lumbar, sacral plexopathies
 4. Leptomeningeal metastases
 5. Epidural spinal cord compression
 - C. Due to invasion of viscera
 - D. Due to invasion of blood vessels
 - E. Due to invasion of mucous membranes
- II. Pain associated with cancer therapy
 - A. Postoperative pain syndromes
 1. Postthoracotomy syndrome
 2. Postmastectomy syndrome
 3. Postradical neck dissection
 4. Postamputation syndromes
 - B. Postchemotherapy pain syndromes
 1. Painful polyneuropathy
 2. Aseptic necrosis of bone
 3. Steroid pseudorheumatism
 4. Mucositis
 - C. Postirradiation pain syndromes
 1. Radiation fibrosis of brachial or lumbosacral plexus
 2. Radiation myelopathy
 3. Radiation-induced peripheral nerve tumors
 4. Mucositis
- III. Pain indirectly related or unrelated to cancer
 - A. Myofascial pains
 - B. Postherpetic neuralgia
 - C. Chronic headache syndromes

Table 31.3 Pain Syndromes Commonly Encountered among Patients with Gynecologic Cancer

Acute Pain Syndromes

At any stage of disease:

Postoperative pain

Mucositis

In advanced stages of disease:

Recurrent bowel obstruction

Ureteral obstruction

Movement-related pain in brachial/lumbosacral plexopathy

Movement-related pain from bony lesions

Cancer-Related Chronic Pain Syndromes

Brachial/lumbosacral plexopathy

Chronic abdominal pain: bowel obstruction, ascites, hepatomegaly

Tenesmoid pain

Bone pain from metastases

Treatment-Related Chronic Pain Syndromes

Postmastectomy syndrome

Radiation-induced plexopathy

Chemotherapy-induced peripheral neuropathy (paclitaxel, cisplatin)

Comprehensive Assessment

A comprehensive assessment that incorporates this pain-related information can be used to elaborate a problem list that guides the priorities and direction of therapy. In many situations, such as acute postoperative pain or chronic pain related to a well-characterized lesion (e.g., pathologic fracture), the assessment issues are simple and the problem list is brief and straightforward. In other cases, most often in populations with advanced disease, a complex group of symptoms, medical disorders, and psychosocial disturbances greatly complicate the assessment process. In these cases, a comprehensive assessment encourages efficient selection of an appropriate multimodal therapy.

The biopsychosocial model implied by this clinical reality has provided a framework for pain research. A consensus has been reached that the core outcome domains for studies of chronic pain are pain intensity, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, and other symptoms and adverse events (43).

Patients whose pain had been responsive to pain medication but experience an increase in pain intensity or a change in pain characteristics should be comprehensively reassessed as the initial step in management. The goal is to determine whether specific factors responsible for the change can be identified. Relapse or disease progression, for example, may be amenable to primary therapeutic strategies, such as chemotherapy to address disease progression associated with loss of analgesic effectiveness. Other factors, such as cord compression, systemic or local infection, and psychological distress (e.g., depression), also may be treatable.

MANAGEMENT OF ACUTE PAIN

Although the treatment of patients with acute pain, particularly postoperative pain, is typically less challenging than the long-term management of chronic pain, the outcomes achieved in routine practice settings are often inadequate. Given the potential efficacy of widely used strategies, such as patient-controlled analgesia (PCA), less-than-satisfactory outcomes may be more related to systems issues, such as access to a pain service or prolonged pharmacy preparation times, than purely clinical issues. Cancer patients also commonly have concurrent medical problems, psychologic disturbances, and prior and current drug exposures that may increase the heterogeneity of the population and diminish the likelihood that routine measures provide adequate relief of pain. The need for clinicians and administrators to attend to the problem of acute pain and provide the resources and systems for expert management is therefore particularly important in this population.

“Routine” Approach to Postoperative Pain

Despite great variability in the pharmacokinetics and pharmacodynamics of single opioid doses (44), and the large proportion of patients who fail to attain adequate analgesia with routine postoperative care, many patients do respond adequately to an opioid, traditionally morphine or meperidine, administered “as needed.” In the cancer population, the starting dose must take into account the prior opioid exposure of the patient. A reasonable starting dose for morphine in opioid-naïve patients, for example, would be 5 to 8 mg every 3 hours as needed, or 1 mg every 6 minutes as needed if a PCA device is used. If the patient has a history of current opioid use for pain, a reasonable starting dose would be the equivalent of 5% to 10% of the total opioid consumption during the previous 24 hours. If the drug or route of administration is changed, an equianalgesic dose table must be consulted to calculate the equivalent total daily dose of the new drug. Once a dose is selected, it can be initially administered every 3 hours as needed. If repetitive dosing is employed, and the dose or interval selected initially is not effective after the first or second dose, an increase in the dose or shortening of the dosing interval should be considered.

As-needed dosing of this type usually is most effective when a procedure is likely to yield pain for a short while. In these cases, the use of an opioid with a short half-life, such as morphine or hydromorphone is preferred; meperidine, although likely to be well tolerated during brief therapy, is generally not preferred because of the availability of safer drugs (see below). The use of the intravenous route through slow injection or brief infusion will reduce distress associated with painful injections.

The proportion of cancer patients with postoperative pain who will be undertreated by an as-needed dosing schedule can be diminished if several factors are recognized. Most important, titration may be needed. The variability in analgesic requirements may require changes in the starting dose, adjustment in the dosing interval during the immediate postoperative period, or both. Some patients require several dose adjustments. Similarly, variability in pain duration after any particular operation is great and the duration of opioid treatment must be flexible and be determined solely by patient response. Some patients have concerns about opioid-induced side effects and addiction, which may augment distress and diminish patient compliance with therapy unless strong reassurance is provided by the physician and other staff.

In some populations, the routine approach to postoperative pain management can be enhanced by the use of a nonopioid

analgesic, specifically a nonsteroidal anti-inflammatory drug (NSAID). In the United States, ketorolac, ibuprofen, and acetaminophen all have been approved for short-term parenteral use. In opioid-naïve patients, a standard dose of ketorolac can provide analgesia equivalent to a parenteral dose of morphine of 10 mg (45). The addition of intravenous ketoprofen (not approved in the United States) to intravenous PCA with tramadol after major gynecologic cancer surgery was shown to significantly reduce opioid consumption (46). At the present time in the United States, patients who are highly predisposed to opioid side effects or toxicity, such as those with severe preexisting lung disease, may benefit from a trial of one of the intravenous nonopioid analgesics, either in lieu of opioid therapy or in combination with an opioid. Ketorolac and ibuprofen should not be used when NSAID treatment is contraindicated.

Patient-Controlled Analgesia

PCA has achieved great popularity in the management of postoperative pain and there is strong evidence that it improves analgesia, decreases the risk of pulmonary complications, and increases patient satisfaction when compared to conventional opioid analgesia (47). Theoretically, the self-administration of small doses on a frequent basis allows the patient to tailor the dose to the pain and enhance a sense of personal control while achieving a more stable plasma drug concentration. However, not all studies of this modality have been positive. For example, a randomized, controlled trial of 227 gynecologic cancer patients undergoing intra-abdominal surgery found that patients who were switched from parenteral to oral morphine on the first postoperative day experienced the same degree of pain control as those who received parenteral morphine via PCA pump (48). The latter studies suggest that careful attention to dosing rather than the availability of a pump per se is the key factor in achieving adequate pain control.

Other Approaches to Acute Pain Management

Numerous alternative approaches to postoperative pain management have been explored. Some require the expertise of pain specialists.

Preemptive Analgesia

The administration of an analgesic prior to surgical tissue injury may reduce postoperative pain and opioid requirements, and possibly have longer-term benefits (49). There are conflicting data, however, and the influence of type of analgesia, timing, and range of outcomes has not been elucidated. The role of this strategy in gynecologic surgery is unclear and it is not generally pursued.

Oral Pretreatment and Postoperative Combination Therapy

Pretreatment with sustained-release morphine or oxycodone reduces postoperative pain and analgesia requirements (50,51). This technique is seldom used, but may be an option in patients whose postoperative pain management is expected to be problematic.

Presurgical or postsurgical addition of an NSAID in combination with an opioid can augment analgesia and reduce the use of opioids, potentially leading to reduction of opioid side effects. A recent controlled trial, for example, demonstrated that postoperative celecoxib improved outcomes and was well tolerated in patients undergoing laparoscopic surgery (52). Equally

important, there is now substantial data demonstrating that the combination of an opioid and gabapentin, a neuronal calcium channel modulator widely used for the treatment of chronic neuropathic pain, improves a range of outcomes in diverse surgeries, including hysterectomy (53).

Intraspinal Analgesia

Epidural analgesia is now common practice in many hospitals. There is strong evidence that analgesia is better with this approach than with parenteral opioids (54–57). There may also be a lower risk of some postoperative complications (58,59). Some studies suggest benefits that are prolonged into the recovery phase after surgery, but the extant data are insufficient to judge these benefits adequately (55). Some side effects are more likely to occur with this technique than with conventional systemic opioid therapy, including pruritus and hypotension; resources, including staff with special competencies, are needed to implement the approach safely.

Given the abundant evidence of better analgesia and related outcomes, patients undergoing major gynecologic surgery should be considered for epidural analgesia if the resources exist to provide it. Although there is less clinical experience in the use of subarachnoid opioid administration for postoperative pain, the technique can also provide excellent relief (60–62).

Regional Anesthetic Techniques

There are numerous regional anesthetic techniques that may be useful for the management of acute pain. The simplest is the application of local anesthetic at the surgical site. Topical anesthetics that are longer acting are in development and may offer substantial benefits in the future.

Neural blockade capable of denervating the painful site is a potential approach in most cases. Catheters that deliver local anesthetic at a dose high enough to produce a sensory block can be placed in the epidural space or along peripheral nerves or plexus. Regional anesthesia can be used during an operation and then continued into the postoperative setting for pain control. For example, a recent study demonstrated that subarachnoid block for vaginal hysterectomy yielded significantly better immediate postoperative analgesia versus standard general anesthesia (63).

Other Approaches

Transcutaneous electrical nerve stimulation (TENS) has been suggested to be a useful modality for incisional pain after abdominal surgery (64). Despite the evident simplicity and safety of the approach, there has been little application of its potential.

Cognitive approaches, including stress reduction, relaxation, hypnosis, and distraction techniques, have also reduced postoperative pain and analgesic requirements (65,66). These techniques are labor intensive and are almost never sufficient as the sole means of analgesia. Nonetheless, studies have established that higher levels of anxiety and depression can negatively influence postoperative pain and analgesic requirements (67), and efforts to reduce anxiety through preoperative education and postoperative psychological interventions are likely to have salutary effects.

MANAGEMENT OF CHRONIC CANCER PAIN

The successful management of acute postoperative pain is an important concern of the gynecologic oncologist, and optimal

pain management should be considered a standard of care. The treatment of chronic pain is a far more challenging problem, particularly among those with advanced illness.

Cancer Pain, Symptom Distress, and Palliative Care

Most cancer patients who experience chronic pain also develop other physical and psychologic symptoms. Pain, fatigue, and psychologic distress are the most prevalent symptoms across populations (68,69). A broad assessment of symptom distress, followed by concurrent therapy of the most problematic symptoms other than pain, is a fundamental aspect of pain management.

Symptom distress, in turn, is only one aspect of the multifaceted problem of suffering (29,30,70). The assessment of suffering requires an evaluation in multiple domains, including the physical, psychologic, social, and spiritual. This in turn requires open and ongoing communication between the clinician and the patient.

The assessment and management of problems that relate to the broad constructs of suffering and quality of life are part of the therapeutic model of palliative care, which focuses on all patients with serious or life-threatening illness and their families. This therapeutic approach aims to reduce illness burden and enhance the quality of life of the patient and family throughout the course of the disease. In the United States, palliative care is rapidly evolving. Specialist care now has a well-defined purview, as codified in a consensus document published by the National Consensus Project for Quality Palliative Care (71). The American Board of Medical Specialties approved Hospice and Palliative Medicine as a formal subspecialty, and in an unprecedented event, ten separate primary boards are cosponsoring, including the American Board of Obstetrics and Gynecology. Specialist care is now being provided by institution-based palliative care programs, which now exist in almost 70% of U.S. hospitals with 50 beds or more. Specialist care in the setting of advanced illness is provided through more than 5,000 hospice agencies in the United States.

Specialist-level palliative care is provided by interdisciplinary teams, each member of which has special competencies. In addition to the board certification for physicians, nurses, and social workers are able to obtain certificates that confirm special knowledge and skills.

In contrast to specialist-level care, generalist-level palliative care should be considered a best practice for oncologists and others involved in the day-to-day management of patients with a serious illness such as a gynecologic cancer. Physicians must understand the necessity of palliative care, that is, interventions that may reduce illness burden or maintain quality of life, from the time of diagnosis onward. They must acknowledge the multidimensional nature of this endeavor, including a focus on communicating well, setting goals, coordinating care, sharing decision making, promoting advance care planning, managing symptoms, providing psychosocial and spiritual support, addressing practical needs in the home, assisting the family as needed, and dealing with the challenges of end-of-life care when this is necessary. Referral to specialist services to address complex needs, or provide hospice home care services, is central to the role of the generalist.

General Principles of Pain Management

The development of a successful strategy for pain management must consider the etiology and pathophysiology of pain, the patient's medical status, and the goals of care. Although the main approach for the management of cancer pain is opioid-based

pharmacotherapy, other interventions, including disease-oriented treatments (e.g., surgery, chemotherapy, or radiation) or other analgesic techniques, may be appropriate in selected cases.

Role of Primary Therapies

Effective treatment of the pathology underlying the pain can be analgesic (72,73). Primary treatment includes antineoplastic therapies and interventions directed at specific structural pathologies (e.g., lysis of adhesions). There is evidence in a limited number of cancers that specific chemotherapy regimens yield analgesic effects and it is a common observation that patients who attain a partial or complete response also experience improved symptoms. In a study of patients with metastatic breast cancer, for example, palliative chemotherapy with doxorubicin with or without vinorelbine resulted in an improvement of pain in 60.4% of the 111 patients who suffered from pain at baseline (74); although patients with an objective tumor response were more likely to have an improvement in pain (84.9%), fully 61% of patients with stable disease also benefited. In a small study of patients with advanced ovarian cancer, palliative chemotherapy was associated with improvement in symptom control, emotional well-being, and global quality of life (75). In a study of patients with recurrent/advanced cervical cancer, 67% of patients experienced improvement of pain after alternating treatment with PBM (platinum, bleomycin, and methotrexate) and PFU (platinum and 5-fluorouracil [5-FU]) (76).

Radiation therapy commonly is used to manage pain and there is evidence that it can provide effective and durable palliation of pain and other symptoms in chemotherapy-refractory patients with ovarian cancer (77,78) and cervical cancer (79). Radiation therapy can also provide analgesia to as many as 80% of those treated for bone metastases (80). Patients with widespread bone metastasis or bone pain refractory to local field radiotherapy may benefit from treatment with radiopharmaceuticals, such as strontium 89 or samarium-153 (81). In addition, analgesia may be an expected result when radiation is used to treat epidural disease, tumor ulceration, cerebral metastases, superior vena cava obstruction, and bronchial obstruction.

Unfortunately, many patients with chronic cancer pain have no option for primary antineoplastic therapy or did not benefit when it was provided. The approach to these patients involves a diverse group of primary analgesic treatments (Table 31.4). Several concurrent interventions are often required to manage the pain. The benefits of analgesic therapies must be balanced against the side effects they produce in a way that optimizes the outcome for the patient. Repeated assessments, performed as part of a broader approach to palliative care, are essential in this process and often lead to adjustments in the therapy.

THERAPEUTIC APPROACHES: PHARMACOLOGIC MANAGEMENT

Prospective trials indicate that more than 70% of patients can achieve adequate relief of cancer pain using a pharmacologic approach (3,12–14). Effective pain management requires expertise in the administration of 3 groups of analgesic medications: NSAIDs, opioid analgesics, and adjuvant analgesics. The term *adjuvant analgesic* is applied to a diverse group of drugs that have primary indications other than pain but can be effective analgesics in specific circumstances, such as in the treatment of neuropathic pain.

A model approach to the selection of these drugs, known as the “analgesic ladder,” was developed by the World Health Organization (WHO) in the 1980s and remains influential today (Fig. 31.2) (3). According to this approach, patients with mild to

Table 31.4 Approaches Used in the Management of Chronic Cancer

PAIN

Primary therapies

Radiation therapy

Chemotherapy

Surgery

Antibiotics

Primary analgesic therapies

Pharmacologic approaches

Interventional approaches

Physiatric approaches

Neurostimulatory approaches

Psychologic approaches

Complementary and alternative medicine approaches

moderate cancer-related pain are first treated with acetaminophen or an NSAID. This drug is combined with an adjuvant drug that can be selected either to provide additional analgesia (i.e., an adjuvant analgesic) or to treat a side effect of the analgesic or a coexisting symptom. Patients who present with moderate to severe pain, or who do not achieve adequate relief after a trial of an NSAID, should be treated with an opioid conventionally used to treat pain of this intensity (previously designated a “weak” opioid), which is typically combined with an NSAID and may be administered with an adjuvant if there is an indication for one. Those who present with severe pain or who do not achieve adequate relief following appropriate administration of

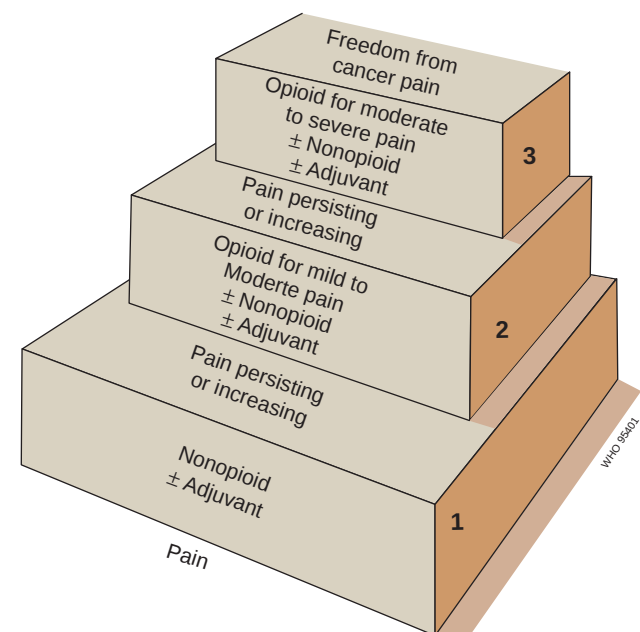


FIGURE 31.2 The 3-step “analgesic ladder” proposed by an expert committee of the Cancer Unit of the World Health Organization. Source: Reproduced with permission from the World Health Organization. *Cancer Pain Relief*. 2nd ed. Geneva, Switzerland: World Health Organization; 1996.

drugs on the second rung of the analgesic ladder should receive an opioid conventionally used for severe pain (previously called a “strong” opioid), which may be combined with an NSAID or an adjuvant drug as indicated.

The analgesic ladder is important historically and is still widely cited in the developing world in an effort to encourage policy makers to expand medical access to opioid drugs. It is a limited clinical guideline in most developed countries, where access to numerous opioid formulations and other analgesic modalities has influenced clinical practice. Nonetheless, the fundamental concept promoted by the analgesic ladder model—opioid therapy on a long-term basis should be considered the mainstay for the therapy of chronic moderate to severe cancer-related pain—remains widely accepted and a very important message of the original paradigm.

Nonsteroidal Anti-Inflammatory Drugs

In the United States, the nonopioid analgesics comprise acetaminophen and the NSAIDs (Table 31.5). These drugs have a well-established role in the treatment of cancer pain (82–85). Based on clinical observations, NSAIDs appear to be especially useful in patients with bone pain or pain related to grossly inflammatory lesions, and relatively less useful in patients with neuropathic pain (86). In addition, NSAIDs have an opioid-sparing effect that may be helpful to prevent the occurrence of dose-related side effects (87,88).

NSAIDs inhibit the enzyme cyclo-oxygenase (COX) to reduce production of peripheral and central prostaglandins, and this action presumably underlies their analgesic effects. There are multiple forms of COX. COX-1 is relatively more constitutive, physiologically active in many tissues, and COX-2 is relatively inducible, produced as part of the inflammatory cascade.

Compounds that are more selective for COX-2 than COX-1 have a lower risk of inducing gastrointestinal adverse effects (89,90), and some drugs that are relatively COX-2 selective have been labeled in this way and promoted for their enhanced gastrointestinal safety. In the United States, the only drug of the latter type now on the market is celecoxib. Rofecoxib and valdecoxib were previously available, but were taken off the market due to concerns related to cardiovascular safety.

The clinical decision to offer a NSAID to a patient with cancer usually hinges on the assessment of drug-related risk. Gastrointestinal toxicity is well recognized, and in recent years, cardiovascular safety has become a prominent concern. Based on numerous studies, it is most reasonable to conclude that all NSAIDs are prothrombotic and pose an increased risk of peripheral vascular disease, myocardial infarction, transient ischemic attacks, and stroke (91,92). Mechanistically, this risk is associated with COX-2 inhibition, whether produced by the nonselective COX-1 and COX-2 inhibitors or by the COX-2 selective drugs. Although the risk varies across drugs, large comparative studies have been retrospective and results have been conflicting. In the United States, all NSAIDs now have a boxed warning in the package insert, which offer cautions about both gastrointestinal and cardiovascular risk. Among all commercially available NSAIDs, naproxen generally is viewed as having the lowest risk of cardiovascular toxicity.

Although all NSAIDs have the potential to produce adverse gastrointestinal effects, ranging from pain or nausea to frank ulceration and hemorrhage, there are important drug-selective differences. The COX-2 selective agents, such as celecoxib, are less likely to cause these effects, as are several of the so-called nonselective agents, such as ibuprofen and diclofenac. Coadministration of a proton pump inhibitor, such as omeprazole or misoprostol, also should be considered to reduce the risk of gastrointestinal damage induced by NSAIDs (93).

Table 31.5 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Class and Generic Name	Trade Name	Approx. Half-Life (h)	Dosing Schedule	Recommended Starting Dose ^a	Comment ^b
<i>P-Aminophenol Derivatives</i>					
Acetaminophen ^c	Tylenol, Datriol, Panadol	3–4	q 4–6 h	650 mg q 4 h (5 doses daily)	Overdosage produces hepatic toxicity. Not anti-inflammatory and therefore not preferred as first-line analgesic or coanalgesic in patients with bone pain. Lack of GI or platelet toxicity; however, may be important in some cancer patients. At high doses, liver function tests should be monitored.
<i>Napthylalkanones</i>					
Nabumetone	Relafen	22–30	q 24 h	500–1,000 mg q 12 h	Appears to have a relatively low risk of GI toxicity; once-daily dosing can be useful.
<i>Salicylates</i>					
Acetylsalicylic acid ^c	Aspirin	3–12 ^d	q 4–6 h	650 mg q 4 h (5 doses daily)	Standard for comparison. May not be tolerated as well as some of the newer NSAIDs.
Diflunisal ^c	Dolobid, Dolobis	8–12	q 12 h	1,000 mg × 1, then 500 mg q 12 h	Less GI toxicity than aspirin
Choline magnesium trisalicylate ^c	Trilisate	8–12	q 12 h	500–1,000 mg q 12 h	Choline magnesium trisalicylate and salsalate have minimal GI toxicity and no effect on platelet aggregation despite anti-inflammatory effects. May therefore be particularly useful in some cancer patients.
Salsalate	Disalacid	8–12	q 12 h	500–1,000 mg q 12 h	

(continued)

Table 31.5 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (Continued)*Propionic Acids*

Ibuprofen ^c	Motrin, Advil, Nuprin	3–4	q 4–8 h	400–600 mg q 8 h	Available over-the-counter.
Naproxen ^c	Naprosyn	13	q 12 h	250–500 mg q 12 h	Available as a suspension.
Naproxen sodium ^c	Aleve, Anaprox, Naprelan	13	q 12 h	275–550 mg q 12 h	—
Fenoprofen	Nalfon, Fenopron, Progesic	2–3	q 6 h	200 mg q 6 h	—
Ketoprofen	Orudis, Oruvail	2–3	q 6–8 h	25–50 mg q 8 h	—
Flurbiprofen ^c	Ansaid	5–6	q 8–12 h	100 mg q 12 h	—
Oxaprozin	Daypro	40	q 24 h	600 mg q 24 h	Once-daily dosing may be useful.

Acetic Acids

Indomethacin	Indocin, Indocid	4–5	q 8–12 h	25 mg q 8 h	Available in sustained-release and rectal formulations. Higher incidence of side effects, particularly GI and CNS, than propionic acids.
Tolmetin	Tolectin	1	q 6–8 h	200 mg q 8 h	
Sulindac	Clinoril	14	q 12 h	150 mg q 12 h	Less renal toxicity than other NSAIDs.
Diclofenac	Voltaren	2	q 6–8 h	25 mg q 8 h	
Ketorolac ^c	Toradol	4–7	q 4–6 h	30–60 mg load, then 15–30 mg q 6 h (parenteral); 10 mg q 6 h (oral)	Only parenteral formulation available. Approved for postoperative use. Experience too limited to evaluate higher doses.

Oxicams

Piroxicam	Feldene	45	q 24 h	20 mg q 24 h	Administration of 40 mg for over 3 wk is associated with a high incidence of peptic ulcer, particularly in the elderly.
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Fenamates

Mefenamic acid ^c	Ponstel, Ponstan	2	q 6 h	250 mg q 6 h	Not recommended for use longer than 1 wk and, therefore, not indicated in cancer pain therapy.
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Pyrazoles

Phenylbutazone	Antadol, Butazolidin	50–100	q 6–8 h	100 mg q 8 h	Not a first-line drug owing to risk of serious bone marrow toxicity. Not preferred for cancer pain therapy.
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Cox-2 Inhibitors

Celecoxib	Celebrex	11	q 12 h	100–200 mg q 12 h	Fewer GI side effects; no effect on platelet function.
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CNS, central nervous system; GI, gastrointestinal; h, hours.

^aStarting dose should be one-half to two-thirds of the recommended dose for the elderly, those on multiple drugs, and those with renal insufficiency. Doses must be individualized. Low initial doses should be titrated upward if tolerated and clinical effect is inadequate. Doses can be incremented weekly. Studies of NSAIDs in the cancer population are meager; dosing guidelines are thus empiric.

^bWith all NSAIDs, stool guaiac and liver function tests, BUN, creatinine, and urinalysis should be monitored; frequency of monitoring should be increased for those on relatively high doses.

^cPain is approved indication.

^dHalf-life of aspirin increases with dose.

Given their risk profile, NSAIDs should be administered with caution to patients with significant predisposing factors for peptic ulcer disease, cardiovascular disease, renal disease, or bleeding diathesis. If there is no strong contraindication for therapy, patients who are predisposed to ulcer disease should be considered for a trial of celecoxib in the United States and patients who may be at relatively high risk of cardiovascular toxicity should be offered naproxen first. In the setting of renal insufficiency, the safest nonopioid to use is acetaminophen, notwithstanding some data that suggest that this drug can also produce renal toxicity (94).

Other factors may also be important in the selection of an NSAID. First, there is substantial variability in the response of individual patients to different agents, and the response to an NSAID in the past should guide drug selection in the present. Second, it may be useful to consider the drug's duration of effect when selecting an NSAID. The need to improve treatment adherence or provide a simpler dosing regimen encourages the use of a drug that can be administered once daily (e.g., nabumetone) or twice daily (e.g., celecoxib and many others), whereas the desire for as-needed dosing suggests the use of a short-duration drug (e.g., ibuprofen). Finally, drug selection may be influenced by cost, which varies greatly among both drugs and pharmacies.

The toxicities associated with the use of NSAIDs are dose-related and often occult until severe morbidity occurs. Although patients with cancer pain are commonly treated with standard doses, it is reasonable to explore the dose range and seek the minimal effective dose for long-term therapy. Dose escalation in poor responders is limited by dose-related toxicities and a ceiling dose for analgesia above which additional dose increments fail to produce more relief (95). If an increase in dose maintains the therapy in the conventionally accepted safe range and provides more analgesia, it should be continued. The lack of additional pain relief following a dose increase, however, suggests that the ceiling has been reached, and the dose can then be lowered to the previously effective dose or the drug can be discontinued. All patients receiving an NSAID should be evaluated periodically for occult fecal blood, changes in blood pressure, and effects on renal or hepatic function.

Opioid Analgesics

Expertise in the administration of opioid analgesics (Table 31.6) is the foundation of cancer pain management. The clinician should have knowledge of opioid pharmacology and a clear grasp of practical guidelines for dosing (96,97).

Opioid Classes

Based on receptor interactions, the opioid analgesics can be divided broadly into pure agonists and agonist-antagonists. The pure agonist drugs used in the management of chronic cancer pain are agonists at the μ -receptor subtype. The agonist-antagonist drugs comprise a mixed agonist-antagonist subclass, which includes drugs that are weak antagonists at the μ receptor and agonists at another receptor subtype, and a partial agonist subclass, which includes drugs that are partial agonists at the μ receptor. In the United States, the mixed agonist-antagonist drugs include pentazocine, nalbuphine, dezocine, and butorphanol, and the partial agonists include buprenorphine.

All the agonist-antagonist drugs share properties that together suggest a limited role in the management of chronic cancer pain. These drugs have a ceiling dose for analgesia, and all have the potential to produce an abstinence syndrome in patients already physically dependent on an agonist drug. Some

of the mixed agonist-antagonists, particularly pentazocine, are also more likely to produce psychotomimetic effects than the pure agonist drugs. In patients with chronic pain, the lack of oral formulations for all but pentazocine and buprenorphine (sublingual formulation) also limits the utility of these drugs. A transdermal buprenorphine patch recently became available in the United States; although this formulation increases the utility of buprenorphine for chronic pain, it has been designed for patients who are opioid-naïve or have very limited opioid exposure, and both this characteristic and its cost presumably will limit its use for cancer pain.

Agonist drugs, the prototype of which is morphine, are preferred in the management of chronic cancer pain (Table 31.6). To optimize the administration of these drugs, widely accepted dosing guidelines must be applied systematically.

“Weak” versus “Strong” Opioids. Unlike the division of the opioids into agonist and agonist-antagonist classes, the distinction between “weak” opioids and “strong” opioids, which was originally incorporated into the WHO analgesic ladder approach (3), is more operational than pharmacologic. The so-called weak opioids are now designated as those that are conventionally administered orally for moderate pain in patients with no or limited prior opioid exposure (second rung of the analgesic ladder), and the so-called strong opioids are those that are conventionally used to treat severe pain or moderate to severe pain in patients already using an opioid (third rung of the analgesic ladder). In the United States, the former group comprises codeine, hydrocodone, dihydrocodeine, oxycodone, and occasionally meperidine. Tramadol, a unique centrally acting analgesic with a mechanism of action that is partly opioid, also is generally included with this group, and tapentadol, a newer analgesic with a mixed mechanism similar to tramadol, may also be included. The other opioids used conventionally on the third rung of the analgesic ladder include morphine, hydromorphone, oxycodone, oxymorphone, levorphanol, fentanyl, and methadone.

The designation of the drugs conventionally used to treat moderate pain as “weak” was a misnomer because none of these drugs is characterized by a ceiling effect that would limit its use. Rather, other considerations have led to the customary use of these opioids at doses limited to those capable of treating moderate pain in the relatively nontolerant patient. For example, the dose of any opioid combined in a single tablet with acetaminophen or aspirin can only be escalated until the dose of the nonopioid coanalgesic reaches a level associated with toxicity. Hydrocodone and dihydrocodeine are available only in such combinations, and most of the other drugs in this group may be administered in this form.

Meperidine should not be used at higher doses because of the risk of enhanced toxicity due to accumulation of a metabolite. A similar concern colored the use of propoxyphene, which is no longer available in the United States. The metabolite of meperidine, normeperidine, has been observed to produce clinically relevant side effects in the cancer population, including tremulousness, hyperreflexia, myoclonus, and even seizures (98). This risk suggests that meperidine should not be used in the management of cancer pain.

As suggested by the analgesic ladder, the simplest approach to the management of moderate pain in the cancer patient with limited or no prior exposure to opioids begins with a combination product containing a nonopioid drug and an opioid, usually codeine, oxycodone, or hydrocodone. The dose can be increased to maximally safe levels of the coanalgesic; in products containing acetaminophen, this is usually 4 g per day. A lower maximal total daily dose—2.6 g—should be applied in the elderly, patients with any type of hepatic dysfunction, and those who may be unable to comply with the instruction to avoid all over-the-counter medications containing this drug.

Table 31.6 Opioid Analgesics

Drug	Dose (mg) Equianalgesic to Morphine 10 mg IM ^a PO	IM	Half-Life (h)	Peak Effect (h)	Duration (h)	Comment ^b
Morphine	20–30 ^c	10	2–3	0.5–1.0	3–6	Standard for comparison
Morphine CR	20–30	10	2–3	3–4	8–12	Various formulations are not bioequivalent
Morphine SR	20–30	10	2–3	2–3	12–24	—
Codeine	200	130	2–3	1.5–2.0	3–6	Combined with aspirin or acetaminophen. Usually for moderate pain. Also available without coanalgesic
Hydromorphone	7.5	1.5	2–3	0.5–1.0	2–4	Potency may be greater, i.e., hydromorphone: morphine = 3:1 rather than 6.7:1 during prolonged use
Oxycodone	20	—	2–3	1	3–4	Combined with aspirin or acetaminophen, for moderate pain; available orally without coanalgesic and useful for severe pain
Oxycodone CR	20	—	2–3	2–3	8–12	—
Oxymorphone	10 (rectal)	1	2–3	1.5–3.0	2–4	—
Oxymorphone CR	20 (oral)	—	2–3	1.5–3.0	2–4	—
Methadone	20	10	12–190	0.5–1.5	4–12	Although 1:1 ratio with morphine was in single-dose study, there is a change with chronic dosing and large dose reduction (75%–90%) is needed when switching to methadone. Risk of delayed toxicity
Levorphanol	4	2	12–15	0.5–1	4–6	Usage limited because only 2 mg tablets are available
Fentanyl	—	—	7–12	—	—	Can be administered as a continuous IV infusion or SC infusion; based on clinical experience, 100 µg/h is roughly equianalgesic to morphine 4 mg/h
Fentanyl TTS	—	—	16–24	—	48–72	Based on clinical experience, 100 µg is roughly equianalgesic to morphine 4 mg
Meperidine	300	75	2–3	0.5–1.0	3–4	Not preferred for cancer patients owing to potential toxicity
Tapentadol	—	—	4–5	1	4–6	—

IM, intramuscular; IV, intravenous; SC, subcutaneous.

^aDose that provides analgesia equivalent to 10 mg intramuscular morphine.

^bAll opioids may produce various common side effects (e.g., constipation, nausea, sedation). Respiratory depression is rare in cancer patients.

^cExtensive survey data suggest that the relative potency of IM:PO morphine of 1:16 changes to 1:23 with chronic dosing.

Selection of an Opioid

The selection of an opioid for severe cancer pain is empirical. Traditionally, morphine was considered to be the preferred first-line drug based on worldwide experience, ease of dosing, and the availability of numerous formulations. The intraindividual variability in the response to the different opioids is very substantial, however, and any of the other drugs may yield a better response in the individual patient. This variability also suggests that therapeutic failure with one drug may be followed by remarkable success with another (99).

The predominant metabolic pathway for morphine is glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), and the accumulation of morphine metabolites may be associated with side effects, such as myoclonus and chronic nausea (100). Renal insufficiency results in accumulation of M3G and M6G (101,102). For this reason, morphine should be administered cautiously to patients with renal insufficiency. The occurrence of morphine toxicity in these patients should be followed by a trial of an alternative opioid, such as hydromorphone or fentanyl. Although the supporting

data are limited, morphine is often viewed unfavorably when patients have very poor renal function or are on dialysis or have renal function that is expected to change. In the latter situations, studies are inadequate to generate guidelines that are evidence based, but hydromorphone and fentanyl are often preferred (103). Given concern about the theoretical accumulation of hydromorphone metabolites, some authors recommend against this drug as well (104).

The selection of an opioid for the treatment of severe cancer pain is also influenced by pharmacokinetic factors, the most salient of which is duration of effect. In an effort to improve adherence and convenience, numerous long-acting modified-release formulations of short half-life opioids have been developed. Oral once-daily or twice-daily formulations of morphine, oxycodone, oxymorphone, and hydromorphone are available in the United States and other countries. Transdermal fentanyl provides a dosing interval of 2 to 3 days and is preferred by some patients.

Although both levorphanol and methadone have relatively long half-lives (Table 31.6), patients typically require doses at least every 6 hours to maintain stable effects. Methadone has

become an increasingly popular drug for chronic pain, presumably because of its low cost, potential for unexpectedly high potency, and relatively low abuse potential and low likelihood of diversion by individuals with a history of substance use disorder. Clinical experience suggests that rotation to methadone after inadequate treatment with another opioid can indeed produce surprisingly good results, an outcome that has been speculated to be related to the d-isomer in the formulation that is commercially available in most countries; this isomer is not an opioid, but rather blocks another receptor (the N-methyl-d-aspartate, NMDA, receptor) which may potentiate analgesia or reverse some degree of opioid tolerance (105,106).

Methadone is a challenging drug to use, however, and clinicians must understand its unique pharmacology to administer it in a safe manner. Methadone's half-life ranges between 12 and 190 hours, and substantial delayed toxicity has been observed many days after methadone treatment was begun or altered (107). Its potential to have an unexpectedly high potency when substituting for another opioid increases the challenge of dose selection when starting the drug. It can prolong the QTc interval (108,109) a risk that suggests the need to obtain a baseline ECG in patients who may be predisposed to this phenomenon and periodic ECG monitoring thereafter (110). Given the increased potential for serious toxicity and the need for prolonged monitoring with methadone, its administration should be undertaken only by clinicians with the knowledge and experience necessary to ensure safety.

The patient's previous favorable experience with opioid drugs should also be considered when choosing an opioid. The exception to this is meperidine, the toxic metabolite of which may accumulate with repeated dosing. A favorable experience with this drug during short-term administration should not be viewed as predictive of the response to chronic dosing.

Routes of Administration

The oral and transdermal routes are preferred in the management of chronic cancer pain. Alternative routes may be required, however, and the clinician must recognize their indications and be familiar with the accepted approaches. In a survey of patients with advanced cancer, more than half required 2 or more routes of administration prior to death and almost a quarter required three or more (111).

Transdermal Delivery. The transdermal route of administration is available for the highly lipophilic opioids buprenorphine and fentanyl (112). Transdermal fentanyl, which offers a 48- to 72-hour dosing interval, is preferred by some patients and may be associated with relatively less constipation (113). The transdermal route may be very useful for the patient who is unable to swallow or absorb an orally administered opioid. This is particularly appropriate when the underlying pain syndrome is relatively stable; pains that are rapidly fluctuating and require multiple supplemental doses may be more easily managed using an ambulatory infusion device with a PCA option. Transdermal fentanyl is relatively contraindicated in patients with anticipated episodes of fever; increased ambient temperature changes the delivery characteristics of the patch and fever may be associated with overdose.

Although buprenorphine is a partial agonist and has a ceiling dose, and a capacity to induce abstinence if administered to a patient who is already physically dependent on another opioid, a recent observational study suggests that some patients with severe cancer can benefit and make use of this formulation until death (114). The transdermal formulation of this drug available in the U.S., provides a relatively low dose range, however, and suggests overall a limited utility in cancer pain.

Rectal. Rectal formulations of oxymorphone, hydromorphone, and morphine are available in the United States. There

also is anecdotal experience with rectal administration of controlled-release morphine or oxycodone tablets. The rectal route usually is considered for patients who are relatively opioid non-tolerant and become temporarily unable to take oral medications. The potency of opioids administered rectally is believed to approximate oral dosing (115). Absorption is variable, and relative potency may be higher or lower than expected depending on a variety of factors, including location of the suppository (low in the rectum, where the blood supply is systemic, or high in the rectum, where blood flows through the portal circulation) and contents of the rectum at the time of dosing.

Transmucosal. Absorption through the oral or nasal cavity potentially can occur with any opioid, and those that are lipophilic and relatively potent may be absorbed sufficiently to have clinical use (116). Multiple types of transmucosal formulations of fentanyl have been approved after having been shown to be safe and efficacious when used as a "rescue" dose for the treatment of breakthrough pain in cancer patients receiving a fixed-schedule opioid (117,118). These formulations include an intraoral lozenge, a buccal tablet, a buccal patch, a sublingual tablet, and a nasal spray. All are efficacious and have an onset of action faster than orally administered drugs. There are very few comparative trials and the appropriate positioning of these drugs against relatively less costly ones in the therapeutic armamentarium for cancer-related breakthrough pain remains uncertain. Patients who demonstrate that a short-acting oral opioid does not satisfactorily address a breakthrough pain due to a slow onset of effect, those with very rapid onset breakthrough pains, and those who have a particularly good response to fentanyl may be considered empirically for a trial of one of these drugs. There are insufficient data to recommend one formulation over another and this decision usually will be based on availability, cost, and patient preference. Given the perception that rapid-onset formulations address an unmet clinical need, other formulations are in development.

In some clinical situations, a trial of an injectable formulation placed under the tongue is reasonable. Although there is considerable experience in the use of sublingual administration of concentrated oral morphine solution during the care of patients at the end of life, this drug is relatively hydrophilic, and is poorly absorbed by this route; it is likely that most of the effects obtained occur following enteral absorption after swallowing.

Intranasal butorphanol is available, but as noted, this opioid is an agonist-antagonist and has characteristics that make it unfavorable for long-term administration to cancer patients. It is rarely used in this setting. Sublingual preparations of buprenorphine indicated in the United States for the office-based treatment of addiction have little evidence of safety and efficacy for cancer pain.

Parenteral Injection. Patients who are unable to swallow or absorb opioid drugs are candidates for long-term parenteral dosing. Repetitive intramuscular or subcutaneous injections are painful and should be rarely considered. Repetitive intravenous injections may be effective, but they usually require skilled nursing and may be associated with prominent "bolus" effects (toxicity at peak concentration, pain breakthrough at the trough, or both). Repetitive dosing through a "butterfly" needle placed under the skin has been used effectively in end-of-life care and experience suggests that the needle can be in place for a week without the development of local pain or other problems.

Continuous Infusion. Continuous infusion eliminates the fluctuations in plasma concentration associated with repetitive bolus injections. Any opioid available in an injectable formulation can be used for continuous infusion. The availability of continuous subcutaneous infusion using ambulatory infusion devices has markedly enhanced the clinical utility of infusion techniques, allowing long-term administration of opioids and other drugs in the home environment (119). A diverse group

of pumps that range considerably in features, complexity, and cost are now available, and the clinician often has the option of selecting a pump based on the needs and resources of the patient. PCA can be combined with continuous infusion to address episodic pains. In most cities, skilled nursing organizations can assist in the management of therapy at home.

Intraspinal Opioids. The discovery of opioid receptors in the spinal cord provided the foundation for the development of techniques to deliver opioid analgesics intraspinally. Intraspinal administration can provide selective analgesia (i.e., without the sensory or motor blockade produced by local anesthetics) at doses lower than those required systemically. The strongest indication for a trial of intraspinal opioid administration is the occurrence of intolerable somnolence or confusion in patients who are not experiencing adequate analgesia during systemic opioid treatment of pain.

Many methods of intraspinal opioid administration are now in use (120). The most commonly used include a percutaneous epidural catheter, which is usually tunneled to the anterior abdominal wall and there connected to an ambulatory infusion pump; a totally implanted epidural catheter connected to a subcutaneous portal, which in turn is connected to an ambulatory pump; and an intrathecal catheter connected to a totally implanted continuous infusion device. The preferred drugs for chronic intraspinal infusion are morphine and hydromorphone, but many others are used empirically, and admixtures (e.g., opioid plus local anesthetic or clonidine, or both) are now commonplace.

The use of intraspinal infusion in the management of cancer pain is likely to increase with further evidence of favorable outcomes in the oncology population (121). Implantable pump systems, which are refilled percutaneously, are often chosen for patients with life expectancies of 3 or more months. A controlled trial that compared neuraxial infusion to comprehensive medical management demonstrated that the spinal opioid treatment improved pain, side effects, quality of life, and even survival (122). The potential utility of neuraxial analgesia is also likely to change with the advent of more choices in drug selection.

Based on a systematic review of the literature (123), an expert panel created an algorithm for the progressive use of an array of drugs during intrathecal therapy (124). Therapy is initiated with a single-agent opioid (either morphine or hydromorphone). If adequate pain relief cannot be achieved, a second agent is added, either bupivacaine or clonidine. Clonidine, an α_2 -adrenergic agonist that was shown in a controlled trial to be effective in neuraxial analgesia (125), is one of several classes of nonopioid and nonanesthetic drugs now being used. Ziconotide, a unique calcium-channel blocker, is now available in the United States and has been shown to be effective for cancer pain in controlled trials (126). A 2007 update of the evidence-based algorithm for drug selection during neuraxial infusion incorporates these and other agents (127). Intraspinal therapy is now often initiated with a combination of drugs in an effort to reduce side effects, such as sensory and motor block, urinary retention, pruritus, and nausea, and potentiate analgesia (128).

Guidelines for the Administration of Opioid Drugs

As noted, all patients who develop moderate to severe persistent pain should be considered for an opioid-based regimen. The opioid-naïve patient usually is offered a short-acting combination product (conventionally used on the analgesic ladder's second rung). It is acceptable, however, to initiate therapy with a long-acting formulation, as long as the dose is appropriate (129). For example, long-acting morphine can be started at a dose of 15 mg twice daily, or 20 to 30 mg once daily, depending on the formulation. Long-acting oxycodone or oxymorphone

can be started at doses of 10 mg twice daily or 5 mg twice daily, respectively. Transdermal fentanyl can be initiated at 12 $\mu\text{g}/\text{h}$ in opioid-naïve patients. Given the availability of these long-acting formulations in doses appropriate for the opioid-naïve, the decision to start a short-acting or long-acting drug in a patient with new-onset persistent pain is a clinical judgment based on patient preference, convenience, cost and availability, and experience.

If a patient is receiving a short-acting drug, but pain is not controlled, it is conventional practice to switch to a single-entity pure μ agonist (third-rung drug), typically in a long-acting formulation. Starting doses may be slightly higher if the patient has been requiring regular administration of the short-acting drug. On a daily basis, the milligram dose of a long-acting drug is the same as the short-acting formulation of the same drug.

Following selection of a starting dose, dose adjustment is almost always required. Once a favorable balance between analgesia and side effects is obtained, this is usually maintained for a prolonged time unless there is progression in the pain-producing pathology. Although several large surveys have established that patients with stable disease usually demonstrate stable dosing patterns, most patients with cancer pain do not have stable disease. Recurrent pain or the new occurrence of side effects necessitates another period of dose titration. Inadequate adjustment of the dose is probably the most common reason for unsuccessful long-term management of cancer pain.

In all cases, the dose of an opioid should be increased until acceptable analgesia is produced or intolerable and unmanageable side effects supervene. Ceiling doses for the pure agonist opioids have not been identified clinically, and occasionally doses can become extremely high—equivalent to grams of morphine per day—as upward dose titration proceeds. The absolute dose of the opioid is immaterial as long as the balance between analgesia and side effects remains acceptable for the patient.

Surveys have demonstrated that one-half to two-thirds of patients with cancer pain will experience clinically significant breakthrough pain (130,131), and it is common to coadminister a short-acting drug—an approach known as “rescue” dosing—to treat it. As described previously, rapid-onset transmucosal formulations have been developed specifically in an effort to improve the management of breakthrough pain, most of which have a time course that is more rapid than the typical time-action profile of an orally administered opioid.

Treatment of common side effects is an essential element in the successful management of opioid therapy (see below). Patients who experience intolerable toxicity despite treatment should be designated as poorly responsive to the specific drug and route, and an alternative strategy for pain control should be implemented (132–134). This may include more sophisticated management of the treatment-limiting side effect, the addition of a pharmacologic or nonpharmacologic analgesic approach that could reduce the opioid requirement, or opioid rotation.

Opioid rotation, or the switching from one drug to another in an effort to improve the outcomes of an opioid regimen, is now widely used, despite guidelines based on experience rather than research (135). Switching requires an appreciation of relative potency, as codified on the equianalgesic dose table (Table 31.6). To switch to another opioid drug or route, the equianalgesic dose table is used to calculate a dose of the new drug that would be theoretically equianalgesic with the old drug or route. With few exceptions, the dosing regimen based on this calculated dose should be reduced by 25% to 50% to account for incomplete cross-tolerance between drugs; a larger reduction, 75% to 90%, is prudent if the new drug is methadone (because of a unique pharmacology in this agent). In contrast, no reduction in the equianalgesic dose is needed if the switch is to transdermal fentanyl (because a reduction is already built into the recommended equianalgesic ratios).

Management of Common Opioid Side Effects

Although there is no maximum dose or ceiling dose for the μ -agonist opioids, the appearance of side effects imposes a practical limit on dose escalation. Given the importance of side effects in determining the response to an opioid, the successful management of common adverse side effects is a fundamental aspect of therapy (Table 31.7) (136).

Constipation is a highly prevalent side effect of opioid therapy. It may contribute to abdominal pain, distension, nausea, and worsening anorexia, and occasionally may progress to obstipation and bowel obstruction. The management of drug-induced constipation should begin with the elimination of non-essential constipatory drugs and, if possible, an increase in both fluid and fiber intake. Fiber should not be increased in those with likely partial bowel obstruction or marked debility because of the potential for worsening obstruction.

Laxative therapy should be considered whenever constipation cannot be controlled through nutritional measures or chronic opioid treatment is undertaken in a patient predisposed to constipation. If there is reason to believe that obstruction or impaction is present, these problems should be addressed before routine laxative therapy is initiated.

There are numerous types of laxatives, including bulk-forming agents, osmotic agents, lubricants, surfactants, contact cathartics, prokinetic drugs, and opioid antagonists (136,137). The conventional first-line approach is a combination of a stool softener, usually docusate, and a cathartic agent, such as senna. Most patients respond to this therapy. The oral lavage agent, propylene glycol, in a powdered formulation offers another well tolerated and usually effective approach. Other osmotic agents, such as lactulose, are often tried in more refractory cases. Lubiprostone, a chloride channel opener, is available in the United States and also may be considered. A variety of other strategies are used seldom, for challenging cases. These include trials of metoclopramide, misoprostol, colchicine, or donepezil.

Opioid antagonist therapy should be considered when constipation has not responded to routine approaches. A parenteral antagonist, methylnaltrexone, is commercially available in the United States and can be used to manage acute constipation, or with dosing 2 to 3 times weekly, chronic constipation (138–140).

This drug does not cross the blood–brain barrier and reverses opioid-induced constipation through local action on opioid receptors in the gut. It does not cause systemic opioid withdrawal. Another peripherally acting opioid antagonist, alvimopan, is approved for the management of postoperative ileus, and has a similar mode of action. Other compounds of this type are in development.

Opioid antagonist therapy for refractory constipation also can be implemented using oral naloxone. This drug has very limited oral bioavailability and a consequent low risk of withdrawal following oral administration. The starting dose is typically 0.8 mg twice daily; the dose is doubled every 2 to 3 days until favorable effects occur or side effects are experienced (138,140). The daily dose needed to reverse constipation usually is 12 to 18 mg per day.

Nausea or vomiting constitutes a problem for some 10% to 30% of cancer patients receiving opioid therapy (141). Potential contributing etiologies should be evaluated and the treatment adjusted accordingly. If the assessment suggests that factors other than opioids are contributing to the nausea, antiemetic therapy may be combined with specific interventions to reverse or minimize these factors. The usual first-line drugs are the dopamine antagonists, including prochlorperazine, metoclopramide, and haloperidol. Patients with refractory nausea may need other pharmacologic approaches. The antiemetic efficacy of corticosteroids is unexplained; these drugs are clearly

Table 31.7 Commonly Used Pharmacologic Approaches in the Management of Opioid Side Effects

Opioid Side Effect	Treatment
Constipation	Approaches for all patients: - Increase fluid intake and dietary fiber - Ensure coanalgesic or adjuvant (comfort and convenience, etc.) Discuss approaches with patient and select one or more: - Daily contact laxative plus stool softener (e.g., senna plus docusate) - Daily osmotic laxative or lavage agent - Intermittent use of laxative Consider alternative approaches in refractory cases: - Enema - Prokinetic agent (metoclopramide) - Methylnaltrexone or another opioid antagonist
Nausea	Several approaches: - If associated with vertigo or if markedly exacerbated by movement, antiveriginous drug (e.g., scopolamine, meclizine) - If associated with early satiety, prokinetic agent (metoclopramide) - In other cases, dopamine antagonist drugs (e.g., prochlorperazine, chlorpromazine, haloperidol, metoclopramide)
Somnolence, mental clouding	If analgesia is satisfactory, reduce opioid dose by 25% to 50% If analgesia is satisfactory and the toxicity involves confusion, consider a trial of a neuroleptic (e.g., haloperidol) If analgesia is satisfactory and the toxicity is somnolence, consider a trial of a psychostimulant (e.g., methylphenidate) Consider pharmacologic approaches to reduce the opioid requirement (addition of a coanalgesic or adjuvant) Consider trial of an alternative opioid If appropriate, consider nonpharmacologic analgesic approaches

beneficial for some patients. Although a 5HT antagonist, such as ondansetron, can be beneficial for patients with refractory symptoms, they are very costly. Some patients respond to a commercially available cannabinoid, such as tetrahydrocannabinol or nabilone. Others appear to benefit from empirical treatment with a drug used for vertigo, such as meclizine or scopolamine. In difficult cases, combinations of drugs from unrelated classes often are tried.

Sedation or mental clouding is very common when an opioid regimen is begun or the dose increased. Most patients develop

tolerance to this effect relatively quickly, but some do not, and some have other factors that cause cognitive impairment and compound the effect of the opioid. If these side effects are mild, reassurance and education are usually sufficient interventions. When toxicity is severe or persistent enough to compromise the benefits of therapy, other interventions are needed. Treatment of potential etiologies other than the opioid (e.g., elimination of another nonessential drug or treatment of a metabolic disturbance), when feasible and indicated, is the first step in the management of neuropsychologic symptoms. If pain is well controlled, it is reasonable to try an opioid dose reduction of 25% to 50%.

Symptomatic therapies for opioid-induced sedation or mental clouding also should be considered (Table 31.7), but few have been well studied in clinical trials. Methylphenidate has been shown to decrease opioid-induced sedation in cancer patients (142–144). The starting dose is 5 mg at breakfast and at lunchtime. Other psychostimulants that have been used empirically for this indication include dextroamphetamine, amphetamine, modafinil, and armodafinil. A role for modafinil in cancer has been suggested by a positive controlled study that demonstrated improvement across cognitive, mood, and fatigue outcome measures, with the maximum benefit at 8 weeks after initiation of treatment (145). A new stimulant drug, atomoxetine, has a pharmacology that may indicate its utility for fatigue but experience is lacking and it has not yet been widely studied (146).

Tolerance, Physical Dependence, and Addiction

The clinical implications of tolerance, physical dependence, and addiction are commonly misunderstood by patients and clinicians. These misapprehensions may lead to concern about adverse events and, possibly, undertreatment of pain.

Tolerance is a pharmacologic property of opioid drugs defined by the need for escalating doses in order to maintain effects (147,148). Patients may have other reasons for declining analgesic effects, however, among which are progressive nociception and increasing psychologic distress. Abundant survey data suggest that the most common reason for dose increase is worsening pain due to progression of a nociceptive lesion. Most patients with stable disease continue to require the same opioid dose for extremely long periods of time (148,149). Fear of analgesic tolerance should never delay the implementation of opioid therapy, and tolerance should not be invoked to explain the need for higher opioid doses unless a comprehensive reassessment has failed to identify an alternative explanation.

Physical dependence also is a pharmacologic property of opioid drugs, which is defined by the occurrence of an abstinence syndrome following abrupt dose reduction or administration of an antagonist (147). Neither the dose nor the duration of dosing required to produce physical dependence is known, and it is prudent to assume that all patients who have received an opioid drug for more than a few days have the potential for withdrawal. This implies that dosing should not be discontinued suddenly and that antagonist drugs, including the agonist-antagonist opioids, should be avoided.

Patients who become physically dependent on opioids appear to develop increased sensitivity to the effects of antagonist drugs. Very small doses of naloxone may produce a severe abstinence syndrome. For this reason, the use of naloxone should be limited to patients with symptomatic respiratory depression. When naloxone must be used in patients receiving chronic opioid therapy, only a dilute solution (e.g., 0.4 mg in 10 mL saline) should be administered and incremental doses should be given only until respiration improves. The goal of this intervention is improved respiration and not a return of consciousness, which may be associated with recurrent pain and withdrawal phenomena.

Both tolerance and physical dependence are distinct from addiction. Because the labels applied to patients can determine the attitudes and behaviors of caregivers, it is extremely important that appropriate terms are used to describe these phenomena. Patients who are perceived to have the capacity for withdrawal should be labeled physically dependent and not “addicted.”

Addiction is a genetic, psychologic, and behavioral syndrome characterized by craving, loss of control over drug use, compulsive use, and continued use despite harm to the patient or others (147). Although abusable drugs, including opioids, can be shown to have reinforcing effects in animals, the capacity to produce addiction should not be considered an inherent property of the drug. Addiction presumably results from an interaction between the drug and a variety of factors that predispose the individual to compulsive use. These factors probably encompass genetic vulnerability, situational factors, and psychologic disturbances, as well as access to the drug.

Cancer patients who engage in aberrant drug-taking behaviors, such as hoarding or selling, unsanctioned dose escalation, or manipulation of the medical system to obtain additional drugs, may or may not meet criteria for the diagnosis of addiction. If such aberrant behaviors are identified, measures should be taken to eliminate them while a detailed assessment is performed to clarify their meaning. In some cases, aberrant drug-related behaviors appear to be driven by uncontrolled pain. This has been termed pseudoaddiction and is managed by improved efforts to provide pain relief. Occasionally, aberrant behaviors are related to a psychiatric disorder other than addiction or to the development of a mild encephalopathy, which leads to confusion about drug taking. These explanations for problematic drug use are not mutually exclusive and the complexity of the clinical situation requires careful assessment, and often referral of the patient to a pain specialist or an addiction medicine specialist. The clinician must avoid the stigmatizing label of addiction for patients who have reasonable alternative explanations for aberrant behaviors, but be willing to render the diagnosis of addiction in those who actually have this disease.

The risk of true iatrogenic addiction is clearly relevant in judging the overall utility of opioid therapy for chronic cancer pain. There is substantial evidence that this risk is extremely low among those with no prior history of abuse or addiction (150). It is now widely accepted that all patients who are being considered for a trial of an opioid should be evaluated for risk factors that may predict aberrant drug-related behavior, such as a history of substance abuse, a family history of substance abuse, and major psychiatric disorder, but that fear of addiction should not be considered a contraindication to opioid therapy of severe cancer pain. Rather, patients should be stratified by risk before therapy begins, and monitored for aberrant drug-related behavior during the course of therapy. Should concerns arise, the clinician may structure therapy in a way to reduce risk, or refer appropriately.

Adjuvant Drugs

Most patients with cancer pain require multiple drugs for symptom management. Some of these adjuvant drugs are used to treat symptoms other than pain, particularly those that occur as side effects of the opioid (Table 31.7). Other drugs are used in an effort to provide additive analgesia. The latter drugs comprise the NSAIDs and the so-called adjuvant analgesics. Adjuvant analgesics may be defined as drugs that are commercially available for indications other than pain but may be analgesic in selected circumstances (151). In recent years, the number of these drugs has increased substantially, and several have become approved for primary pain indications due to the abundance of evidence for analgesic efficacy.

The adjuvant analgesics are particularly helpful in the treatment of pain syndromes that are often relatively less responsive

to opioids, such as neuropathic pains (Table 31.8). Although neuropathic pains, such as postmastectomy syndrome, painful polyneuropathy, and painful plexopathy, can respond well to an opioid regimen, they are relatively more likely to be poorly responsive and are the most common targets of adjuvant analgesic therapy. In most cases, an adjuvant drug should not be initiated until an opioid has been started and titrated; this approach reduces the risk of additive toxicity (152).

In the setting of advanced illness, corticosteroids are among the adjuvant analgesics commonly used to treat neuropathic pain. These drugs also may improve anorexia, nausea, and fatigue. Among the alternative agents for neuropathic pain are anticonvulsants and antidepressants. Evidence for analgesic efficacy is best for specific anticonvulsants, such as gabapentin and pregabalin (153–157); for the tricyclic antidepressants, such as amitriptyline and desipramine (158,159); and for the serotonin and norepinephrine reuptake inhibitors, specifically duloxetine (160). Gabapentin or pregabalin usually is tried first, given their lack of drug-drug interactions, but sequential trials of various drugs often are required before a well tolerated and effective adjuvant analgesic is identified.

If the drugs with relatively good evidence of analgesic efficacy in neuropathic pain are not tolerated or are ineffective, trials of other anticonvulsants or antidepressants may be undertaken empirically. Other second-line agents for neuropathic pain also are considered in refractory cases. Sodium channel blockers may be given orally (e.g., mexiletine) or tried via brief infusion of lidocaine (161,162). NMDA antagonists have limited evidence of efficacy; ketamine is sometimes tried at subanesthetic doses (163,164). Cannabinoids are analgesic (165–167) and a new cannabis derivative (a 1:1 mixture of tetrahydrocannabinol and cannabidiol) is under development specifically for pain related to advanced cancer. Both the gamma-aminobutyric acid (GABA) agonist, baclofen, and the α_2 -adrenergic drugs, tizanidine and clonidine, are sometimes tried in selected patients with refractory neuropathic pain.

The use of topical agents represents another adjuvant analgesic strategy. A lidocaine patch (Lidoderm®) (168,169) is now available and has been shown to be effective in postherpetic neuralgia. This formulation is commonly tried for all types of neuropathic and musculoskeletal pains. Topical creams also are used empirically in patients with cancer pain, including compounds containing other local anesthetics, capsaicin, an NSAID, a tricyclic antidepressant, or an opioid.

Opioid-refractory malignant bone pain is another syndrome for which adjuvant analgesics often are considered. The preferred drugs include bisphosphonates, radiopharmaceuticals, and calcitonin. Although the bisphosphonates carry the risks of renal insufficiency and osteonecrosis of the jaw, there is evidence that they can improve overall morbidity associated with bone metastases, and a trial of one of these agents is typically considered in the setting of significant bone pain (170).

Adjuvant analgesics also are commonly employed in the setting of bowel obstruction that is not surgically correctable. Aggressive pharmacotherapy, particularly in those with advanced disease, may control symptoms and obviate the need for drainage procedures. Treatment usually involves the combination of anticholinergic drugs (e.g., scopolamine or glycopyrrolate), octreotide, corticosteroids, and opioids (171).

THERAPEUTIC APPROACHES: OTHER APPROACHES IN CHRONIC PAIN MANAGEMENT

Although most patients with cancer pain can achieve adequate relief with pharmacologic approaches alone, a multimodality strategy always should be considered in an effort to optimize

Table 31.8 Adjuvant Analgesics

Indication	Drugs
Neuropathic pain	Antidepressants
	Tricyclic antidepressants
	Amitriptyline
	Desipramine
	“Newer” antidepressants
	Duloxetine
	Anticonvulsants
	Gabapentin
	Pregabalin
	Carbamazepine
	Phenytoin
	Valproate
	Clonazepam
	Lamotrigine
	Sodium channel blockers
	Mexiletine
	Tocainide
	α_2 -adrenergic agonists
	Clonidine
	Tizanidine
	NMDA receptor antagonists
	Ketamine
	Dextromethorphan
	Cannabinoids
	Tetrahydrocannabinol (THC)
	Topical anesthetics
	Capsaicin
	Lidocaine
	Miscellaneous
	Baclofen
	Calcitonin
Bone pain	Bisphosphonates (e.g., pamidronate)
	Calcitonin
	Radiopharmaceuticals (e.g., strontium 89 and samarium 153)
Bowel obstruction	Scopolamine
	Glycopyrrolate
	Octreotide
Multipurpose	Corticosteroids
	Dexamethasone
	Prednisone

the balance between analgesia and side effects, promote better function, or concurrently manage other problems. Multiple therapies commonly are needed to address the broader palliative care concerns of the patient and family, which derive from the complex interaction between pain and suffering (Fig. 31.1).

When the focus is pain control, there are a large number of noninvasive and invasive approaches that may be considered adjunctive to opioid-based pharmacotherapy. Only a small minority of patients will require an invasive analgesic modality if the other therapies are optimally administered.

Interventional Approaches

The interventional strategies include injections, neural blockade, and implant therapies. Trigger point injections may be considered within the purview of all practitioners. Myofascial pains are extremely common in patients with chronic cancer pain, and the use of local anesthetic injections into painful trigger points may be a useful adjunctive approach in these patients (172).

The advances in neuraxial infusion of opioids and other drugs, as described previously, have largely supplanted the neurodestructive approaches that were employed in the past for pain syndromes refractory to systemic opioid therapy. Nonetheless, some types of neural blockade continue to be widely used (120). Sympathetic nerve blocks with local anesthetic are used to manage those cancer-related neuropathic pains that are presumed to be perpetuated at least in part by sympathetic efferent function. Injection of sympathetic nerves innervating viscera also block visceral afferent and the pain relief that results may be largely related to the interruption of the nociceptive input (172).

Temporary somatic nerve blocks may be diagnostic, prognostic, or therapeutic. Diagnostic blocks elucidate the afferent pathways involved in the experience of pain. Prognostic blocks are implemented prior to a neurolytic procedure, and although extensive clinical experience indicates that a favorable response does not predict permanent relief following neurolysis, the failure to achieve pain relief with local anesthetic is commonly viewed as a contraindication to a destructive procedure. Repeated therapeutic blocks with local anesthetic are occasionally used in cancer patients who obtain substantial and fairly prolonged relief after such a temporary block. Recently, local anesthetics have been used to provide more prolonged neural blockade through techniques of perineural or epidural infusion.

Neural blockade with neurolytic solutions, usually alcohol or phenol, have been developed to denervate virtually any area of the body (120). Their use is very limited, however, because of the short-term risks associated with the injection of these substances, such as damage to soft tissues and local hemorrhage or infection, and the longer-term risks of neuritis and deafferentation pain. The one generally accepted exception is celiac plexus blockade for the management of epigastric pain due to neoplastic invasion of the celiac axis. The response to neurolytic celiac plexus blockade in pain due to pancreatic cancer has been observed to be so satisfactory that earlier use is warranted whenever the typical pain syndrome occurs (173).

Intermittent nitrous oxide inhalation is an anesthetic technique that has been proven to be useful in the management of severe breakthrough pain in patients with advanced cancer (174). Although the availability of masks that reduce ambient leakage of the gas has increased the potential usefulness of this approach, it continues to be applied rarely.

Neurostimulatory Approaches

It has been appreciated for some time that stimulation of afferent neural pathways may result in analgesia. The best-known

application of this principle is TENS. Other approaches include counterirritation (i.e., systematic rubbing of the painful part), percutaneous electrical nerve stimulation, dorsal column stimulation, and brain stimulation. Published experience in the use of these modalities for the management of cancer pain is meager. Surveys of the techniques that have been used most extensively in nonmalignant pain (TENS and dorsal column stimulation) suggest that the majority of patients will achieve analgesia soon after the approach is implemented but fewer obtain prolonged relief. A trial of TENS is usually considered in patients with neuropathic pain that has been proven to be difficult to manage with opioids.

Physiatric Approaches

Although evidence from clinical trials is lacking, the potential for analgesic effects from physiatric therapies, including the use of orthoses or prostheses, occupational therapy and physical therapy, and modalities such as heat, cold, vibration, and ultrasound, is well accepted. For example, refractory movement-induced pains may be partially relieved by bracing the painful part, such as in patients with back pain due to metastatic lesions of the spine and those with arm pain related to a malignant brachial plexopathy, and a well-fitting prosthesis can reduce stump pain. In addition to the potential for salutary effects on symptoms, physical therapy and occupational therapy can potentially forestall painful complications, such as contractures, and generally increase well-being.

Neurosurgical Approaches

Procedures designed to denervate the painful area surgically have been developed for every level of the nervous system from peripheral nerves to cortex. Historically, the most useful approach has been cordotomy. Like neurolytic blocks, however, these procedures are rarely considered now, largely due to the advent of more sophisticated, nonneurodestructive interventions such as neuraxial infusion.

Psychologic Approaches

Some patients or families who present with severe psychologic distress may benefit from a multidisciplinary approach in which psychologic interventions are emphasized within a program designed to palliate symptoms and provide family support. These goals may be accomplished in some cases through referral to a hospice or palliative care program. Occasionally, patients with psychiatric disorders are identified, indicating the need for further assessment and treatment by an appropriate specialist (175).

Specific cognitive and behavioral approaches also have been applied in the management of pain and related symptoms (176,177). Cognitive approaches include relaxation training, distraction techniques, hypnosis, and biofeedback, all of which may enhance a patient's sense of personal control and reduce pain. Although many of these approaches require experienced personnel to implement, several forms of relaxation training can be taught by the nonspecialist. Behavioral therapy, which has achieved wide acceptance in the management of nonmalignant pain, is occasionally considered in patients with limited disease whose level of functional impairment is perceived to be out of proportion to the effects of the neoplasm. Cognitive and behavioral psychologic approaches can focus the patient's attention on issues related to function and quality of life and reduce rumination about the disease.

Complementary and Alternative Medicine Approaches

Therapies that are typically considered to be complementary or alternative have had a growing role in pain management (178). These approaches often are very attractive to patients because they endorse a holistic strategy that is perceived as providing hope and self-control. Some interventions that are termed “complementary” are actually used routinely by specialists in pain medicine or palliative care. These include mind-body therapies (e.g., relaxation, meditation, and others), nutritional support, acupuncture, and massage. Other interventions, such as homeopathy, naturopathy, and many others, are considered to be far outside the mainstream and are rarely suggested (179). Health care professionals have the difficult task of expressing concerns about some of the latter therapies, while respecting patients’ pursuit of complementary

treatments that may be beneficial or, at least, offer no significant chance of harm.

CONCLUSION

Pain is highly prevalent among patients with gynecologic tumors. The clinicians involved in the care of these patients have a challenging task in being able to provide state-of-the-art management approaches for both acute pain and chronic pain. Fortunately, the most effective strategy for both acute and chronic pain, namely, opioid-based pharmacotherapy, is clearly within the purview of all practitioners. The knowledge and skills necessary to optimize this therapy, and integrate it with the broader principles of palliative care, are fundamental to the practice of gynecologic oncology.

REFERENCES

1. Kanner RM. The scope of the problem. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, PA: FA Davis Co.; 1996:40–47.
2. van den Beuken-van Everdingen, de Rijke JM, Kessels AG, et al. High prevalence of pain in patients with cancer in a large population-based study in The Netherlands. *Pain*. 2007;132(3):312.
3. Teuissen SC, Wesker W, Kruitwagen C, et al. Symptom prevalence in patients with incurable cancer: a systematic review. *J Pain Symptom Manage*. 2007;34(1):94.
4. World Health Organization. *Cancer Pain Relief*. 2nd ed. Geneva, Switzerland: World Health Organization; 1996.
5. Ferrell B, Smith S, Cullinane C, et al. Symptom concerns of women with ovarian cancer. *J Pain Symptom Manage*. 2003;25:528–538.
6. Olson SH, Mignone L, Nakrasieve C, et al. Symptoms of ovarian cancer. *Obstet Gynecol*. 2001;98:212–217.
7. Portenoy RK, Kornblith AB, Wong G, et al. Pain in ovarian cancer: prevalence, characteristics, and associated symptoms. *Cancer*. 1994;74:907–915.
8. Costantini M, ripamonti C, Beccaro, et al. Prevalence, distress, management, and relief of pain during the last 3 months of cancer patients’ life. Results of an Italian mortality follow-back survey. *Ann Oncol* 2009;20(4):729–735.
9. Gartner R, Jensen MB, Nielsen J, et al. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA*. 2009;302(18):1985–1992.
10. Anderson KG, Henrik K. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. *J Pain*. 2011;12(7):725–746.
11. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. *Anesthesiology*. 2000;93:1123–1133.
12. Moulin DE, Foley KM. Review of a hospital-based pain service. In: Foley KM, Bonica JJ, Ventafridda V, eds. *Advances in Pain Research and Therapy*. Vol 16. New York, NY: Raven Press; 1990:413–427.
13. Meuser T, Pietruck C, Radbruch L, et al. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow up study of symptoms prevalence, severity and etiology. *Pain*. 2001;93(3):247–257.
14. Beck SL, Towsley GL, Berry PH, et al. Core aspects of satisfaction with pain management: cancer patients’ perspectives. *J Pain Symptom Manage*. 2010;39:100–115.
15. Walker VA, Hoskin PJ, Hanks GW, et al. Evaluation of WHO analgesic guidelines for cancer pain in a hospital-based palliative care unit. *J Pain Symptom Manage*. 1988;3:145–149.
16. Caraceni A, Portenoy RK. a working group of the IASP task force on cancer pain. An international survey of cancer pain characteristics and syndromes. *Pain*. 1999;82:263–274.
17. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med*. 1994;330:592–596.
18. Deandrea S, Montanari M, Moja L, et al. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol*. 2008;19(12):1985–1991.
19. Deandrea S, Montanari M, Moja L, et al. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol*. 2008;19(12):1985–1991.
20. Foley K. How well is cancer pain treated? *Palliat Med*. 2011;25(5):398–401.
21. Jacob A, Carr DB, Payne R, et al. *Management of Cancer Pain (Adults)*. Clinical practice guideline no. 9. (no. 94-0592). Rockville, MD: U.S. Department of Health and Human Services, Public Health Service; 1994.
22. Newell S, Sanson-Fisher RW, Girgis A, et al. The physical and psychosocial experiences of patients attending an outpatient medical oncology department: a cross-sectional study. *Eur J Cancer Care*. 1999;8:73–82.
23. Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. *Oncology*. 1998;12:369–377.
24. National Comprehensive Cancer Network Practice Guidelines in Oncology: Cancer-Related Fatigue; 2011.
25. Merskey H, Bogduk N, eds. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle, WA: IASP Press; 1994.
26. Portenoy RK. Cancer pain: pathophysiology and syndromes. *Lancet*. 1992;339:1026–1031.
27. Cherny NI, Coyle N, Foley KM. Suffering in the advanced cancer patient: a definition and taxonomy. *J Palliat Care*. 1994;10:57–70.
28. Portenoy RK. Pain and quality of life: theoretical aspects. In: Osoba D, ed. *Quality of Life in Cancer Patients*. New York, NY: CRC Press; 1991:279–292.
29. Kellgren JH. On distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci*. 1939;4:35–46.
30. Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. *Pain*. 1990;41:167–234.
31. Gerwin RD. Myofascial and visceral pain syndromes: Visceral-somatic pain representations. *J Musculoskelet*. 2002;10:165–175.
32. Foley KM. Pain syndromes in patients with cancer. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, PA: FA Davis Co.; 1996:191–215.
33. Gonzales GR, Elliott KJ, Portenoy RK, et al. The impact of a comprehensive evaluation in the management of cancer pain. *Pain*. 1991;47:141–144.
34. Boureau F, Doubrere JF, Luu M. Study of verbal description in neuropathic pain. *Pain*. 1990;42:145–152.
35. Grond S, Radbruch L, Meuser T, et al. Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain*. 1999;79:15–20.
36. Chen ML, Chang HK, Yeh CH. Anxiety and depression in Taiwanese cancer patients with and without pain. *J Adv Nurs*. 2000;32:944–951.
37. Golden RN, McCartney CF, Haggerty JJ, et al. The detection of depression by patient self-report in women with gynecologic cancer. *Int J Psychiatry Med*. 1991;21:17–27.
38. Evans DL, McCartney CF, Nemeroff CB, et al. Depression in women treated for gynecologic cancer: clinical and neuroendocrine assessment. *Am J Psychiatry*. 1986;143:447–452.
39. Chang VT, Janjan N, Jain S, et al. Update in cancer pain syndromes. *J Palliat Med*. 2006;9(6):1414–1434.
40. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106:337–345.
41. Austin KL, Stapleton JV, Mather LE. Multiple intramuscular injections: a major source of variability in analgesic response to meperidine. *Pain*. 1980;8:47–62.
42. Stouten EM, Armbruster S, Houmes RJ, et al. Comparison of ketorolac and morphine for

- postoperative pain after major surgery. *Acta Anaesth Scand*. 1992;36:716–721.
43. Tuncer S, Pirdudak L, Balat O, et al. Adding ketoprofen to intravenous patient-controlled analgesia with tramadol after major gynecologic cancer surgery: a double-blinded, randomized, placebo-controlled clinical trial. *Eur J Gynaecol Oncol*. 2003;24:181–184.
 44. Ballantyne JC, Carr DB, Chalmers TC, et al. Postoperative patient-controlled analgesia: meta-analyses of initial randomized trials. *J Clin Anesth*. 1993;5:182–193.
 45. Pearl ML, McCauley DL, Thompson J, et al. A randomized controlled trial of early oral analgesia in gynecologic oncology patients undergoing intra-abdominal surgery. *Obstet Gynecol*. 2002;99:704–708.
 46. Katz J, Cohen L. Preventive analgesia is associated with reduced pain disability 3 weeks but not 6 months after major gynecologic surgery by laparotomy. *Anesthesiology*. 2004;101(1):169–174.
 47. Bellissant E, Estebe JP, Seville V, et al. Effect of preoperative oral sustained-release morphine sulfate on postoperative morphine requirements in elective spine surgery. *Fundam Clin Pharmacol*. 2004;18(6):709–714.
 48. Reuben SS, Steinberg RB, Maciolek H, et al. Preoperative administration of controlled-release oxycodone for the management of pain after ambulatory laparoscopic tubal ligation surgery. *J Clin Anesth*. 2002;14(3):223–227.
 49. White PF, Sacan O, Tufanogullari B, et al. Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. *Can J Anaesth*. 2007;54(5):342–348.
 50. Mathiesen O, Moynich S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. *BMC Anesthesiol*. 2007;7:6.
 51. Marret E, Remy C, Bonnet F, et al. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *Br J Surg*. 2007;94(6):665–673.
 52. Liu SS, Wu CL. The effect of analgesic technique on postoperative patient-reported outcomes including analgesia: a systematic review. *Anesth Analg*. 2007;105(3):789–808.
 53. Simon DA, Connor JP, Kushner DM, et al. Epidural analgesia superior to patient-controlled analgesia for postoperative pain relief in gynecologic oncology surgery. *J Pelvic Med Surg*. 2007;13(4):191–196.
 54. Yavuz L, Eroglu F, Ozsoy M. The efficacy of intravenous versus epidural tramadol with patient-controlled analgesia (PCA) in gynecologic cancer pain. *Eur J Gynaecol Oncol*. 2004;25(2):215–218.
 55. Rawal N, Sjostrand U, Christofferson E, et al. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function. *Anesth Analg*. 1984;63:583–592.
 56. De Leon-Casasola OA, Parker BM, Lema MJ, et al. Epidural analgesia versus intravenous patient-controlled analgesia. Differences in the postoperative course of cancer patients. *Reg Anesth*. 1994;19:307–315.
 57. Swart M, Sewell J, Thomas D. Intrathecal morphine for caesarean section: an assessment of pain relief, satisfaction and side-effects. *Anaesthesia*. 1997;52:373–377.
 58. Sarma VJ, Bostrom UV. Intrathecal morphine for the relief of post-hysterectomy pain—a double-blind, dose-response study. *Acta Anaesthesiol Scand*. 1993;37:223–227.
 59. Fleron MH, Weiskopf RB, Bertrand M, et al. A comparison of intrathecal opioid and intravenous analgesia for the incidence of cardiovascular, respiratory, and renal complications after abdominal aortic surgery. *Anesth Analg*. 2003;97:2–12.
 60. Sprung J, Sanders MS, Warner ME, et al. Pain relief and functional status after vaginal hysterectomy: intrathecal versus general anesthesia. *Can J Anaesth*. 2006;53(7):690–700.
 61. Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain*. 2003;7:181–188.
 62. Good M, Anderson GC, Stanton-Hicks M, et al. Relaxation and music reduce pain after gynecologic surgery. *Pain Manag Nurs*. 2002;3:61–70.
 63. Weis OF, Sriwatanakul K, Weitraus M, et al. Reduction of anxiety and postoperative analgesic requirements by audiovisual instruction. *Lancet*. 1983;1:43–44.
 64. Ozalp G, Sarioglu R, Tuncel G, et al. Preoperative emotional states in patients with breast cancer and postoperative pain. *Acta Anaesthesiol Scand*. 2003;47:26–29.
 65. Curtis EB, Krech R, Walsh TD. Common symptoms in patients with advanced cancer. *J Palliat Care*. 1991;7:25–29.
 66. Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. *Qual Life Res*. 1994;3:183–189.
 67. Cassell EJ. *The Nature of Suffering and the Goals of Medicine*. New York, NY: Oxford University Press; 1991.
 68. <http://www.nationalconsensusproject.org>.
 69. Ellison NM. Palliative chemotherapy. In: Berger A, Weissman D, Portenoy RK, eds. *Principles and Practice of Supportive Oncology*. Philadelphia, PA: Lippincott-Raven Publishers; 2002: 667–669.
 70. McIlmurray M. Palliative medicine and the treatment of cancer. In: Doyle D, Hanks GWC, Cherny N, et al. eds. *Oxford Textbook of Palliative Medicine*. Oxford, UK: Oxford University Press; 2004:229–239.
 71. Geels P, Eisenhauer E, Bezjak A, et al. Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. *J Clin Oncol*. 2000;18:2395–2405.
 72. Doyle C, Crump M, Pintilie M, et al. Does palliative chemotherapy palliate? Evaluation of expectations, outcomes, and costs in women receiving chemotherapy for advanced ovarian cancer. *J Clin Oncol*. 2001;19:1266–1274.
 73. Chambers SK, Lamb L, Kohorn EI, et al. Chemotherapy of recurrent/advanced cervical cancer: results of the Yale University PBM-PFU protocol. *Gynecol Oncol*. 1994;53:161–169.
 74. Gelblum D, Mychalczak B, Almadrones L, et al. Palliative benefit of external-beam radiation in the management of platinum refractory epithelial ovarian carcinoma. *Gynecol Oncol*. 1998;69:36–41.
 75. Tinger A, Waldron T, Peluso N, et al. Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma. *Int J Radiation Oncology Biol Phys*. 2001;51:1256–1263.
 76. Spanos WJ Jr, Pajak TJ, Emami B, et al. Radiation palliation of cervical cancer. *J Natl Cancer Inst Monogr*. 1996;21:127–130.
 77. Falkner U, Jarhult J, Wersall P, et al. A systematic overview of radiation therapy effects in skeletal metastases. *Acta Oncol*. 2003;42:620–633.
 78. Hillegonds DJ, Franklin S, Shelton DK, et al. The management of painful bone metastases with an emphasis on radionuclide therapy. *J Natl Med Assoc*. 2007;99(7):785–794.
 79. Eisenberg E, Berkey CS, Carr DB, et al. Efficacy and safety of nonsteroidal antiinflammatory drugs for cancer pain: a meta-analysis. *J Clin Oncol*. 1994;12:2756–2765.
 80. Lomen PL, Samal BA, Lamborn KR, et al. Flurbiprofen for the treatment of bone pain in patients with metastatic breast cancer. *Am J Med*. 1986;80:83–87.
 81. Mercadante S. The use of anti-inflammatory drugs in cancer pain. *Cancer Treat Rev*. 2001;27: 51–61.
 82. Wallenstein DJ, Portenoy RK. Nonopioid and adjuvant analgesics. In: Berger AM, Portenoy RK, Weissman DE, eds. *Principles and Practice of Palliative Care and Supportive Oncology*. Philadelphia, PA: Lippincott-Raven Publishers; 2002:84–97.
 83. Mercadante S, Cassuccio A, Agnello A, et al. Analgesic effects of non-steroidal anti-inflammatory drugs in cancer pain due to somatic or visceral mechanisms. *J Pain Symptom Manage*. 1999;17:351–356.
 84. Mercadante S, Sapio M, Caligara M, et al. Opioid-sparing effect of diclofenac in cancer pain. *J Pain Symptom Manage*. 1997;14:15–20.
 85. Mercadante S, Fulfaro F, Casuccio A. A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects of dose-escalation and a pharmacoeconomic analysis. *Eur J Cancer*. 2002;38:1358–1363.
 86. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*. 2000;343:1520–1528.
 87. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. *JAMA*. 2000;284:1247–1255.
 88. Waksman JC, Brody A, Phillips SD. Nonselective nonsteroidal antiinflammatory drugs and cardiovascular risk: are they safe? *Ann Pharmacother*. 2007;41:1163–1173.
 89. Hinz B, Renner B, Brune K. Drug insight: cyclooxygenase-2 inhibitors—a critical appraisal. *Nat Clin Pract Rheumatol*. 2007;3:552–560.
 90. Peng S, Duggan A. Gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Expert Opin Drug Saf*. 2005;4:157–169.
 91. McLaughlin JK, Lipworth L, Chow W-H, et al. Analgesic use and chronic renal failure: a critical review of the epidemiologic literature. *Kidney Int*. 1998;54:679–686.
 92. Fine P, Portenoy RK. *Opioid Analgesia*. 2nd ed. New York, NY: McGraw Hill; 2007.
 93. Bruera EB, Portenoy RK, eds. *Cancer Pain*. 2nd ed. London: Assessment and management. New York, NY: Cambridge University Press; 2010:89–163.
 94. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol*. 1983;13:180–185.
 95. Galer BS, Coyle N, Pasternak GW, et al. Individual variability in the response to different opioids: report of five cases. *Pain*. 1992;49:87–91.
 96. Sjogren P. Clinical implications of morphine metabolites. In: Portenoy RK, Bruera E, eds. *Topics in Palliative Care*. Vol 1. New York, NY: Oxford University Press; 1997:163–175.

97. Peterson GM, Randall CT, Paterson J. Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. *Eur J Clin Pharmacol*. 1990;38:121–124.
98. Portenoy RK, Foley KM, Stulman J, et al. Plasma morphine and morphine-6-glucuronide during chronic morphine therapy for cancer pain: plasma profiles, steady-state concentrations and consequences of renal failure. *Pain*. 1991;47:13–19.
99. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*. 2004;28(5):497–504.
100. Murtagh FE, Chai MO, Donohoe P, et al. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother*. 2007;21(2):5–16.
101. Bryson J, Tamber A, Seccareccia D, et al. Methadone for treatment of cancer pain. *Curr Oncol Rep*. 2006;8:282–288.
102. Inturrisi CE. Pharmacology of methadone and its isomers. *Minerva Anesthesiol*. 2005;71:435–437.
103. Mercadante S. Morphine vs. methadone in the pain treatment of advanced-cancer patients followed-up at home. *J Clin Oncol*. 1998;16:3656–3661.
104. Kornick CA, Kilborn MJ, Santiago-Palma J, et al. QTc interval prolongation associated with intravenous methadone. *Pain*. 2003;105:499–506.
105. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage*. 2005;29:385–391.
106. Coyle N, Adelhardt J, Foley KM, et al. Character of terminal illness in the advanced cancer patient: pain and other symptoms in the last 4 weeks of life. *J Pain Symptom Manage*. 1990;5:83–93.
107. Portenoy RK, Southam M, Gupta SK, et al. Transdermal fentanyl for cancer pain: repeated dose pharmacokinetics. *Anesthesiology*. 1993;28:36–43.
108. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy and quality of life. *J Pain Symptom Manage*. 1997;13:254–261.
109. Muriel C, Failde I, Micó JA, et al. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther*. 2005;27:451–462.
110. Beaver WT, Feise GA. A comparison of the analgesic effect of oxymorphone by rectal suppository and intramuscular injection in patients with postoperative pain. *J Clin Pharmacol*. 1977;17:276–291.
111. Weinberg DS, Inturrisi CE, Reidenberg B, et al. Sublingual absorption of selected opioid analgesics. *Clin Pharmacol Ther*. 1988;44:335–342.
112. Coluzzi PH, Schwartzberg L, Conroy JD Jr, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain*. 2001;91:123–130.
113. Portenoy R, Taylor D, Messina J, et al. A randomized, placebo-controlled study of fentanyl buccal tablets for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain*. 2006;22:805–811.
114. Wilcock A, Jacob JK, Charlesworth S, et al. Drugs given by a syringe driver: a prospective multicentre survey of palliative care services in the UK. *Palliat Med*. 2006;20(7):661–664.
115. Swarm RA, Karanikolas M, Cousins MJ. Anaesthetic techniques for pain control. In: Doyle D, Hanks GWC, Cherny N, et al. eds. *Oxford Textbook of Palliative Medicine*. Oxford, UK: Oxford University Press; 2010:734–755.
116. Du Pen SL, Du Pen AR. Intraspinal analgesic therapy in palliative care: evolving perspective. In: Portenoy RK, Bruera EB, eds. *Topics in Palliative Care*. Vol 4. New York, NY: Oxford University Press; 2000:217–235.
117. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol*. 2002;20:4040–4049.
118. Bennett G, Serafini M, Burchiel K, et al. Evidence-based review of the literature on intrathecal delivery of pain medication. *J Pain Symptom Manage*. 2000;20:S12–36.
119. Hassenbusch SJ, Portenoy RK, Cousins M, et al. Polyanalgesic Consensus Conference 2003: an update on the management of pain by intraspinal drug delivery—report of an expert panel. *J Pain Symptom Manage*. 2004;27:540–563.
120. Eisenach JC, DuPen S, Dubois M, et al. Epidural clonidine analgesia for intractable cancer pain. *Pain*. 1995;61:391–399.
121. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA*. 2004;291:63–70.
122. de Leon-Casasola OA. Interventional procedures for cancer pain management: when are they indicated? *Cancer Invest*. 2004;22:630–642.
123. Klepstad P, Kaasa S, Jystad A, et al. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain*. 2003;101:193–198.
124. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81:129–134.
125. Caraceni A, Martini C, Zecca E, et al. a working group of an IASP task force on cancer pain. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med*. 2004;18:177–183.
126. Mercadante S, Portenoy RK. Opioid poorly responsive cancer pain. Part 1: Clinical considerations. *J Pain Symptom Manage*. 2001;21:144–150.
127. Mercadante S, Portenoy RK. Opioid poorly responsive cancer pain. Part 2: Basic mechanisms that could shift dose-response for analgesia. *J Pain Symptom Manage*. 2001;21:255–264.
128. Mercadante S, Portenoy RK. Opioid poorly responsive cancer pain. Part 3: Clinical strategies to improve opioid responsiveness. *J Pain Symptom Manage*. 2001;21:338–354.
129. Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. *J Clin Oncol*. 2002;20:348–352.
130. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician*. 2006;74:1347–1354.
131. Kyle G. Constipation and palliative care—where are we now? *Int J Palliat Nurs*. 2007;13(1):6–16.
132. Culppepper-Morgan JA, Inturrisi CE, Portenoy RK, et al. Treatment of opioid-induced constipation with oral naloxone: a pilot study. *Clin Pharmacol*. 1992;52:90–95.
133. Gatti A, Sabato AF. Management of opioid-induced constipation in cancer patient: focus on methylnaltrexone. *Clin Drug Investig*. 2012.
134. Deibert P, Xander C, Blum HE, et al. Methylnaltrexone: the evidence for its use in the management of opioid-induced constipation. *Core Evid*. 2009;15:247–258.
135. Paulson DM, Kennedy DT, Donovick RA, et al. Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction—a 21-day treatment-randomized clinical trial. *J Pain*. 2005;6:184–192.
136. Campora E, Merlini L, Pace M, et al. The incidence of narcotic-induced emesis. *J Pain Symptom Manage*. 1991;6:428–430.
137. Bruera E, Miller MJ, MacMillan K, et al. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. *Pain*. 1992;48:163–166.
138. Bruera E, Driver L, Barnes E, et al. Patient controlled methylphenidate for cancer related fatigue: a preliminary report. *J Clin Oncol*. 2003;4439–4443.
139. Wilwerding MB, Loprinzi CL, Maillard JA, et al. A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong opioids. *Support Care Cancer*. 1995;3:135–138.
140. Kaleita TA, Wellich DK, Graham CA, et al. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors (abstract). *J Clin Oncol*. 2006;24:58s.
141. Portenoy RK. Tolerance to opioid analgesics: clinical aspects. In: Hanks GW, ed. *Palliative Medicine: Problem Areas in Pain and Symptom Management*. Plainview, NY: Cold Spring Harbor Laboratory Press; 1994:49–66.
142. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. *Ann N Y Acad Sci*. 1981;362:161–172.
143. Portenoy RK. Acute and chronic pain. In: Ruiz P, Strain E, eds. *Louinson & Ruiz's Substance Abuse: A Comprehensive Textbook*. 5th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2011:695–720.
144. Lussier D, Portenoy RK. Adjuvant analgesics in pain management. In: Hanks G, Cherny N, Christakis N, eds. *Oxford Textbook of Palliative Medicine*. 4th ed. Oxford, UK: Oxford University Press; 2010:706–733.
145. Backonja MM, Canafix DM, Cundy KC. Efficacy of Gabapentin enacarbil vs. placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral Gabapentin. *Pain Med*. 2011;12:1098–1108.
146. Sandercock D, Cramer M, Wo J, et al. Gabapentin extended release for the treatment of painful diabetic peripheral neuropathy. Efficacy and tolerability in a double-blind, randomized, controlled clinical trial. *Diabetes Care*. 2009;32(2).
147. Gilron I, Flatters SJ. Gabapentin and pregabalin for the treatment of neuropathic pain: a review of laboratory and clinical evidence. *Pain Res Manag*. 2006;11(suppl. A):16A–29A.
148. van Seventer R, Feister HA, Young JP Jr, et al. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Curr Med Res Opin*. 2006;22:375–384.
149. Caraceni A, Zecca E, Martini C, et al. Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain. *J Pain Symptom Manage*. 1999;17:441–445.

150. Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain*. 1996;64:293–302.
151. Watson CPN. The treatment of neuropathic pain: antidepressants and opioids. *Clin J Pain*. 2000;16:S49–55.
152. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology*. 2006;67(8):1411–1420.
153. Sinclair R, Westlander G, Cassuto J, et al. Post-operative pain relief by topical lidocaine in the surgical wound of hysterectomized patients. *Acta Anaesthesiol Scand*. 1996;40:589.
154. Sloan P, Basta M, Storey P, et al. Mexiletine as an adjuvant analgesic for the management of neuropathic cancer pain. *Anesth Analg*. 1999;89:760–761.
155. Mercadante S, Arcuri E, Tirelli W, et al. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage*. 2000;20:246–252.
156. Ogawa S, Kanamura T, Noda K, et al. Intravenous microdrip infusion of ketamine in subanaesthetic doses for intractable terminal cancer pain. *Pain Clin*. 1994;7:125–129.
157. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. *Ann Pharmacother*. 2006;40:251–260.
158. Campbell FA, Tramer MR, Carroll D, et al. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ*. 2001;323:13–16.
159. Iskedjian M, Bereza B, Gordon A, et al. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin*. 2007;23(1):17–24.
160. Galer BS, Rowbotham MC, Perander J, et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80:533–538.
161. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Ann Pharmacother*. 2002;36:236–240.
162. Lipton A. Efficacy and safety of intravenous bisphosphonates in patients with bone metastases caused by metastatic breast cancer. *Clin Breast Cancer*. 2007;7(suppl. 1):S14–S20.
163. Jervoise H, Andreyev N, Davidson SE, et al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. *Gut*. 2012;61(2):179–192.
164. Mercadante S, Catala E, Arcuri E, et al. Celiac plexus block for pancreatic cancer pain: factors influencing pain, symptoms and quality of life. *J Pain Symptom Manage*. 2003;26(6):1140–1147.
165. Parlow JL, Miline B, Tod DA, et al. Self-administration nitrous oxide for the management of incident pain in terminally ill patients: a blinded case series. *Palliat Med*. 2005;19(1):3–8.
166. Roth AJ, Massie MJ. Psychiatric complications in cancer patients. In: Lenhard RE, Osteen RT, Gansler T, eds. *Textbook of Clinical Oncology*. Atlanta, GA: American Cancer Society; 2001:837–852.
167. Brothers BM, Thornton LM, Anderson B. Cognitive and behavioral interventions. In: Holland JC, ed. *Psychooncology*. New York, NY: Oxford University Press; 2010:415–421.
168. Meyer TJ, Mark MM. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. *Health Psychol*. 1995;14:101–108.
169. Pan CX, Morrison S, Ness J, et al. Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life: a systematic review. *J Pain Symptom Manage*. 2000;20:374–387.
170. Cohen L, Russell N, Garcia MK, et al. Integrative oncology. In: Holland JC, ed. *Psychooncology*. New York, NY: Oxford University Press; 2010:447–554.
171. Deandrea S, Montanari M, Moja L, et al. Prevalence of undertreatment in cancer pain. A review of published literature. In: Portenoy RK, ed. *Treatment of Cancer Pain*. Lancet. 2011;377:2236–2247.
172. Fairchild A. Under-treatment of cancer pain. *Curr Opin Support Palliat Care*. 2010;4(1):11–15.
173. Portenoy RK, Dhingra LK. Assessment of cancer pain. Mar. 2011. www.uptodate.com.
174. Portenoy RK, Dhingra LK, Portenoy A. *Overview of Cancer Pain Syndromes*. Sept. 2011. www.uptodate.com.
175. Kaplan R, Portenoy RK. *Cancer Pain Management: Interventional Therapies*. Sept. 2011. www.uptodate.com.
176. Portenoy RK, Ebtasam A, Keilson Y. *Cancer Pain Management: Use of Acetaminophen and Non-steroidal Antiinflammatory Drugs*. Oct. 2011. www.uptodate.com.
177. Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. *The Oncologist*. 2004;9(5):571–591.
178. Portenoy RP, Ebtasam A, Keilson Y. *Adjuvant Analgesic Drugs Used in Cancer Pain*. <http://www.uptodate.com/contents/cancer-pain-management-adjuvant-analgesics-coanalgesics>.
179. Deer T, Krames ES, Hassenbusch SJ. Polyanalgesic consensus conference 2007: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation*. 2007;10(4):300–328.

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Nutrition Support of Patients with Gynecologic Cancer

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INTRODUCTION

Cachexia and weight loss are common manifestations of cancer and exert major impacts on quality of life and survival. Malnutrition is a complex, multifactorial phenomenon that leads to progressive weight loss and deficiency of specific nutrients. Both cancer and its various therapeutic modalities contribute to cachexia. Advances in understanding nutritional requirements and intermediary metabolism, and major technologic progress in the ability to provide nutritional support, have made it possible to feed almost any patient with cancer. Nevertheless, the indications for and the appropriate use of the various modalities of nutritional support are still evolving, and many questions remain unanswered.

Malnutrition in most patients with cancer is usually a manifestation of general calorie-protein deficits that result in progressive weight loss and weakness; however, it is important to recognize that in some patients, specific nutrient deficiencies, such as magnesium deficiency or vitamin B12 deficiency, can be present even in the absence of weight loss and can contribute significantly to morbidity and even mortality.

Gynecological malignancies and their multimodal therapies may be associated with severe malnutrition. Although some nutritional problems occur in patients with cervical and endometrial cancer, they are most commonly seen in those with ovarian cancer, particularly in advanced stages when intra-abdominal metastasis severely impairs gastrointestinal function. Because of the high incidence of malnutrition and its impact on the patient with cancer, nutritional assessment and appropriate therapy should be integral parts of the overall treatment plan.

NUTRITIONAL ASSESSMENT

Nutritional assessment in cancer patients is an ongoing process. It should be a part of the patient's initial evaluation and should be updated periodically. It is especially important to determine the nutritional state prior to therapeutic interventions as well as during and after an acute illness, with the goal of identifying those patients who could benefit from a specific form of nutritional support. The nutritional assessment method used must be simple, accurate, and inexpensive. Anthropometric parameters, serum protein measurements, and immunologic tests have classically formed the basis of the nutritional evaluation; however, they all have significant deficiencies.

Anthropometric and Biochemical Markers

Anthropometric measurements such as weight, skin fold thickness, mid-arm muscle circumference, and creatinine/height

index can all provide useful information but have major limitations. Change in weight is the single most useful measurement of the nutritional status when the change does not reflect changes in total body water. The often-present edema, effusions, ascites, or intravenous hydration limit the use of weight as a nutritional parameter. In addition, inaccuracies in scales and different clothing in hospitals and at home can often be sources of misleading information on changes in weight. Measurements of skin folds and mid-arm muscle circumference (1) are useful tools in studies but have very limited use in clinical practice. A creatinine/height index derived by dividing the patient's 24-hour creatinine excretion by that of a healthy person of the same height offers a sensitive measure of early protein calorie malnutrition (2) but requires collection of a 24-hour urine specimen and is affected by alterations in renal function, which may not be indicative of the nutritional state.

Low levels of serum proteins such as albumin, prealbumin, transferrin, and retinol-binding protein were classically thought to represent malnutrition. However, in the malnourished sick patient, low levels of these proteins can be nonspecific. They are dependent on intact hepatic synthetic function as well as hydration status. At times, they can be low as a manifestation of severe illness (infection, metastatic cancer, multisystem organ failure) without being a reflection of the nutritional state. In addition, they can function as acute phase reactants and therefore be in the normal or elevated range in a clinically malnourished patient. The role of serum protein measurements in the nutritional assessment of an ill patient with cancer is therefore very limited. Similar limitations apply to the role of immunologic parameters such as total lymphocyte count and delayed cutaneous hypersensitivity. In simple starvation, both of these measures may be decreased and can return to normal with initiation of nutritional support. However, in the cancer patient undergoing chemotherapy, surgery, or radiotherapy or in the midst of an acute illness, these parameters have little determinative value in the assessment of the nutritional state (3,4).

The above parameters have been combined to create numerous nutritional assessment indices. The most extensively studied is the Prognostic Nutritional Index (PNI), which factors measurements of serum albumin, serum transferrin, triceps skin fold, and delayed cutaneous hypersensitivity (5). Buzbey et al. prospectively studied the PNI in patients undergoing gastrointestinal surgery and found that it could accurately stratify patients into high, intermediate, or low risk of developing postoperative complications (6). It must be understood, however, that the index is only as good as the parameters from which it is calculated, and the same limitations outlined above are present in any of these indices.

Subjective Global Assessment

The clinical assessment of the nutritional status has always been used to some extent as part of the general medical history

and physical examination. The validity of a formal clinical assessment of the nutritional status was demonstrated in a landmark study by Baker et al., who developed the Subjective Global Assessment (SGA) (7). The SGA is based on a complete history and physical examination, with special emphasis on six areas: change in weight, dietary intake, gastrointestinal symptoms, functional capacity, physiologic stress, and physical signs of nutritional deficiencies. These data are used to place the patient into one of three groups. Group “A” (normal nutritional status) is made up of those patients without restriction of food intake or absorption, no change in functional status, and stable or increasing weight. Group “B” (mild malnutrition) consists of patients with evidence of decreased food intake and functional status but little or no change in body weight, while those with severe reduction in food intake, functional status, and loss of weight comprise group “C” (severe malnutrition).

The SGA has consistently been shown to be reproducible and reliable in identifying patients at risk for developing complications associated with malnutrition. In the initial study of 59 patients electively admitted to a general surgical ward interobserver reproducibility in classification of the nutritional status was 81%, and in a later study of 202 patients, it was found to be 91% (7,8). Group assignment based on the SGA had prognostic significance on the ensuing clinical course. The initial study by Baker and colleagues showed a significant increase in incidence of infection, use of antibiotics, and length of hospitalization in Group “C” when compared to Group “A” (7). In the follow-up study of 202 patients undergoing gastrointestinal surgery, the rate of septic and nonseptic complications in Group “C” was 7 times greater than in Group “A” (8). However, it must be recognized that although nutritional parameters are used to determine the SGA, the classification may still represent severity of illness rather than specific nutritionally related complications. Only a determination that the classification predicts which patients will respond favorably to nutritional support (with a decrease in complications) can validate the specificity of this technique. Nevertheless, the SGA provides a simple, reproducible, and accurate method to identify patients who are malnourished who could possibly benefit from nutritional support. Clinical assessments similar to the SGA have been shown to be superior to immunologic testing, plasma protein measurements, and bioelectrical impedance in providing a useful evaluation of nutritional status (7–12).

More recently, the SGA has been shown to predict survival and tolerance to chemotherapy among women with ovarian cancer (13,14). It is now considered the preferred method of nutritional assessment for patients with gynecological cancers (15).

PREVALENCE OF MALNUTRITION

The prevalence of malnutrition depends on the tumor type and stage, the organs involved, and the anticancer therapy. Concurrent nonmalignant conditions such as diabetes and intestinal diseases can be important contributing factors.

The prevalence of weight loss during the 6 months preceding diagnosis of cancer was reported from a multicenter cooperative study of patients with 12 types of cancer (16). The lowest frequency (31% to 40%) and severity of weight loss were found in patients with breast cancer, hematologic cancers, and sarcomas. Intermediate frequency of weight loss was found in patients with colon, prostate, and lung cancer (54% to 64%). Patients with cancer of the pancreas and stomach had the highest frequency (over 80%) and severity of weight loss. Approximately 35% of the patients with lung cancer lost more than 5% of their body weight. This underscores the

fact that even if the tumor does not involve the gastrointestinal tract directly, there can be significant weight loss because of systemic and metabolic derangements and loss of appetite. The study did not report on patients with gynecologic malignancies, in whom weight loss can also be very frequent and severe. Other studies revealed that over 40% of patients receiving medical treatment for a variety of cancers were malnourished (17,18). Among surgical patients in a Veterans Administration hospital, 39% of those undergoing a major operation for cancer were malnourished, as judged by either a nutrition risk index or a combination of weight loss and low serum proteins (19). Data on the prevalence and impact of malnutrition in patients with gynecologic tumors mirror the observations in patients with other cancers. In a study of 67 consecutive patients hospitalized with gynecologic cancers at the University of Texas, it was found that 54% of the women were malnourished as determined by the PNI (20). In 1983, Tunca (21) examined the nutritional state of gynecologic oncology patients at time of diagnosis using serum albumin, serum transferrin, immune response, and weight loss. Patients with advanced (stage III or IV) ovarian carcinoma had the highest incidence of severe malnutrition, while those with cancer of the cervix, endometrium, or vulva reported weight loss with no indication of malnutrition from serum markers or immune response testing. Twenty of the 21 patients with advanced ovarian carcinoma were anergic to recall antigens, and the mean levels of all serum markers examined were significantly lower than those found in patients with early (stage I or II) ovarian carcinoma or cancer of the cervix, vulva, or endometrium. Orr et al. (22,23) assessed the degree of protein-calorie malnutrition and evidence of vitamin deficiency in 78 patients with untreated cervical cancer. The incidence of protein-calorie malnutrition as assessed by anthropometrics, serum markers, and immune testing was directly related to tumor stage: 4% in stage I, 20% in stage II and III, and 60% in stage IV disease (22). Two-thirds of patients with untreated cervical cancer were found to have reduced blood levels of at least one vitamin. Mean serum levels of folate, *b*-carotene, and vitamin C at the time of admission were all significantly below control values (23). Similar observations of significant protein-calorie malnutrition were seen in 25 patients with endometrial cancer (24). Using the SGA to study 194 patients with gynecologic cancers, Laky showed that 24% of all patients were malnourished. The prevalence of malnutrition was highest in ovarian cancer (67%) and lowest in endometrial cancer (6%) (15).

SIGNIFICANCE OF MALNUTRITION

The impact of malnutrition on the cancer patient was demonstrated in a report by Warren in 1932 (25). Based on data from autopsies, the conclusion was that cachexia was the leading cause of death in a group of 400 patients with various cancers. More recent studies have confirmed the significant impact of malnutrition on the quality of life and prognosis of the cancer patient. In the aforementioned multicenter, cooperative study of patients receiving chemotherapy (16), those who presented with weight loss at the time of diagnosis had decreased performance status and survival compared with those without weight loss. In a study of patients with limited, inoperable lung cancer, weight loss was a major predictive factor for survival (17). The negative impact of malnutrition was also demonstrated in surgical patients with malignant and benign diseases. Malnourished patients undergoing a major operation were at greater risk for postoperative morbidity and mortality than were well-nourished patients (19,26).

The impact of malnutrition on patients with a primary gynecologic malignancy is striking. While examining the role of total parenteral nutrition (TPN) in their patients, Terada and colleagues noted that those patients who developed major complications such as a fistula, wound infection, pneumonia, renal failure, respiratory failure, or those who died had significantly more weight loss and lower serum transferrin levels at the time of presentation (27). They concluded that these parameters might be of value in predicting clinical outcome in patients requiring nutritional support. This was confirmed in a study by Geisler, who found that in patients with ovarian cancer, those patients who were malnourished had increased postoperative complications. This difference could be mitigated if preoperative nutritional support could reverse the malnutrition (28). Several other studies have confirmed the relationship of malnutrition to poor surgical outcome in patients with primary gynecologic malignancies. Burnett et al. (29) reported that in 92 gynecologic oncology patients requiring colonic surgery, those who were classified as malnourished on the basis of serum markers were significantly more likely to develop major perioperative complications or die. Donato et al. (30) reported that of the 104 patients with ovarian carcinoma undergoing intestinal surgery, those considered to be malnourished on the basis of serum protein measurements and weight loss preoperatively had significantly more infectious complications, while other variables including preoperative bowel obstruction, extent of debulking, number of intestinal procedures, or hand versus stapled anastomosis failed to correlate with the rate of infectious complications (30). Poor nutritional status has been shown to be an independent predictor of prolonged postoperative ICU stay in patients with ovarian cancer (31).

In addition to predicting surgical outcome and perioperative complications, malnutrition is associated with increased neutropenic fever following chemotherapy, prolonged hospital stay, decreased quality of life, and reduced overall survival among women with gynecologic cancers (13,14,15,20,32).

ETIOLOGY OF MALNUTRITION

Cancer can induce a wide variety of derangements in the nutritional status, ranging from generalized malnutrition with severe weight loss and muscle wasting to a single nutrient deficiency. The etiology of malnutrition in the cancer patient is multifactorial. Nutritionally relevant derangements can be induced by the tumor locally (i.e., gastrointestinal obstruction), by malabsorption, or by humoral factors produced by the tumor itself or by reaction of the immune system to the tumor. All modalities of cancer therapy, surgery, radiation, chemotherapy, immunotherapy, and palliative treatments, may be associated with side effects and complications that can impair the nutritional status.

The etiologic factors of malnutrition in the cancer patient, whether caused by tumor or antitumor therapies, can be classified into three major categories: decreased food intake, malabsorption, and metabolic derangements that result in inefficient, wasteful metabolism.

Impaired Food Intake and Absorption

Both tumor and cancer treatment modalities can lead to decreased food intake through direct effects on the gastrointestinal tract or systemic effects leading to anorexia. Obstruction of the gastrointestinal tract can be caused by any gynecologic malignancy through external compression, or more rarely, by direct invasion. Although at times localized obstructions can be relieved surgically or endoscopically, the obstruction due to

peritoneal carcinomatosis often seen in advanced ovarian cancer is particularly difficult to manage surgically. Often, draining gastrostomy with parenteral nutrition (when appropriate) is the only option for providing nutrition and symptomatic relief (33–35).

Tumors can induce anorexia without local involvement of the gastrointestinal tract. The pathophysiology of this phenomenon is not well understood. Norton et al. (36) utilized a model of surgically coupled tumor-bearing and normal rats with parabiotic cross-circulation to show that tumor-induced anorexia is mediated by circulating substances. Tumor-induced impairment of smell and taste has been well described (26,37–40), but the mechanism has not been defined. There is growing evidence that glycoproteins, cytokines, and neuropeptides play an important role in the pathogenesis of cancer cachexia. Bernstein et al. (41,42) demonstrated in a rat model that infusion of tumor necrosis factor (TNF) mimics tumor induced anorexia and these effects are mediated via the area postrema and the caudal medial nucleus of the solitary tract in the central nervous system.

Therapies used for gynecologic malignancies often result in complications that impair nutrient intake and absorption. Surgical interventions can lead to fistulae, short bowel syndrome, infections, and ileus, all of which impair oral intake significantly. In a review of 12 years of colonic surgery in gynecologic oncology patients, the rate for major systemic complications (myocardial infarction, pulmonary embolism, renal failure, sepsis) was 13.7%, and the rate of major bowel complications (abscess, fistulae, hemorrhage, obstruction) was 12.1% (29). Adjuvant radiation and chemotherapy have been shown to increase the incidence of major complications after pelvic exenteration (43).

Radiotherapy can lead to various derangements in the structure and function of the gastrointestinal tract. Damage to the gastrointestinal tract following radiation to the abdomen and pelvis most commonly affects the small bowel, followed by the transverse colon, sigmoid, and rectum. Predisposing risk factors include previous abdominal surgery, pelvic inflammatory disease, thin body habitus, hypertension, and diabetes mellitus (44). In general, a dose of 5,000 rads is the threshold for significant injury. In the acute phase of radiation enteritis, virtually all patients experience anorexia, nausea, and vomiting, which are thought to be mediated by effects of serotonin on the gut (45) and the central nervous system (46). This is followed 2 to 3 weeks later by direct injury to the intestinal mucosa, resulting in diarrhea and mild to moderate malabsorption. Most patients will have complete resolution of these acute symptoms. However, a significant minority of patients who received radiotherapy will experience chronic dysfunction of the gastrointestinal tract (47). There is often a latent period of 1 to 2 years, and possibly as long as 20 years, before the symptoms of chronic radiation enteropathy surface (48,49). In a review of 102 patients with radiation enteritis after treatment for cervical or endometrial cancer, the median time to development of severe symptoms such as obstruction or perforation was 18 months (50).

Chronic radiation enteropathy is characterized pathologically by transmural injury leading to submucosal fibrosis, edema, lymphatic ectasia, and obliterative endarteritis, which can induce colicky abdominal pain, diarrhea, steatorrhea, ulceration, perforation, stricture, and fistula formation (44). Yeoh et al. (51) retrospectively studied the effects of pelvic irradiation given for the treatment of cervical cancer in 30 randomly selected women who had undergone radiotherapy 1 to 6 years earlier. Significant dysfunction of the gastrointestinal tract was detected. Nineteen of the patients had frequency of bowel movements, bile acid absorption, and vitamin B₁₂ absorption outside of the control range. The authors concluded that abnormal gastrointestinal function is essentially an inevitable long-term complication of pelvic irradiation (51). Huaebye and colleagues (52)

prospectively studied the gastrointestinal motility patterns in 41 patients with chronic abdominal complaints after radiotherapy for gynecologic cancer. Impaired fasting motility was found in 29% of patients, and motor response after a meal was attenuated in 24%. Postprandial delay of the migrating motor complex was found to be an independent predictor of malnutrition as assessed by weight loss and serum albumin. Impaired motility of the small bowel, therefore, is a key factor in the symptoms experienced by patients with chronic radiation enteropathy (52). Chronic radiation enteritis predisposes to numerous secondary complications. Danielsson et al. (53) studied 20 patients with chronic or intermittent diarrhea occurring in women 2 or more years after receiving radiotherapy for gynecologic tumors. Bile acid malabsorption was detected in 65% of patients, while evidence of bacterial overgrowth on D-xylose or cholyl-glycine breath tests was found in 45%. Treatment with bile acid binders or antibiotics resulted in a significant decline in the number of daily bowel movements. The authors concluded that treatment of these secondary complications of radiation-induced enteropathy can offer significant symptomatic relief. In 47 patients with gynecologic malignancies who had gastrointestinal complaints lasting more than 4 months after radiotherapy, Kwitko et al. (54) found 19 partial small bowel obstructions, 11 cases of malabsorption, and 5 fistulae. The mortality from radiation damage to the small bowel in this report was 32%. More recently, Boland reported on a 25-year experience with postresection short bowel syndrome secondary to radiation therapy. The majority of the cases were in women who received pelvic radiation for gynecologic cancers (55). Improved fractionation of radiotherapy and protective shielding of the intestine where possible have reduced these complication rates (56). More recent studies of patients who received radiation therapy for uterine cancer found the prevalence of significant chronic radiation enteritis to be approximately 4% (57).

Chemotherapy is often associated with decreased food intake. Mucositis and diarrhea are commonly seen during therapy with cytotoxic agents that affect the replicating cells of the intestinal mucosa, such as 5-fluorouracil, methotrexate, and bleomycin. The vinca alkaloids can cause ileus and constipation mediated by toxic effects on gastrointestinal neural pathways, while cisplatin and nitrosoureas are highly emetic (58,59). Significant nausea, vomiting, stomatitis, and diarrhea occur in 15% of patients receiving intravenous taxol and 55% in those receiving the drug orally (60). In addition to direct effects on the GI tract, chemotherapy in women with gynecologic cancers has significant effects on olfactory and gustatory function, leading to reduced appetite and weight loss (61).

The psychological impact of a malignancy and its associated therapies can also lead to decreased nutrient intake. Depression is a frequent cause of anorexia in this population, with up to 58% of cancer patients having depressive symptoms and 38% meeting criteria for major depression (62).

Metabolic Derangements

Even with normal nutrient intake patients with cancer are at risk for malnutrition due to inefficient nutrient utilization and wasteful metabolic pathways. Compared to simple starvation, cancer cachexia is associated with altered metabolism of carbohydrates, fat, protein, vitamins, and minerals. Therefore, in order to optimize nutritional support in the cancer patient, it is imperative to consider metabolic derangements along with problems of ingestion, digestion, and absorption.

Increase in basal energy expenditure has been reported in many but not all studies of patients with malignancy (63–69). In patients with newly diagnosed small cell lung cancer, Russel et al. (67) showed a mean increase of 37% in basal energy expenditure, which fell substantially in those who responded to chemotherapy. Similar findings have been reported for gastric

cancer (64) and sarcoma (70). Elevated basal energy expenditure will drop after tumor resection (71). There are limited data on the metabolic rate in patients with gynecologic cancers (69). Dickerson et al. (72) used indirect calorimetry to determine the resting energy expenditure in 31 patients with ovarian cancer and 30 patients with cervical cancer. Fifty-five percent of those with ovarian cancer were found to be hypermetabolic (BEE >110% predicted by the Harris-Benedict equation), while only 13% of patients with cervical cancer were hypermetabolic. These differences could not be explained by differences in the extent of disease, nutritional status, body temperature, or nutrient intake.

Abnormalities in carbohydrate metabolism in cancer patients include glucose intolerance and peripheral insulin resistance (73–76). These most often become apparent in the patient with advanced metastatic cancer found to have hyperglycemia, which is refractory to high-dose insulin infusion (76,77). In comparison, in simple starvation, patients are most often euglycemic or hypoglycemic. The hyperglycemia seen in cancer patients is exacerbated by increased hepatic gluconeogenesis. Shaw et al. (78) showed that this increase in glucose production is correlated with tumor burden and decreases after tumor resection. An increase in wasteful metabolic cycles such as the Cori cycle likely also contributes to altered glucose metabolism in cancer patients. Tumor cells produce lactate, which is used as substrate for gluconeogenesis in the Cori cycle and reconverted to glucose. For each cycle, there is a net loss of four high-energy phosphate bonds, leading to a large amount of energy wasted in this futile cycle. Though initial studies showed that the increase in the Cori cycle had a large contribution to increased energy expenditure in patients with metastatic disease and weight loss, subsequent studies show that an increase in the Cori cycle has only a minor role in alterations of glucose metabolism. There is ongoing research identifying other futile cycles (79).

Lipid metabolism may also be abnormal in patients with a malignancy. There is often increased lipolysis with weight loss, and this leads to a decrease in fat mass, which can be out of proportion to the loss of lean body mass (75,80). In addition, patients with cancer are often hyperlipidemic, and this may be mediated by TNF- α (81). In contrast to normal homeostasis, cancer patients fail to suppress lipolysis with glucose infusion (78). Several causes of increased lipolysis have been proposed, including decreased food intake, stress response to illness with adrenal medullary stimulation and increased circulating catecholamine levels, insulin resistance, and release of lipolytic factors produced by the tumor itself or by myeloid tissue cells (82). One such factor has been well characterized (83). Lipid mobilizing factor (LMF), a 24-kDa glycoprotein produced by tumors has been shown to stimulate increased lipid mobilization from adipocytes (84). LMF is thought to act through binding of β -adrenergic receptors and subsequent upregulation of mitochondrial uncoupling proteins (85,86). Animal studies have shown that LMF causes loss of body weight (specifically a loss of body fat), which is independent of caloric food intake (87). The activity of LMF in the urine and serum of cancer patients has been shown to correlate with the degree of weight loss (88) and tumor burden (89). In addition to its effect on lipid metabolism, there is preliminary evidence that LMF may protect tumor cells from free radical toxicity and may therefore make tumors less responsive to certain chemotherapeutic agents that induce oxidative damage (90).

High total body protein turnover, with increased synthesis and catabolism, characterizes the alterations of protein metabolism seen in cancer patients (91,92). This results in depletion of muscle mass and loss of nitrogen, and contrasts with the adaptive decrease in protein turnover seen in patients with uncomplicated starvation (93). Total parenteral nutrition given to patients with cancer will result in gains of weight and body fat, net gains

of total body nitrogen, but no suppression of the high protein flux (92,93). The predominant mechanism of muscle protein loss in cancer patients is an ubiquitin-associated pathway (94). In this pathway polyubiquitin chains are attached to proteins, which are then recognized and degraded by a proteasome complex. This pathway is regulated, in part, by proteolysis-inducing factor (PIF). PIF is a 24-kDa glycoprotein produced by human tumors and was found in the urine of cancer patients who were losing weight, but not in the urine of cancer patients who were maintaining their weight. In fact, PIF expression directly correlates with the severity of weight loss. There are multiple mechanisms by which PIF induces weight loss. PIF has a direct effect on skeletal muscle by decreasing protein synthesis and increasing protein degradation by upregulating the ubiquitin-proteasome dependent pathway. PIF also increases the expression of proinflammatory cytokines (i.e., interleukin-6 and -8), which independently cause weight loss, and induces the shedding of syndecans (transmembrane proteoglycans), which has been shown to be related to increased metastases and mortality (79,95). Effective treatment of the underlying cancer has been shown to reverse ubiquitin-dependent proteolysis of skeletal muscle (96). Better understanding of this process holds the promise of improving therapy to attenuate the loss of protein seen in patients with cancer (97).

Cytokines play an important role in inducing the metabolic derangements seen in the cancer patient (69). They mediate increased energy expenditure, whole body protein turnover, rise in serum triglyceride levels, and high glycerol turnover (25,98). TNF can be detected in the serum of cancer patients (99), and in animal models, it causes protein wasting, depletion of body fat, and anorexia (100,101). High serum levels of interleukin-1 and interleukin-6 are also present in patients with advanced cancer and cachexia. Interventions to downregulate these cytokines result in improved appetite, body weight, and quality of life (102).

The combined effects of these wasteful and inefficient alterations in metabolism make it difficult to restore nutritional status in the patient with cancer and cachexia despite the use of specialized nutritional support. This is in contrast with what is seen in patients with uncomplicated starvation who exhibit changes in metabolism, which act to conserve energy and body tissues, and in whom nutritional support is highly efficacious in reversing the effects of malnutrition.

NUTRITIONAL THERAPIES

There are four types of nutritional therapies: parenteral nutrition, enteral nutrition, oral dietary therapy, and drug therapy aimed at improving appetite and food intake. Depending on the patient's condition, nutritional support in the cancer patient has two distinct objectives: (a) provision of nutrition during anticancer therapies to counteract their nutritionally related side effects and improve outcome following these therapies and (b) support in patients with long-term or permanent severe impairment of the gastrointestinal tract. In these patients, nutritional support may be required for indefinite periods of time. Results of numerous clinical trials support the use of nutritional support only in limited situations during anticancer therapies. In the group with prolonged gastrointestinal failure, nutritional support may be a lifesaving therapy because patients could die of starvation without TPN or enteral feeding.

Total Parenteral Nutrition

TPN is an effective method for delivery of nutrients directly into the blood, and thus overcomes the major causes of cancer-induced

weight loss, including decreased food intake and dysfunction of the gastrointestinal tract. Survival for more than 20 years in patients nourished exclusively by TPN clearly demonstrates the life-saving role of this method of nutritional support. Initially, it seemed logical that TPN would be an effective adjuvant therapy for most cancer patients undergoing radiation therapy, surgery, or chemotherapy because of the accompanying cachexia and inability to eat adequately. Randomized studies, however, have shown that TPN only benefits a select subgroup of cancer patients during anticancer therapy.

Efficacy

In patients receiving chemotherapy with or without radiation therapy, TPN can lead to improvements of several nutritional parameters. Both body weight and body fat increase (93). Deficits of specific vitamins, minerals, and trace elements can be corrected, and hydration status can be improved (93,103). TPN, however, does not alter many of the metabolic derangements encountered in the cancer patient. Increased glucose oxidation and turnover persist (78,104), as does muscle proteolysis (105,106) and increased lipolysis (107). Finally, TPN does not stop the overall losses of body nitrogen (108). The relevant issue for the clinician is the effect of TPN on the morbidity and mortality associated with cancer therapy and whether TPN can allow more intense therapy as was initially hoped. Numerous randomized trials have examined this issue. Studies of patients undergoing chemotherapy for carcinoma of the ovary (33), lung (109,110), colon (108), testes (111), lymphoma (112), and other tumors (113) have been conducted. However, the patients in these studies were largely unselected. Many were not malnourished and others had adequate oral intake with intact gastrointestinal function, making intravenous nutrition unnecessary, futile, and potentially harmful. Numerous meta-analyses concluded that nondiscriminatory use of TPN in patients undergoing chemotherapy offers no improvement in mortality, response to chemotherapy, or reduction in treatment associated complications (114–116). This conclusion was echoed in a consensus statement from the National Institutes of Health, the American Society for Parenteral and Enteral Nutrition, and the American Society for Clinical Nutrition (117). The improvement in nutritional parameters afforded by TPN in patients receiving chemotherapy is not necessarily translated into improved clinical outcome. Thus, the routine use of TPN in these patients is not indicated.

There are circumstances, however, in which nutritional support with parenteral nutrition should be considered. These include prevention of the effects of starvation in a patient unable to tolerate oral or enteral feedings for a prolonged period of time (usually more than 7 to 10 days), maximization of performance status in a malnourished patient prior to chemotherapy or surgery, and in patients undergoing bone marrow transplantation (118). TPN may have a stimulatory effect on tumor cell cycle kinetics (119). It was hoped that this effect would induce improved tumor response to cell cycle-specific chemotherapy. Conclusive proof of such a response remains elusive.

A few randomized studies have examined the use of TPN in patients receiving radiotherapy to the abdomen and pelvis (120–123). These studies did not show any clear benefit from the routine administration of TPN.

The role of TPN in the perioperative period has been extensively studied (19,124–128). In an early study by Mueller et al. (128), 10 days of preoperative TPN was associated with nutritional improvement and significant reduction in major postoperative complications and mortality. These impressive results have not been confirmed in subsequent studies. At Memorial Sloan-Kettering Cancer Center, a prospective study of 117 patients undergoing curative resection for pancreatic cancer randomized to receive TPN or intravenous fluids in the postoperative period

showed no benefit from routine use of postoperative TPN (129). The group receiving TPN had a significant increase in postoperative infectious complications. The largest prospective randomized trial investigating the role of TPN in the perioperative setting was the Veterans Administration Cooperative Study (19). In this study, 395 patients were randomized to receive 7 to 15 days of preoperative and 3 days of postoperative TPN, or oral feeding plus intravenous fluids. TPN did not improve morbidity or 90-day mortality. However, subgroup analysis showed that patients considered to be severely malnourished had fewer infectious complications if they received TPN. The authors concluded that the routine administration of preoperative TPN should be limited to patients who are severely malnourished, unless there are other specific indications.

Randomized studies specifically examining the role of perioperative TPN in patients with gynecologic malignancies are lacking. In a report by Terada (27), perioperative parenteral nutritional support was given to 84 of 99 patients. There were no major complications attributed to TPN, but 27% of the patients experienced minor complications: 11% due to central line placement or catheter sepsis, 2% due to fluid overload, and 13% had metabolic complications. There was no report on overall perioperative morbidity or mortality in comparison to patients who did not receive perioperative TPN.

These data and others provided the basis for a consensus statement from the National Institutes of Health, the American Society for Parenteral and Enteral Nutrition, and the American Society for Clinical Nutrition regarding the use of perioperative TPN, which states the following: (a) 7 to 10 days of preoperative TPN in a malnourished patient with gastrointestinal cancer results in a 10% reduction in postoperative complications; (b) routine use of postoperative TPN in malnourished surgical patients who did not receive preoperative TPN results in a 10% increase in complications; (c) if by postoperative day 5 to 10 a patient is unable to tolerate oral or enteral feedings, then TPN is indicated to prevent the adverse effects of starvation. This panel, however, cautioned that in the majority of studies looking at perioperative TPN, the amount and type of parenteral nutrition given was not optimal, and often patients were given excess calories. Therefore, the results may differ with the provision of relatively hypocaloric formulas (117). It is reasonable to extend these recommendations to the gynecologic oncology patient undergoing surgery (Table 32.1).

Composition of TPN Solution

Once the decision to proceed with parenteral nutritional support is made, access to a large bore central vein should be obtained. This allows the use of calorically dense, hypertonic solutions,

which are often necessary in severely ill patients who may have restriction on the amount of intravenous fluids they can receive. The solution must provide the protein and caloric needs, fluid, minerals, trace elements, and vitamins. Although indirect calorimetry and nitrogen balance can be used to determine energy and protein requirements, they are too costly and cumbersome for routine use. There are numerous formulas, charts, and tables that can provide estimates of protein and calorie requirements. Estimates of nutrition requirements are based on weight and adjusted for the degree of physiologic stress encountered by the patient. Generally, patients require approximately 30 Kcal/kg nonprotein calories, 1 g/kg amino acids, and about 2,000 mL of fluid. As illness severity increases and organs' functions change, adjustments may be required. Nonprotein calories can be provided as dextrose or lipid, and the relative amounts of these should also be individualized. Lipids provide 9 Kcal/g compared to 3.4 for dextrose (in dextrose solutions, glucose is present as glucose-monohydrate; hence, a gram contains less than 4 Kcal). Lipid calories are particularly useful in patients who have high caloric requirements but cannot tolerate a large fluid load. In addition, lipids are useful in patients with severe pulmonary or hepatic dysfunction as glucose metabolism produces more carbon dioxide, which can add to the burden of the ailing lung and can lead to fatty infiltration of the liver. Up to 60% of caloric requirements can be provided as lipid, but serum triglyceride levels must be monitored closely. Appropriate electrolyte content of TPN solutions is of critical importance. The amounts have to be tailored to the patient's requirements and organ's function. Care must be taken to prevent potentially fatal hypokalemia or hypophosphatemia (particularly in the patient with severe weight loss), which can be precipitated by insulin induced transport of the minerals to the intracellular space when inadequate amounts are given. Other electrolyte disorders, such as cisplatin-induced hypomagnesemia and SIADH, are common in the patient with gynecologic malignancy and must be addressed when ordering TPN. The TPN solution must also contain vitamins, minerals, and trace elements. Typically, these are available as standard commercial combination products. However, certain patients require specific modifications. For example, a patient with persistent diarrhea requires zinc supplementation in excess of the amounts present in standard trace element solutions.

Complications

Complications associated with TPN can be classified as catheter related, metabolic, or infections. Catheter complications most often occur during placement of a central venous catheter and include pneumothorax, hemothorax, arterial injury, and hematoma. These can all be minimized when the procedure is performed by an experienced physician (130). Cobb et al. (131) reported a 3% incidence of pneumothorax, arrhythmia, thrombus, or bleeding during 523 intravenous catheter placements. A more recent study of subcutaneous peripheral infusion ports in women with gynecologic malignancies demonstrated a thrombosis rate of 26% during a mean follow-up of 105 days. The authors concluded that other types of vascular access devices may be preferable in this patient population (132).

Metabolic derangements are frequently encountered during support with TPN, and the prescribing physician must be well versed in the pathophysiology of these disorders. Hyperglycemia is the most common abnormality (130), and if not corrected, can lead to an osmotic diuresis, dehydration, acidosis, and hyperosmolar coma. One metabolic complication that deserves special mention is the "refeeding syndrome." In chronically ill patients with severe malnutrition, there is often a depletion of total body phosphorus and potassium. The phosphorous deficits may be masked by increased renal phosphorous absorption designed to maintain normal serum levels. When nutritional support is

Table 32.1 Indications for TPN in Hospitalized Patients with Gynecological Cancers

Perioperative	• 7–10 d preoperatively in a malnourished patient (who cannot be fed enterally) • Postoperative complications that prevent oral or enteral intake for more than 7–10 d • Enterocutaneous fistula • No indication for routine use
During radiation or chemotherapy	• Maximization of performance status prior to therapy in a malnourished patient who cannot be fed enterally • Severe persistent (more than 7–10 d) mucositis, diarrhea, ileus, or emesis • No indication for routine use
General	• After 7–10 d of inability to tolerate oral or enteral feeding due to any cause

initiated, the infusion of a large glucose load with subsequent surge in insulin leads to increased cellular uptake of phosphorous and potassium, which may induce severe life-threatening hypokalemia and hypophosphatemia (133,134). These disorders cause widespread tissue and organ dysfunction, including muscle weakness, rhabdomyolysis, heart failure, cardiac arrhythmias, and respiratory failure, and may result in death in extreme cases (134). Therefore, in patients with evidence of severe undernutrition, nutrition support should be initiated with small amounts of dextrose calories, supplemental phosphorous and potassium, and careful monitoring of serum phosphorous and electrolytes.

TPN has been associated with cholestatic liver disease, as well as fatty infiltration of the liver and glycogen deposition. These abnormalities have been attributed to infusion of excessive glucose calories, imbalance of amino acids, and rarely, fatty acid deficiency (135). Elevation of serum transaminases may occur, but it is generally mild (135,136). Severe liver dysfunction in adult TPN recipients is rare and requires a search for causes other than TPN.

Infections are particularly serious complications in patients with malignancy receiving TPN. In an evaluation of seven studies comparing TPN plus chemotherapy to chemotherapy alone, Klein and Koretz found four studies that showed an increase in infectious complications in patients receiving TPN (122). A meta-analysis by the American College of Nutrition showed a fourfold increase in infections when patients receiving chemotherapy were given TPN (114). In a prospective, randomized study of TPN following pancreatic resection, recipients of TPN had significantly more infectious complications (129). Data from a VA randomized cooperative study showed that patients with mild to moderate malnutrition given perioperative TPN had increased rates of infections, while those with severe malnutrition developed significantly fewer infections when supported with TPN (19). Infectious complications are related to both central venous catheters and a variety of sites (wound infection, abscess, and pneumonia).

Home TPN

Long-term TPN in the home can be a lifesaving treatment in an appropriately selected group of patients. It is clear that cancer patients who have had severe gastrointestinal injury, such as massive intestinal resection or severe radiation enteritis, and in whom the cancer has been cured or is well controlled, benefit from long-term TPN at home (137). Survival rates and TPN-related complications in such patients are comparable to those seen in patients with benign diseases (Crohn's disease, intestinal necrosis) who require home TPN. Among patients with widely metastatic disease and poor prognosis, home TPN offers very limited benefit (106). Only 15% of such patients survive longer than 1 year on home TPN (52). Recently developed techniques for placing feeding tubes make it possible to hydrate and feed patients enterally, even in the presence of gastrointestinal obstruction (118), and thus obviate the need for home TPN in patients with upper gastrointestinal tract dysfunction. In terminally ill patients, TPN should be avoided. The concern that such patients should not be "starved to death" is not a justification for TPN. A recent uncontrolled study of terminally ill cancer patients hospitalized at a long-term care facility suggested that these patients did not experience hunger or thirst, and that in those who experienced such symptoms, small amounts of food alleviated the symptoms (138). In such patients, the utilization of TPN either in the home or at health care facilities cannot be justified.

For patients with inoperable bowel obstruction due to metastatic ovarian cancer, predicting which patients will benefit from home TPN can be difficult (139). In a review of 9,897 days of

home TPN administered to 75 patients with various cancers and intestinal obstruction, it was shown that a Karnofsky performance status greater than 50 at the initiation of TPN could accurately predict which patients would have improved quality of life while on home TPN. The authors concluded that home TPN should be avoided if the performance status is below this level (140). In addition, patients with a life expectancy of less than 2 to 3 months will not benefit from home TPN (106,140). In a study from Yale-New Haven Hospital of 17 patients with inoperable bowel obstruction due to malignancy, patients with ovarian cancer had the shortest survival (39 days) compared to patients with colon cancer (90 days) and appendiceal cancer (184 days) (141). Therefore, only a highly selected minority of patients with inoperable bowel obstruction can potentially benefit from home TPN. A recent study from Brown University evaluated 55 patients with terminal ovarian cancer and found the use of TPN conferred a median survival benefit of 4 weeks (142). Currently, the best selection criteria for such patients are a fair or better performance status and the potential for further antitumor therapy (Table 32.2).

Enteral Nutrition

Enteral feeding delivers a liquid-nutrient formula into the gastrointestinal tract through tubes placed into the stomach or small intestine. As in oral feeding, an adequately functioning small intestinal mucosa is required for absorption of nutrients. Enteral feeding can overcome many difficulties encountered in patients with a wide variety of gastrointestinal tract dysfunction. A proximal gastrointestinal obstruction can be bypassed; tubes can be placed distal to obstructions as far as the jejunum, and thus circumvent obstructing lesions of the oral cavity, esophagus, stomach, duodenum, or proximal jejunum (143,144). The liquid-nutrient formula can be delivered as a slow, continuous infusion, thus maximizing absorption by a limited intestinal surface, which can be overwhelmed by the higher volume delivered during oral feeding. Such an approach may be useful in patients with radiation enteritis, short bowel syndrome (with adequate remaining short bowel, usually 3 to 4 ft), or partial obstruction of the bowel.

Route of Administration and Nutrient Formula

Short-term (<2 weeks) access to the gastrointestinal tract can be obtained through nasogastric or nasoenteric tubes. Patients requiring longer nutritional support should have a gastrostomy or jejunostomy tube placed endoscopically, radiologically, or surgically. In comparison to nasal tubes, gastrostomy or jejunostomy tubes are wider (15 to 24 Fr) and therefore less likely to be obstructed by medications or nutrient solutions. In addition, they are fixed in the stomach or the upper intestine and do not migrate into the esophagus. Thus, the risk of aspiration is considerably decreased (143). These tubes are more comfortable and aesthetically pleasing (145). These benefits were demonstrated in a randomized study of patients after an acute dysphagic stroke, which showed patients fed with a gastrostomy

Table 32.2 Indications for Home TPN in Patients with Gynecological Cancers

- Severe chronic radiation enteropathy
- Short bowel syndrome
- Persistent enterocutaneous fistula
- Selected patients with obstruction due to peritoneal carcinomatosis. (Selection based on performance status and potential for further chemotherapy)

tube had more optimal provision of nutrients, achieved a better nutritional state, and had less mortality than those fed with nasogastric tubes (146). Patients with gastrostomy tubes have been shown in prospective studies to receive over 90% of prescribed feedings compared to only 55% in patients fed through nasal tubes. These differences are largely attributed to nasogastric tube dislodgment (147). In a randomized study of 33 women with gynecologic malignancies, enteral feedings through a needle catheter jejunostomy maintained postoperative nutrition as measured by serum transferrin levels and was associated with few complications (148). The authors concluded that women with gynecologic cancers should have a jejunostomy placed at the time of operation if it is anticipated that long-term nutritional support will be required.

Endoscopically placed percutaneous gastrostomy tube (PEG) has become the procedure of choice for placement of enteral feeding tubes because of its ease, safety, and the ability to perform it on an outpatient basis. Percutaneous jejunostomy (PEJ) tubes can also be placed endoscopically (144). PEJs allow for continued enteral feeding in patients with gastric resection, gastric outlet obstruction, or gastroparesis. Major complications (bleeding, peritonitis, abdominal wall abscess, colonic perforation, and aspiration) from PEG and PEJ placement are rare, occurring in 0 to 2.5% of patients, while minor complications (wound infection, tube migrations, or leak) are seen in 5% to 15% (70,144,149,150). More than 100 different enteral feeding formulas are currently commercially available (151). They are designed to provide complete nutrition, single nutrients, or only fluids and electrolytes. Formulas differ in protein concentration, calories, osmolality, and percentage of nonprotein calories delivered as carbohydrates or fats. Enteral feeding formulas, which provide 1,500 to 2,000 Kcal/day, normally contain all the necessary nutrients including proteins, vitamins, minerals, and trace elements. In addition, there are disease-specific formulations for patients with diabetes or hepatic, renal, or pulmonary dysfunction. The choice of formula should be individualized, and it often helps to minimize problems such as diarrhea, bloating, or hyperglycemia (143).

Enteral solutions may be administered by either bolus feedings or continuous infusion (143). Bolus feeding is possible when the tip of the feeding tube is in an intact stomach. Up to 500 mL of a feeding formula can be infused over 10 to 15 minutes by a syringe or gravity into the stomach. The pyloric sphincter regulates flow into the duodenum. All bolus feedings should be done with the patient sitting upright to minimize the risk of aspiration. When the tip of the feeding tube is distal to the pylorus, continuous feeding must be employed to avoid abdominal distention and diarrhea. Rates as high as 150 mL/hour are generally well tolerated (143).

Efficacy

Data from randomized trials examining the efficacy of enteral nutrition given as an adjuvant therapy in patients receiving chemotherapy for a variety of cancers have failed to demonstrate a clear benefit in terms of survival or response to treatment (152–156). The validity of the conclusions of these studies, however, is limited by their small size and poor design. Similar difficulties plague the studies examining the role of standard enteral nutrition in the perioperative period (157–160). While recent data examining early (postoperative day 1) enteral feeding in patients following resection of an upper gastrointestinal tract tumor showed improved protein metabolism, there is no evidence that this translates into improved clinical outcome (161). In a prospective, randomized study of early enteral feeding in 195 patients after resection of upper gastrointestinal malignancy there was no proven benefit. Complication rates, mortality, and length of hospital stay were not affected by early postoperative enteral feedings (162). Therefore, routine use of enteral nutrition

support in patients receiving chemotherapy or undergoing operations for cancer cannot be justified. Accepted indications for enteral nutrition in cancer patients include (a) obstruction of the upper digestive tract in those in whom enteral access can be safely obtained beyond the site of obstruction, (b) the presence of chronic malnutrition due to inadequate oral intake, and (c) perioperative support of the malnourished patient (163).

Complications

Enteral nutrition is generally safe if careful attention is paid to the following: (a) choice of an appropriate formula, (b) infusion into an appropriate portion of the gastrointestinal tract, (c) use of the correct infusion method, and (d) an ongoing clinical and metabolic monitoring of the patient. The most serious complication of enteral feeding is aspiration, which occurs in 1% to 32% of patients (152,164,165). The risk is minimized by keeping patients upright during bolus feedings and using jejunal feedings if there is predisposition for aspiration, gastroparesis, or an impaired gag reflex. Diarrhea is reported in 5% to 30% of patients receiving enteral nutrition (166). While the diarrhea may be related to underlying disorders of the gastrointestinal tract, such as radiation enteritis or short bowel syndrome, a commonly overlooked cause is medications. Patients on enteral feeding often receive magnesium-containing antacids or antibiotics, both of which may induce diarrhea. Metabolic complications include dehydration, azotemia, hyperglycemia, and hyperkalemia. These are usually due to the patient's underlying disease and can be avoided with the choice of the proper formula and careful monitoring.

Home Enteral Nutrition

Home enteral nutrition (HEN) is increasingly being used to provide nutrients and fluids outside the hospital. Cancer is the most common indication for its use and accounts for 42% of all patients receiving HEN (137,143). It is a safe therapy in patients with cancer, with only a 0.4% annual rate of complications requiring hospitalization (167). The overall 1-year survival for cancer patients on HEN is 30%. However, in patients with cancer of the head and neck who have been successfully treated, HEN has provided good nutrition for periods exceeding 7 years (70,143). Regular medical follow-up is essential to ensure appropriate functioning of the feeding tube and optimization of the nutrition regimen. This form of therapy is useful in patients with gynecologic malignancies with upper gastrointestinal tract obstructions that cannot be treated surgically.

Oral Dietary Therapy

Patients who are able to eat but have impairment of the gastrointestinal tract or have special metabolic requirements may benefit from a specialized oral dietary therapy. Often, this may obviate the need for more costly and complex interventions such as parenteral nutrition. In oral dietary therapy, the regular diet is modified based on the pathophysiologic changes induced by the underlying disorder, with the goal of providing the most optimal nutrition possible (158). When the main problem is inadequate food consumption, various commercial oral supplements can be used, but usually for only short periods because of taste fatigue. Some preparations provide complete nutrition, while others are intended to supplement deficits of specific nutrients. Problems common in patients with gynecologic malignancies, such as partial small bowel obstruction, chronic radiation enteritis, and short bowel syndrome, may all be amenable to dietary therapies. In partial small bowel obstruction or motility dysfunction, a diet comprised of frequent, small, calorically dense meals with minimal

amounts of fiber is indicated. Patients with radiation enteritis should receive a low-fat, low-fiber, and lactose-free diet. Dietary management of short bowel syndrome patients includes frequent small meals, limitation of fiber, lactose, and simple sugars, taking liquids separately from meals, and supplementation of calcium and zinc orally and magnesium and vitamin B₁₂ parenterally.

Bye et al. (168) conducted a prospective, randomized trial of a low-fat, low-lactose diet in 143 women with gynecologic malignancies undergoing radiation therapy. The intervention group had significantly less diarrhea. Diarrhea in the control group correlated with increased fatigue and decreased physical function. The authors concluded that diet intervention during radiotherapy reduced the severity of diarrhea, influenced patients' ability to cope with diarrhea, and gave them more control over their situation.

The successful implementation of prescribed diets depends to a large extent on a dietician converting the prescribed diet to a meal plan and working with the patient to implement it. In a prospective, randomized study of 57 patients undergoing chemotherapy for ovarian, breast, or lung cancer, those who received intensive dietary counseling had improved long-term food intake (169). Similar data have been demonstrated in cancer patients undergoing radiotherapy (170) and in patients with acute leukemia undergoing induction chemotherapy (171).

Pharmacologic Agents

Agents that will reverse the wasting seen in advanced cancers have long been sought to complement or replace the provision of nutrients via the oral, enteral, or parenteral route. Hormones, appetite stimulants, and most recently, cytokine antagonists have been examined. Studies of growth hormone (172,173) IGF-I alone (173) or IGF-I with insulin (174) in cancer bearing rodent models showed significant attenuation of tumor-induced weight loss. In human clinical trials, these agents provided modest gain in weight but no improvement in quality of life or other benefits (175).

Hormones

Ghrelin, a potent orexigenic peptide hormone produced by the stomach has been shown to increase appetite and caloric intake in normal individuals and in animal models of cancer cachexia. It was therefore hypothesized that ghrelin may be an effective treatment for cancer-induced cachexia. One small randomized study showed that intravenous ghrelin led to a marked increase in energy and caloric intake, with no side effects (176). There was concern that its use would be limited by its promotion of cellular proliferation and invasion of certain types of cancer, but a randomized, placebo-controlled, double-blind, double cross-over study demonstrated that ghrelin was safe and well tolerated, but unfortunately did not show any change in nutritional intake (177).

Appetite Stimulants

Anabolic steroids have no proven efficacy in treating cancer cachexia. In a murine model, administration of norandrolone propionate resulted in weight gain, but this was largely due to fluid retention (178). In human trials, steroids produced transient improvement of nutritional parameters and appetite, but continued use is associated with negative nitrogen balance, net calcium loss, glucose intolerance, and immunosuppression (175).

Megestrol acetate is a progestational agent that has been shown to improve appetite and ameliorate weight loss in numerous, but not all, studies of patients with cancer and cachexia (175). Doses in these studies ranged from 160mg/day - 1200mg/

day, and maximal weight gain was generally seen within 8 weeks. However, the change in weight is largely due to increased adipose tissue and edema (179). Nevertheless, improvement in quality of life has consistently been demonstrated in several large prospective studies in patients with cancer cachexia treated with megestrol acetate (180,181). It is generally well tolerated but can exacerbate underlying diabetes mellitus, increase thrombotic risk, and rarely lead to adrenal suppression. Dronabinol, a marijuana derivative, has shown some promise in small studies, improving appetite and causing weight gain; however, large randomized trials are lacking (175).

Cytokine Inhibitors

Inhibitors of cytokines involved in cancer cachexia and anorexia have the potential to be potent agents in the treatment of malnutrition in cancer. Monoclonal antibodies against TNF lead to improved food intake and diminished loss of protein and fat in murine models of cancer cachexia (167). Similar data are available for anti-IL-6 (182,183) and anti-IFN- γ (184). Suramin, a direct IL-6 receptor antagonist, decreased several key parameters of cachexia in tumor-bearing mice (185). In a recent study from Japan, a novel inhibitor of IL-1 and TNF- α showed that direct injection of the drug into tumor did not alter tumor growth but did result in attenuation of loss of body weight and epididymal fat in tumor-bearing mice (186). Human studies utilizing the anticytokine approach are limited. Pentoxifylline and thalidomide have been shown to inhibit TNF- α , but only thalidomide improved weight loss associated with AIDS and tuberculosis (187). Interestingly, recent data showed that the clinical anticachexia effects of megestrol acetate are due, at least in part, to the inhibition of cytokines (102) (Table 32.3).

Drugs to Relieve Symptoms

The use of medications to relieve cancer- or treatment-related symptoms that impair oral intake is an important adjuvant to nutritional support in these patients. For example, optimal antiemetic therapy can now adequately control acute and delayed emesis in 70% to 90% of patients (188). Despite this, the incidence of chemotherapy-induced nausea and emesis is underestimated by oncologists and nurses (189). This highlights the importance of a careful history and review of systems when completing a nutritional evaluation of a cancer patient. Many cancer patients assume that nausea and vomiting are normal during treatment and will not report it as a problem unless specifically asked.

ETHICAL CONSIDERATIONS

Prior to the advent of enteral and parenteral feedings, the inability to receive nutrients through oral intake inevitably led to wasting and death. Therefore, in the majority of patients, the natural history of cancer led to death because of dehydration and starvation (190). In patients with potentially curable or stable disease, nutritional support, when indicated, is an important and often critical part of the overall treatment plan. On the other hand, the role of nutritional support in the terminally ill is a subject filled with ethical and legal dilemmas. These problems come to light when the wishes of the patient or the patient's representative are not in agreement with the recommendations of the physicians. For example, a patient may wish to forego nutritional support despite recommendations that such a therapy should be given. Alternatively, patients or their representatives may want to initiate or continue TPN even after all anticancer therapies have failed and the patient is in a terminal state. Two general principles apply: in the first case, autonomy, and in the second, medical futility.

Table 32.3 Pharmacologic Agents Used for the Treatment of Cancer Cachexia and Anorexia

Class of Agent	Example	Efficacy	Adverse Effects
Hormones	Insulin, IGF, GH	Attenuation of tumor-induced weight loss, <i>no</i> improvement in survival or quality of life demonstrated	Hypoglycemia, Hypokalemia
Anabolic Steroids	Oxandrolone, Nandrolone	Transient improvement in appetite	Fluid retention, Net loss of calcium and nitrogen, Hyperglycemia, Immunosuppression
Progestational Agents	Megestrol Acetate	Improved appetite, weight, and quality of life	Weight gain is mostly due to fluid retention and adipose tissue, May exacerbate diabetes mellitus, Rare cases of adrenal insufficiency
Cannabinoids	Dorabinol	Improved appetite and weight gain in small studies	CNS effects (slurred speech, nausea, dizziness, sedation)
Cytokine Inhibitors	Pentoxifylline, Thalidomide, Suramin Monoclonal Antibodies to IL-1, IL-6, and TNF- α	Improved food intake and attenuation of protein loss in animal models	Clinical studies pending

CNS, central nervous system; GH, growth hormone; IGF, insulin-like growth factor; IL, interleukin; TNF, tumor necrosis factor.

Autonomy is the right of competent patients to make decisions over their care and implies that the physician must solicit these decisions. It was not until the mid-1960s, a time of vast societal changes and challenges to authority, that autonomy began to supersede the Hippocratic tradition with its emphasis on the authoritarian role of the physician. This principle is clearly outlined in a report from the President's Commission for the study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which states: "The voluntary choice of a competent and informed patient should determine whether or not life sustaining therapy will be undertaken, while health care institutions and professionals should try to enhance patients' abilities to make decisions on their own and to promote understanding of the available options" (191). With regard to most treatments (operations, chemotherapy, radiation therapy), the patient's knowledge and experience may be very limited, and thus, the physician's recommendations may form as the sole basis for the patient's decisions. This is not the case with nutrition. People understand the role of nutrition in sustaining life, and it is often hard for a lay person to understand why parenteral nutrition may not be indicated or even harmful when the patient has no other source of nourishment. In such situations, it is the responsibility of the physician to thoroughly explain the reasons for withholding TPN.

The principle of medical futility often surfaces in discussion of nutritional support of the cancer patient, especially if the disease is advanced and unresponsive to therapy. There are four aspects to medical futility (192): (1) lack of physiologic rationale for the proposed therapy; (2) failure of the same therapy in a previous attempt; (3) all possible treatments for the underlying disease have failed; (4) the therapy will not improve quality of life or achieve a goal of care (such as living to see a particular life event). In the case of parenteral (and rarely enteral) nutritional support of the cancer patient, aspects 3 and 4 may be specifically applicable.

It should be noted that these principles, autonomy and medical futility, should govern decisions for both initiation and withdrawal of an ongoing therapy. As stated in the report from the President's Commission, "A justification that is adequate for not commencing a treatment is also sufficient for ceasing it. Moreover, establishing a higher requirement for cessation might

unjustifiably discourage vigorous initial attempts to treat seriously ill patients that sometimes succeed" (191).

Religious beliefs will often strongly influence decisions regarding nutritional support. Publicly stated opinions on the subject include: (1) a statement from the Archbishop of Canterbury that removal from life support was permitted if it was better to allow the patient to die (193). (2) a report from the National Conference of United States Catholic Bishops that stated that Catholics are not required to use extraordinary means when recovery is hopeless and only the burden of care remains, (194) and (3) a review of Orthodox Jewish rabbinical decisions that concluded "the imperative to preserve life, supersedes, with a few exceptions, quality of life considerations" (195).

For the gynecologic oncologist, management of the patient with an inoperable bowel obstruction due to peritoneal carcinomatosis is a difficult and recurrent problem. A recent review attempted to outline the role of parenteral nutrition in this population (139). TPN should be considered in only those patients with a good performance status, and careful attention must be paid to medical and symptomatic outcomes, as well as ethical considerations. It is interesting to note the views of patients on various life-sustaining treatments. In a study from the University of Michigan, 90% of women undergoing treatment for a gynecologic cancer could envision a time when they would refuse ventilatory support, but only 37% could foresee a time when they would refuse artificial nutrition (196). It is important for the physician and other members of the health care team to inform the patient and the family that in the terminally ill, provision of food and water by enteral or parenteral routes will not improve comfort (138,190) and, in fact, may add to discomfort (138,197–199). At Memorial Sloan-Kettering Cancer Center, TPN is used infrequently in patients with gynecologic cancer and bowel obstruction due to malignant carcinomatosis who do not receive any further anticancer therapy. TPN is used under these conditions only when it is judged that it will enhance the quality of life of a patient who is not at imminent risk of dying in spite of the widely metastatic disease. When considering the chance of improving the quality of life, the burden of TPN administration and monitoring and the risk of complications have to be considered.

REFERENCES

1. Trosian M, Mullen JL. Nutritional assessment. In: Kaminski M, ed. *Hyperalimentation: A Guide for Clinicians*. New York, NY: Marcel Dekker; 1985:47.
2. Nixon DW, Heymsfield SB, Cohen AE, et al. Protein-calorie undernutrition in hospitalized cancer patients. *Am J Med*. 1980;69:491.
3. Dowd PS, Heatley RV. The influence of undernutrition on immunity. *Clin Sci Mol Med*. 1984;66:241.
4. Meakins JL, Christou NV, Shizgal HM, et al. Therapeutic approaches to energy in surgical patients. *Ann Surg*. 1979;190:286.
5. Mullen JL, Buzby GP, Waldman MT, et al. Prediction of operative morbidity and mortality by preoperative nutritional assessment. *Surg Forum*. 1979;30:80.
6. Buzby GP, Mullen JF, Matthews DC, et al. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg*. 1980;139:160.
7. Baker JP, Detsky AS, Wesson DE, et al. Nutritional assessment: a comparison of clinical judgment and objective measurements. *N Engl J Med*. 1982;306:969.
8. Detsky AS, Baker JP, O'Rourke K, et al. Predicting nutrition associated complications for patients undergoing gastrointestinal surgery. *JPEN*. 1987;11:440.
9. Detsky AS, Baker JP, Mendelson RA, et al. Evaluating the accuracy of nutritional assessment techniques applied to hospitalized patients: methodology and comparisons. *JPEN*. 1984;8:153.
10. Crowe PJ, Snyman AM, Dent DM, et al. Assessing malnutrition in gastric carcinoma: bioelectrical impedance or clinical impression? *Aust N Z J Surg*. 1992;62:390.
11. Ottow RT, Bruining HA, Jeekel J. Clinical judgement versus delayed hypersensitivity skin testing for the prediction of postoperative sepsis and mortality. *Surg Gynecol Obstet*. 1984;159:475.
12. Pettigrew RA, Hill GL. Indicators of surgical risk and clinical judgement. *Br J Surg*. 1986;73:47.
13. Gupta D, Lammersfeld CA, Vashi PG, et al. Can subjective global assessment of nutritional status predict survival in ovarian cancer? *J Ovarian Res*. 2008;15(1):5.
14. Phippen NT, Lowery WJ, Barnett JC, et al. Evaluation of the Patient-Generated Subjective Global Assessment (PG-SGA) as a predictor of febrile neutropenia in gynecologic cancer patients receiving combination chemotherapy: a pilot study. *Gynecol Oncol*. 2011;123:360–364.
15. Laky B, Janda M, Cleghorn G, et al. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. *Am J Clin Nutr*. 2008;87(6):1678–1685.
16. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *Am J Med*. 1980;69:491.
17. Lanzotti VJ, Thomas DR, Boyle LE. Survival with inoperable lung cancer. *Cancer*. 1977;39:303.
18. Ollenschlager G, Viell B, Thomas W, et al. Tumor anorexia: causes, assessment, treatment. *Recent Results Cancer Res*. 1991;121:249.
19. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med*. 1991;325:525.
20. Santos JT, Canada T, Latson B, et al. Prognostic nutritional index in relation to hospital stay with gynecologic cancer. *Obstet Gynecol*. 2000;95(6 pt 1):844–846.
21. Tunca JC. Nutritional evaluation of gynecologic cancer patients during initial diagnosis of their disease. *Am J Obstet Gynecol*. 1983;147:893.
22. Orr JW Jr, Wilson K, Bodiford C, et al. Nutritional status of patients with untreated cervical cancer.I. Biochemical and immunologic assessment. *Am J Obstet Gynecol*. 1985;151:625.
23. Orr JW Jr, Wilson K, Bodiford C, et al. Nutritional status of patients with untreated cervical cancer.II. Vitamin assessment. *Am J Obstet Gynecol*. 1985;151:632.
24. Orr JW Jr, Wilson K, Bodiford C, et al. Corpus and cervix cancer: a nutritional comparison. *Am J Obstet Gynecol*. 1985;153:775.
25. Warren RS, Starnes HF, Gabrilove JL, et al. The acute metabolic effects of tumor necrosis factor administration. *Arch Surg*. 1987;122:1396.
26. Dempsey DT, Mullen JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? *Am J Clin Nutr*. 1985;47(suppl. 2):352.
27. Terada KY, Christen C, Roberts JA. Parenteral nutrition in gynecology. *J Repro Med*. 1988;33:957.
28. Geisler JP, Linnemeier GC, Thomas AJ, et al. Nutritional assessment using prealbumin as an objective criterion to determine whom should not undergo primary radical cytoreductive surgery for ovarian cancer. *Gynecol Oncol*. 2007;160(1):128–131.
29. Burnett AF, Potkul RK, Barter JF, et al. Colonic surgery in gynecologic oncology.Risk factor analysis. *J Repro Med*. 1993;38:137.
30. Donato D, Angelides A, Irani H, et al. Infectious complications after gastrointestinal surgery in patients with ovarian carcinoma and malignant ascities. *Gynecol Oncol*. 1992;44:40.
31. Diaz-Montes TP, Zahurak ML, Bristow RD. Predictors of extended intensive care unit resource utilization following surgery for ovarian cancer. *Gynecol Oncol*. 2007;107(3):464–468.
32. Gupta D, Liss CG, Vashi PG, et al. Impact of improved nutritional status on survival in ovarian cancer. *Support Care Cancer*. 2010;18(3):373–381.
33. Abu-Rustum NR, Barakat RR, Venkatraman E, et al. Chemotherapy and total parenteral nutrition for advanced ovarian cancer with bowel obstruction. *Gynecol Oncol*. 1997;64:493.
34. Jong P, Sturgeon J, Jamieson CG. Benefit of palliative surgery for bowel obstruction in advanced ovarian cancer. *Can J Surg*. 1995;38:454.
35. Zoetmulder FA, Helmerhorst TJ, Van Coevorden F, et al. Management of bowel obstruction in patients with advanced ovarian cancer. *Eur J Cancer*. 1994;30A:1625.
36. Norton JA, Moley JF, Green MV, et al. Parabolic transfer of cancer anorexia/cahcxia in male rats. *Cancer Res*. 1985;45:5547.
37. Carson JA, Gormican A. Taste acuity and food attitudes of selected patients with cancer. *J Am Diet Assoc*. 1977;70:361.
38. Dewys WD. Anorexia as a general effect of cancer. *Cancer*. 1979;43:2013.
39. Dewys WD, Walters K. Abnormalities of taste sensation in cancer patients. *Cancer*. 1975;36:1988.
40. Trant AS, Serin J, Douglass HO. Is taste related to anorexia in cancer patients? *Am J Clin Nutr*. 1982;36:45.
41. Bernstein IL. Neural mediation of food aversions and anorexia induced by tumor necrosis factor and tumors. *Neurosci Biobehav Rev*. 1996;20:177.
42. Bernstein IL, Taylor EM, Bentson KL. TNF induced anorexia and learned food aversions are attenuated by area postrema lesions. *Am J Physiol*. 1991;260:906.
43. Orr JW Jr, Shingleton HM, Hatch KD, et al. Gastrointestinal complications associated with pelvic exenteration. *Am J Obstet Gynecol*. 1983;145:325.
44. Turtel PS, Shike M. Diseases of the small bowel. In: Shils ME, Olsen JA, Shike M, et al. eds. *Modern Nutrition in Health and Disease*. 9th ed. Philadelphia, PA: Williams & Wilkins; 1999:1151.
45. Scarantino CW, Ornitz RD, Hoffman LG, et al. On the mechanism of radiation-induced emesis: the role of serotonin. *Int J Radiat Oncol Biol Phys*. 1994;30:825.
46. Bodis S, Alexander E 3rd, Kooy H, et al. The prevention of radiosurgery-induced nausea and vomiting by ondansetron: evidence of a direct effect on the central nervous system chemoreceptor trigger zone. *Surg Neurol*. 1994;42:249.
47. Sedgwick DM, Howard GC, Ferguson A. Pathogenesis of acute radiation injury to the rectum. A prospective study in patients. *Int J Colorect Dis*. 1994;9:23.
48. Kinsella TJ, Bloomer WD. Tolerance of the intestine to radiation therapy. *Surg Gynecol Obstet*. 1980;151:273.
49. Lojdic TA, Lang JA. Treatment of radiation enteritis: a comparison study. *Am J Gastroenterol*. 1983;78:481.
50. Libotte F, Autier P, Delmelle M, et al. Survival of patients with radiation enteritis of the small and large intestine. *Acta Chir Belg*. 1995;95:190.
51. Yeoh E, Horowitz M, Russo A, et al. A retrospective study of the effects of pelvic irradiation for carcinoma of the cervix on gastrointestinal function. *Int J Rad Oncol Bio Phys*. 1993;26:229.
52. Husebye E, Hauer-Jensen M, Kjørstad K, et al. Severe late radiation enteropathy is characterized by impaired motility of the proximal small intestine. *Dig Dis Sci*. 1994;39:2341.
53. Danielson A, Nhylin H, Persson H, et al. Chronic diarrhoea after radiotherapy for gynaecological cancer: occurrence and aetiology. *Gut*. 1991;32:1180.
54. Kwitko Ao, Pieterse AS, Hecker R, et al. Chronic radiation injury to the intestine: a clinico-pathological study. *Aust N Z J Med*. 1982;12:272.
55. Boland E, Thompson J, Rochling F, et al. A 25-year experience with postresection short-bowel syndrome secondary to radiation therapy. *Am J Surg*. 2010;200(6):690–693.
56. Curran WJ. Radiation-induced toxicities: the role of radioprotectants. *Semin Radiat Oncol*. 1998;4(suppl. 1):2.
57. Kagei K, Tokuyue K, Okumura T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 2003;55(5):1265–1271.
58. Bajorin D, Kelsen D. Toxicity of antineoplastic therapy. In: Turnbull ADM, ed. *Surgical Emergencies in the Cancer Patient*. Chicago, USA: Year Book Medical Publishers; 1987:14.
59. Mitchell EP, Schein PS. Gastrointestinal toxicity of chemotherapeutic agents. *Semin Oncol*. 1982;9:52.
60. Calabresi P, Chabner B. Chemotherapy of neoplastic diseases. In: Gilman AG, Rall TW, Nies AS, et al. eds. *The Pharmacologic Basis of Therapeutics*. New York, NY: Pergamon Press; 1990:1201.
61. Steinbach S, Hummel T, Bohner C, et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for

- breast cancer or gynecologic malignancies. *J Clin Oncol*. 2009;27(11):1899-1905.
62. Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr*. 2004;32:57-71.
 63. Arbiet JM, Lees DE, Corsey R, et al. Resting energy expenditure in controls and cancer patients with localized and diffuse disease. *Ann Surg*. 1984;199:292.
 64. Dempsey DT, Furer ID, Knox LS, et al. Energy expenditure in malnourished gastrointestinal cancer patients. *Cancer*. 1984;53:1265.
 65. Hansell DT, Davies JWL, Burns HJG. The relationship between resting energy expenditure and weight loss in benign and malignant disease. *Ann Surg*. 1986;203:240.
 66. Peacock JL, Inculter RI, Corsey R, et al. Resting energy expenditure and body cell mass alterations in sarcoma patients. *Surg Forum*. 1986; 90:195.
 67. Russel DM, Shike M, Marliss EB, et al. Effects of total parenteral nutrition and chemotherapy on the metabolic derangements in small cell lung cancer. *Cancer Res*. 1984;44:1706.
 68. Warnold I, Lundholm K, Schersten T. Energy balance and body composition in cancer patients. *Cancer Res*. 1978;38:1801.
 69. Gadducci A, Cosio S, Fanucchi A, et al. Malnutrition and cachexia in ovarian cancer patients: pathophysiology and management. *Anticancer Res*. 2001;21(4B):2941-2947.
 70. Shike M, Berner YN, Gerdes H, et al. Percutaneous endoscopic gastrostomy and jejunostomy for long-term feeding in patients with cancer of the head and neck. *Otolaryngol Head Neck Surg*. 1989;101:549.
 71. Lutetich JD, Mullen JL, Feurer ID, et al. Ablation of abnormal energy expenditure by curative tumor resection. *Arch Surg*. 1990;125:337.
 72. Dickerson RN, White KG, Curicillo PG, et al. Resting Energy expenditure of patients with gynecologic malignancies. *J Am Coll Nutr*. 1995;15:448.
 73. Holroyde CP, Gabuzda TG, Putnam RC, et al. Altered glucose metabolism in metastatic carcinoma. *Cancer Res*. 1975;35:3710.
 74. Holroyde CP, Skutches CL, Boden G, et al. Glucose metabolism in cachectic patients with colorectal cancer. *Cancer Res*. 1984;44:5910.
 75. Kern KA, Norton JA. Cancer cachexia. *JPEN*. 1988;12:286.
 76. Lundholm K, Holm G, Schersten T. Insulin resistance in patients with cancer. *Cancer Res*. 1978;38:4665.
 77. Cersosimo E, Pisters PW, Pesola G, et al. The effect of graded doses of insulin on peripheral glucose uptake and lactate release in cancer cachexia. *Surgery*. 1991;109:459.
 78. Shaw JH, Wolfe RR. Glucose and urea kinetics in patients with early and advance gastrointestinal cancer: the response to glucose infusion, parenteral feeding, and surgical resection. *Surgery*. 1987;101:181.
 79. Tisdale MJ. Mechanisms of cancer cachexia. *Physiol Rev*. 2009;89(2):381-410.
 80. McAndrew PF. Fat metabolism and cancer. *Surg Clin North Am*. 1986;66:1003.
 81. Beutler B, Cerami A. Cachectin and tumour necrosis factor as two sides of the same biological coin. *Nature*. 1986;320:584.
 82. Klein S, Wolfe RR. Whole-body lipolysis and triglyceride-fatty acid cycling in cachectic patients with esophageal cancer. *J Clin Invest*. 1990;86:1403.
 83. Todorov PT, McDevitt TM, Meyer DJ, et al. Purification and characterization of a tumor lipid-mobilizing factor. *Cancer Res*. 1998;58:2353.
 84. Hirai K, Hussey HJ, Barber MD, et al. Biological evaluation of a lipid-mobilizing factor isolated from the urine of cancer patients. *Cancer Res*. 1998;58:2359.
 85. Russel ST, Hirai K, Tisdale MT. Role of beta3-adrenergic receptors in the action of a tumour lipid mobilizing factor. *Br J Cancer*. 2002;86:424.
 86. Bing C, Russell ST, Beckett EE, et al. Expression of uncoupling proteins-1, -2 and -3 mRNA is induced by an adenocarcinoma-derived lipid-mobilizing factor. *Br J Cancer*. 2002;86:612.
 87. Russell ST, Zimmermann TP, Domin BA, et al. Induction of lipolysis in vitro and loss of body fat in vivo by zinc-alpha2-glycoprotein. *Biochim Biophys Acta*. 2004;1636:59.
 88. Groundwater P, Beck SA, Barton C, et al. Alteration of serum and urinary lipolytic activity with weight loss in cachectic cancer patients. *Br J Cancer*. 1990;62:816.
 89. Beck SA, Groundwater P, Barton C, et al. Alterations in serum lipolytic activity of cancer patients with response to therapy. *Br J Cancer*. 1990;62:822.
 90. Sanders PM, Tisdale MJ. Role of lipid-mobilising factor (LMF) in protecting tumour cells from oxidative damage. *Br J Cancer*. 2004;90(6):1274.
 91. Eden E, Ekman L, Bennegard K, et al. Whole body tyrosine flux in relation to energy expenditure in weight losing cancer patients. *Metabolism*. 1984;33:1020.
 92. Norton JA, Stein TP, Brennan MF. Whole body protein synthesis and turnover in normal man and malnourished patients with and without known cancer. *Ann Surg*. 1981;194:123.
 93. Shike M, Russel DM, Detsky A, et al. Changes in body composition in patients with small cell lung cancer. The effect of total parenteral nutrition as an adjunct to chemotherapy. *Ann Intern Med*. 1984;101:303.
 94. Hasselgren PO, Wray C, Mammen J. Molecular regulation of muscle cachexia: it may be more than the proteasome. *Biochem Biophys Res Commun*. 2002;290:1.
 95. Falconer JS, Fearon KC, Plester CE, et al. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. *Ann Surg*. 1994;219(4): 325-331.
 96. Tilgnaç T, Temparis S, Combaret L, et al. Chemotherapy inhibits skeletal muscle ubiquitin-proteasome-dependent proteolysis. *Cancer Res*. 2002;62:7133.
 97. Attaix D, Auroousseau E, Combaret L, et al. Ubiquitin-proteasome-dependent proteolysis in skeletal muscle. *Reprod Nutr Dev*. 1998; 38:153.
 98. Warren RS, Donner DB, Starnes HF, et al. Modulation of endogenous hormone action by recombinant human tumor necrosis factor. *Proc Natl Acad Sci USA*. 1987;84:8619.
 99. Balkwill F, Osborne R, Burke F, et al. Evidence for tumor necrosis factor/cachectin production in cancer. *Lancet*. 1987;1:1229.
 100. Fong Y, Mildawer LL, Merano M, et al. Cachectin/TNF or IL-1a induces cachexia with redistribution of body protein. *Am J Physiol*. 1989;256:R659.
 101. Tracey KJ, Wei H, Manoque KR, et al. Cachectin/TNF induces cachexia, anorexia and inflammation. *J Exp Med*. 1987;167:1211.
 102. Mantovani G, Maccio A, Lai P, et al. Cytokine activity in cancer-related anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate. *Semin Oncol*. 1998;2(suppl. 6):45.
 103. Lowry SF, Smith JC, Brennan MF. Zinc and copper replacement during total parenteral nutrition. *Am J Clin Nutr*. 1981;34:1853.
 104. Shaw JH, Humberstone DM, Wolfe RR. Energy and protein metabolism in sarcoma patients. *Ann Surg*. 1988;207:283.
 105. Jeevanandam M, Horowitz GS, Lowry SF, et al. Cancer cachexia and protein metabolism. *Lancet*. 1984;1:1423.
 106. Sharp JW, Roncagli T. Home parenteral nutrition in advanced cancer. *Canc Pract*. 1993;1:119.
 107. Shaw JH, Wolfe RR. Fatty acid and glycerol kinetics in septic patients and in patients with gastrointestinal cancer. The response glucose infusion and parenteral feeding. *Ann Surg*. 1987;205:368.
 108. Nixon DW, Moffitt S, Lawson DH, et al. Total parenteral nutrition as an adjunct to chemotherapy of metastatic colorectal cancer. *Cancer Treat Rep*. 1981;65(suppl. 5):121.
 109. Serrou B, Cupissol D, Plagne R, et al. Parenteral intravenous nutrition (PIVN) as an adjunct to chemotherapy in small cell anaplastic lung carcinoma. *Cancer Treat Rep*. 1981;65(suppl. 5):151.
 110. Valdivieso M, Bodner GP, Benjamin RS, et al. Role of intravenous hyperalimentation as an adjunct to intensive chemotherapy for small cell bronchogenic carcinoma. *Cancer Treat Rep*. 1981;65(suppl. 5):154.
 111. Samuels MI, Selig DE, Ogden S, et al. IV hyperalimentation and chemotherapy for stage III testicular cancer: a randomized study. *Cancer Treat Rep*. 1981;65:615.
 112. Daly JM, Reynolds J, Thom A, et al. Immune and metabolic effects of arginine in the surgical patient. *Ann Surg*. 1988;208:512.
 113. Fletcher JP, Little JM. A comparison of parenteral nutrition and early post operative enteral feeding on the nitrogen balance after major surgery. *Surgery*. 1986;100:21.
 114. American College of Physicians position paper. Parenteral nutrition in patients receiving cancer chemotherapy. *An Intern Med*. 1989;110:734.
 115. Klein S, Simes J, Blackburn GL. Total parenteral nutrition and cancer clinical trials. *Cancer*. 1986;58:1378.
 116. McGeer AJ, Detsky AS, O'Rourke K. Parenteral nutrition in cancer patients undergoing chemotherapy: a meta-analysis. *Nutrition*. 1990; 6:233.
 117. Klein S, Kinney J, Jeejeebhoy MB, et al. Nutrition support in clinical practice: Review of published data and recommendations for future research directions. *Am J Clin Nutr*. 1997;66:683.
 118. Weisdorf SA, Lysne J, Wind D, et al. Positive effects of prophylactic total parenteral nutrition on long term outcome of bone marrow transplantation. *Transplantation*. 1987;43:833.
 119. Baron PL, Lawrence W, Chan WM, et al. Effects of parenteral nutrition on cell cycle kinetics of head and neck cancer. *Arch Surg*. 1986;121: 1282.
 120. Ghavimi F, Shils ME, Scott BF, et al. Prospective study of nutritional support during pelvic irradiation: Comparison of children requiring abdominal radiation and chemotherapy with and without total parenteral nutrition. *J Pediatr*. 1982;4:530.
 121. Kinsella TJ, Malcom A, Bothe A, et al. Prospective study of nutrition support during pelvic irradiation. *Int J Radiat Oncol Biol Phys*. 1981;7:543.
 122. Klein S, Koretz RL. Nutrition support in patients with cancer: what do the data really show? *Nutr Clin Pract*. 1994;9:91.

123. Van Eys J, Copeland EM, Cangier A, et al. A clinical trial of hyperalimentation in children with metastatic malignancies. *Med Pediatr Oncol.* 1980;8:63.
124. Detsky AS, Baker JP, O'Rourke K, et al. Perioperative parenteral nutrition: a metaanalysis. *Ann Intern Med.* 1989;107:195.
125. Fan ST, Lo M, Lai ECS, et al. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Eng J Med.* 1994;331:1547.
126. Hotler AR, Fischer JE. The effects of perioperative hyperalimentation on complications in patients with carcinoma and weight loss. *J Surg Res.* 1977;23:31.
127. Hotler AR, Rosen HM, Fischer JE. The effects of hyperalimentation on major surgery in malignant disease: a prospective study. *Acta Chir Scand.* 1976;86(Suppl):466.
128. Mueller JM, Brenner U, Dienst C, et al. Perioperative parenteral feeding in patients gastrointestinal cancer. *Lancet.* 1982;1:68.
129. Brennan MF, Pisters PWT, Posner M, et al. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. *Ann Surg.* 1994;220:436.
130. Weisner RL, Bacon J, Butterworth LE. Central venous alimentation: a prospective study of the frequency of metabolic abnormalities among medical and surgical patients. *JPEN.* 1982;6:421.
131. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary artery catheters. *N Eng J Med.* 1992;327:1062.
132. Cunningham MJ, Collins MB, Kredentser DC, et al. Peripheral infusion ports for central venous access in patients with gynecologic malignancies. *Gyn Oncol.* 1996;60:397.
133. Solomon SM, Kirby DF. The refeeding syndrome: a review. *JPEN.* 1990;14:90.
134. Weisner RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. *Am J Clin Nutr.* 1981;34:393.
135. Lowry SF, Brennan MF. Abnormal liver function during parenteral nutrition: relation to infusion excess. *J Surg Res.* 1979;26:300.
136. Burt ME, Lowry SF, Gorschboth C, et al. Metabolic alterations in non-cachectic animal tumor systems. *Cancer.* 1981;47:2138.
137. Howard L, Ament M, Fleming R, et al. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology.* 1995;109:355.
138. McCann RM, Hall WJ, Groth-Junker A. Comfort care for terminally ill patients. *JAMA.* 1994;272:1263.
139. Philip J, Depczynski B. The role of total parenteral nutrition for patients with irreversible bowel obstruction secondary to gynecological malignancy. *J Pain Sympat Manag.* 1997; 13:104.
140. Cozzaglio L, Balzola F, Cosentino F, et al. Outcome of cancer patients receiving home parenteral nutrition. Italian society of parenteral and enteral nutrition (S.I.N.P.E.) *JPEN.* 1997;21:339.
141. August DA, Thorn D, Fisher RL, et al. Home parenteral nutrition for patients with inoperable malignant bowel obstruction. *JPEN.* 1991;15:323.
142. Brard B, Weitzen S, Strubel-Lagan S, et al. The effect of total parenteral nutrition on the survival of terminally ill ovarian cancer patients. *Gynecol Oncol.* 2006;103:176.
143. Shike M. Enteral feeding. In: Shils ME, Olsen JA, Shike M, et al. eds. *Modern Nutrition in Health and Disease.* 9th ed. Philadelphia, PA: Williams & Wilkins; 1999:1643.
144. Shike M, Latkany L. Direct percutaneous endoscopic jejunostomy. *Gastro Endo Clin NA.* 1998;8:569.
145. Daly JM. Malnutrition. In: Wilmore DW, Brennan MF, Harken AH, et al. eds. *Care of the surgical patient. Section VII: Special problems in perioperative care.* New York, NA: Scientific American, Inc.; 1994:1.
146. Norton B, Homer-Ward M, Donnelly MT, et al. A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke. *BMJ.* 1996;312:13.
147. Di Lorenzo C, Lachman R, Hyman PE. Intravenous erythromycin for postpyloric intubation. *J Pediatr Gastroenterol Nutr.* 1990;11:45.
148. Spirtos NM, Ballon SC. Needle catheter jejunostomy: a controlled, prospective, randomized trial in patients with gynecologic malignancy. *Am J Obst Gyn.* 1988;158:1285.
149. Safadi BY, Marks JM, Ponsky JL. Percutaneous endoscopic gastrostomy. *Gastro Endo Clin of NA.* 1998;8:551.
150. Ponsky JL, Gauderer MW, Stellato TA. Percutaneous endoscopic gastrostomy. Review of 150 cases. *Arch Surg.* 1983;118:913.
151. Shils ME, Olsen JA, Shike M, et al. eds. *Modern nutrition in health and disease.* 9th ed. Philadelphia, PA: Williams & Wilkins; 1999: A-206.
152. Strong RM, Condon SC, Solinger MR, et al. Equal aspiration rates from postpylorus and intragastric-placed small-bore nasogastric feeding tubes: a randomized, prospective study. *JPEN.* 1992;16:59.
153. Evens Wk, Nixon DW, Daly JM. A randomized study of oral nutritional support versus as lib nutritional intake during chemotherapy for advanced colorectal and non-small-cell lung cancer. *J Clin Oncol.* 1987;5:113.
154. Elkort RJ, Baker FL, Vitale JJ, et al. Long-term nutritional support as an adjunct to chemotherapy. *JPEN.* 1981;5:385.
155. Bozzetti F. Effects of artificial nutrition on the nutritional status of cancer patients. *JPEN.* 1989;4:406.
156. Bounous G, Gentile JM, Hugon J. Elemental diet in the management of the intestinal lesion produced by 5-fluorouracil in man. *Can J Surg.* 1971;14:312.
157. Smith RC, Hartemink RJ, Hollinshead JW, et al. Fine bore jejunostomy feeding following major abdominal surgery: a controlled randomized clinical trial. *Br J Surg.* 1985;72:458.
158. Shils ME, Shike M. Nutritional support of the cancer patient. In: Shils ME, Olsen JA, Shike M, et al. eds. *Modern Nutrition in Health and Disease.* 9th ed. Philadelphia, PA: Williams & Wilkins; 1999:1297.
159. Ryan JA, Page CP, Babcock L. Early postoperative jejunal feeding of elemental diet in gastrointestinal surgery. *Am Surg.* 1981;47:393.
160. Flynn MB, Leighty FF. Preoperative outpatient nutritional support of patients with squamous cancer of the upper aerodigestive tract. *Am J Surg.* 1987;154:359.
161. Hochwald SN, Harrison LE, Heslin MJ, et al. Early postoperative enteral feeding improves whole body protein kinetics in upper gastrointestinal cancer patients. *Am J Surg.* 1997;174:325.
162. Heslin MJ, Latkany L, Leung D, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal tract malignancy. *Ann Surg.* 1997;226:577.
163. Kirby DF, Teran JC. Enteral feeding in critical care, gastrointestinal diseases, and cancer. *Gastro Endo Clin of NA.* 1998;8:623.
164. Mullan H, Roubenoff RA, Roubenoff R. Risk of pulmonary aspiration among patients receiving enteral nutrition support. *JPEN.* 1992;16:160.
165. Montecalvo MA, steger KA, Farber HW, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. *Crit Care Med.* 1992;20:1377.
166. Bliss DZ, Guenter PA, Settle RG. Defining and reporting diarrhea in tube-fed patients—what a mess! *Am J Clin Nut.* 1992;55:753.
167. Sherry BA, Gelin J, Fong Y, et al. Anticachectin/ tumor necrosis factor-alpha antibodies attenuate development of cachexia in tumor models. *FASEB J.* 1989;3:1956.
168. Bye A, Ose T, Jaasa S. Quality of life during pelvic radiotherapy. *Acta Obst Gyn Scand.* 1995;74:147.
169. Ovensen L, Allingstrup L, Hannibal J, et al. Effects of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *J Clin Oncol.* 1993;11:2043.
170. Macia E, Moran J, Santos J, et al. Nutritional evaluation and dietetic care in cancer patients treated with radiotherapy: prospective study. *Nutrition.* 1991;7:205.
171. Ollenschlager G, Thomas W, Konkol K, et al. Nutritional behaviour and quality of life during oncological polychemotherapy: results of a prospective study on the efficacy of oral nutrition therapy in patients with acute leukemia. *Eu J Clin Invest.* 1992;22:546.
172. Bartlett DL, Stein TP, Torosian MH. Effect on growth hormone and protein intake on tumor growth and host cachexia. *Surgery.* 1995;117:260.
173. Ng EH, Rock CS, Lazarus DD, et al. Insulin-like growth factor preserves host lean tissue mass in cancer cachexia. *Am J Physiol.* 1992;262:R426.
174. Tomas FM, Chandler CS, Coyle P, et al. Effects of insulin and insulin-like growth factors on protein and energy metabolism in tumour-bearing rats. *Biochem J.* 1994;301:769.
175. Ottery FD, Walsh D, Strwford A. Pharmacologic management of anorexia/cachexia. *Semin Oncol.* 1998;25(2 suppl. 6):35.
176. Neary NM, Small CJ, Wren AM, et al. Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. *J Clin Endocrinol Metab.* 2004;89(6):2832–2836.
177. Strasser F, Lutz TA, Maeder MT, et al. Safety, tolerability and pharmacokinetics of intravenous ghrelin for cancer-related anorexia/cachexia: a randomized, placebo-controlled, double-blind, double-crossover study. *Br J Cancer.* 2008;98(2):300–308.
178. Lyden E, Cvetkovska E, Westin T. Effects of nandrolone propionate on experimental tumor growth and cancer cachexia. *Metabolism.* 1995;44:445.
179. Strang P. The effect of megestrol acetate on anorexia, weight loss and cachexia in cancer and AIDS patients. *Anticancer Res.* 1997;17:657.
180. Beller E, Tattersall M, Lumley T, et al. Improved quality of life with megestrol acetate in patients with endocrine-insensitive advanced cancer; a randomised placebo-controlled trial.

- Australasian megestrol acetate cooperative study group. *Ann Oncol*. 1997;8:277.
181. Skarlos DV, Fountzilas G, Pavlidis N, et al. Megestrol acetate in cancer patients with anorexia and weight loss. A hellenic co-operative oncology group (HeCOG) study. *Acta Oncol*. 1993;32:37.
 182. Fujimoto-Ouchi K, Tamura S, Mori K, et al. Establishment and characterization of cachexia-inducing and non-inducing clones of murine colon 26 carcinoma. *Int J Cancer*. 1995;61:522.
 183. Gelin J, Moldawer LL, Lonnroth C, et al. Role of endogenous tumor necrosis factor alpha and interleukin 1 for experimental tumor growth and the development of cancer cachexia. *Cancer Res*. 1991;51:415.
 184. Matthys P, Dijkmans R, Proost P, et al. Severe cachexia in mice inoculated with interferon-gamma-producing tumor cells. *Int J Cancer*. 1991;49:77.
 185. Strassmann G, Kambayashi T. Inhibition of experimental cancer cachexia by anti-cytokine and anti-cytokine receptor therapy. *Cytokines Mol Ther*. 1995;1:107.
 186. Yamamoto N, Kawamura I, Nishigaki F, et al. Effect of FR143430, a novel cytokine suppressive agent, on adenocarcinoma colon26-induced cachexia in mice. *Anticancer Res*. 1998;18:139.
 187. Haslett PA. Anticytokine approaches to the treatment of anorexia and cachexia. *Semin Oncol*. 1998;2(suppl. 6):53.
 188. Licitra L, Spinazze S, Roila F. Antiemetic therapy. *Crit Rev Oncol Hematol*. 2002;43:93.
 189. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer*. 2004;100:2261.
 190. Warren S. The immediate causes of death in cancer. *Am J Med Sci*. 1932;184:610.
 191. President's Commission for the Study of Ethical Problems in Medicine and Behavior Research. Deciding to forego life sustaining treatment. A report on the ethical, medical, and legal issues in treatment decisions. Washington, DC: United States Government Printing Office; 1983;3,61.
 192. Shils ME. Nutrition and medical ethics: the interplay of medical decisions, patients' rights, and the judicial system. In: Shils ME, Olsen JA, Shike M, et al. eds. *Modern Nutrition in Health and Disease*. 9th ed. Philadelphia, PA: Williams & Wilkins; 1999:1689.
 193. Coggan HD, Edwin Stevens Lecture. On dying and dying well. Moral and spiritual aspects. *Proc R Soc Med*. 1977;70:75.
 194. Position of the American Dietetic Association: legal and ethical issues in feeding permanently unconscious patients. *J Am Diet Assoc*. 1995;95:231.
 195. Scostak RZ. Jewish ethical guidelines for resuscitation and artificial nutrition and hydration of the dying elderly. *J Med Ethics*. 1994;20:93.
 196. Brown D, Roberts JA, Elkins TE, et al. Hard choices: the gynecologic cancer patient's end-of-life preferences. *Gyn Oncol*. 1994;55:355.
 197. Zerwekh JV. The dehydration question. *Nursing*. 1983;13:47.
 198. Schmitz P. The process of dying with and without feeding and fluids by tube. *Law Med Health Care*. 1991;19:23.

33

Quality-of-Life Issues in Gynecologic Oncology

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INTRODUCTION

Health-related quality of life (HRQoL) is an increasingly important endpoint in clinical trials and a fundamentally important issue for patients. Quality of life (QoL) is a multifaceted and complex paradigm that reflects patients' experiences with disease, treatment, and accompanying long-term sequelae (1,2). While a specific definition of QoL may require articulating the patient's status on physical, functional, emotional, and social well-being (3), it can also encompass the disparate aspects of patient demography (age, ethnicity, education, income), social circumstances (relationships and roles), and spiritual issues. It is no longer acceptable to pursue curative treatment with the hope of improving mortality without consideration of treatment morbidity and without including patient-centered decision-making and QoL implications. Therefore, this chapter provides an overview of state-of-the-science perspectives broadly incorporating medical interventions (e.g., recent clinical trials) that have influenced QoL and other patient-reported outcomes, and gynecologic cancer survivorship issues, including several challenging symptoms (e.g., fatigue, neurotoxicity, lymphedema) and long-term concerns (e.g., sexual dysfunction, reproductive concerns, emotional well-being).

QUALITY OF LIFE

QoL is an abstract, multidimensional construct that covers the subjective perceptions of the positive and negative aspects of patients' experiences. We all know good QoL, but it is rarely simple. It integrates symptoms, physical, emotional, social, and cognitive functions, and reflects the impact of cancer and the side effects of treatment (4,5). Figure 33.1 lists elements of QoL (6–8).

Considering well-being or QoL is as old as Aristotle's concept of eudaimonia, or "good." The first attempt to quantitatively measure the impact of cancer was described in 1949, when Karnofsky and Burchenal reported a simple 11 (0 to 10) point scale for the clinical evaluation of chemotherapy. This was simplified into the ECOG (Eastern Cooperative Oncology Group) Zubrod scale (0 = asymptomatic, 1 = symptomatic, 2 = functional for more than half the day, 3 = functional for less than half the day, 4 = moribund). Performance status probably remains the single most significant bias that contributes to the big differences between the results of phase 2 studies (9). Early QoL studies rapidly revealed considerable discrepancy between observers and between the doctor's and his or her patient's evaluation of the patient's QoL, and it became clear that any method for

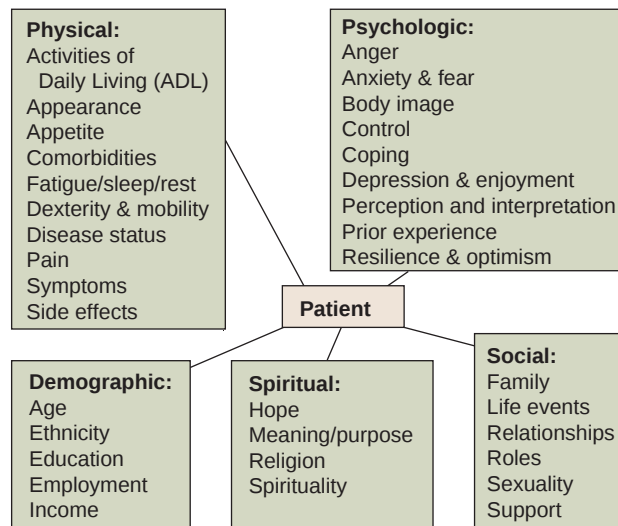


FIGURE 33.1. Elements of quality of life. Note: ADL, activities of daily living. Source: Modified from Ferrell B, Smith SL, Cullinane CA, et al. Psychological well being and quality of life in ovarian cancer survivors. *Cancer* 2003;98:1061–1071; Gralla RJ. Silk purse in Atlanta: a commentary on SWOG 9509, an advanced non-small cell lung cancer trial. *Oncologist* 1999;4:188–190; Kornblith AB, Thaler HT, Wong G, et al. Quality of life of women with ovarian cancer. *Gynecol Oncol* 1995;59:231–242.

measuring QoL, quintessentially subjective, would have to rely on patients themselves and not caregivers (10). Patient-reported outcomes (PROs) are now widely considered an excellent methodology to evaluate the utility of treatment. A simple composite measure of clinical benefit (measurements of pain [analgesic consumption and pain intensity], Karnofsky performance status, and weight) was used as the primary efficacy measure in a small but randomized study that led to Food and Drug Administration (FDA) approval of gemcitabine in advanced pancreatic cancer (11). Quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWIST) was an important addition as duration of symptoms, where they occur in the trajectory of the disease, and their source (disease or treatment) all influence their perception and impact (12). Large randomized controlled trials incorporating QoL endpoints have reported that docetaxel is associated with less neurotoxicity than paclitaxel (13), and erythropoietin (rHuEpo) significantly impacts anemia and fatigue (14). As physical functioning deteriorates, relational, spiritual, and psychologic issues become relatively more important (15,16). QoL has been shown to predict survival in numerous disease settings (17,18). In the Heart and Soul Study, a study of outcomes in 1,024 patients with coronary artery disease,

depressive symptoms were more predictive of overall health than conventional measures of cardiac function such as ejection fraction and ischemia (19). Work conducted within the Gynecologic Oncology Group (GOG) has suggested that baseline QoL scores predict survival and may serve as an early barometer of patients who may or may not respond to aggressive treatment (20,21).

HRQoL is also recognized as a crucial component in medical decision-making research, for instance, if 2 treatments are shown to have equal efficacy, a HRQoL benefit could determine the preferable choice of therapy (22). Measurement and comparison of longitudinal changes in PROs are essential in evaluating clinical trials. Response-shift effects or the change in an individual's internal beliefs, values, and perception based on health changes is viewed as a recognized confounder. Therefore, response shift effects should be assessed and adjusted for in clinical trials, allowing for a cautious approach to ensure that detected changes in HRQoL are truly due to treatment, intervention, or disease rather than measurement error (22).

Quantitative measure of patient outcomes is dependent on the use of validated instruments of psychometric data. Such questionnaires, or scales, list items (questions about particular constructs) in related domains (dimension or focus of behavior or experience). Retesting between subjects and over time establishes reliability (test-retest, interobserver variation, and correlation with related instruments), responsiveness, and applicability (generalizability or external validity). Good scales have to be (a) internally consistent (similar domains report agreement—Cronbach's $\alpha \geq 0.7$), (b) stable (reliability coefficient), (c) equivalent or superior to other scales purporting to measure the same thing (kappa statistics), and (d) accepted by patients and experts. Approximately 500 instruments have been developed (23). Commonly used tools include the Functional Assessment of Cancer Therapy (FACT—with gynecologic and symptom subscales), the European Organization for the Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30), Hospital and Anxiety Depression Scale (HADS), Profile of Mood States (POMS), Rotterdam Symptom Checklist (RSCL), MOS-Short Form 36 (SF-36), and Visual Analogue Scale (VAS).

The Functional Assessment of Cancer Therapy (FACT) instrument (scale) is a 27- (generic core) to 50-item compilation of specific subscales composed of physical, social/family, emotional, functional, and disease-specific well-being concerns (<http://www.facit.org/>) (24,25). The EORTC also developed a similar QoL instrument consisting of a core component applicable to all cancer patients and modules developed for specific cancer sites (26). EuroQol-5Dimension (EQ5D) utilizes a brief 5-item questionnaire covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and a thermometer VAS ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) (26).

For much of the last decade, the research agenda has been dominated by the comparison of instruments that evaluate the harder to measure aspects of clinical care (Fig. 33.2) (27,28). These studies have helped develop tools that have allowed important randomized clinical trials to now report QoL data (13,29). Formalizing the evaluation of HRQoL is becoming established, with ongoing debate over methodology and the distillation of a minimum set of criteria for assessing outcomes in cancer clinical trials that inform decisions in clinical practice (30). New modeling approaches that account for nonrandom omission of data are beginning to be accepted (31). Evaluating QoL helps describe populations, predict outcomes, and guide decisions (trade-offs and gambles), and can screen for dysfunction, help allocate resources, and improve awareness as patients approach end-of-life issues (32,33).

A novel approach to PROs is now funded by the National Institutes of Health (NIH). The Patient-Reported Outcomes Measurement Information System (PROMIS) network, which

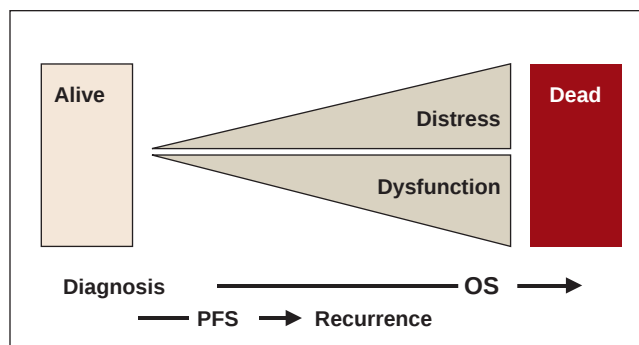


FIGURE 33.2. Health-related quality of life—measuring the grey outcomes. Black and white outcomes: PFS, progression-free survival; OS, overall survival.

is part of the NIH Roadmap Initiative, aims to improve how PROs are selected and assessed in clinical research. PROMIS is establishing a publicly available resource of self-reported health domain measures, including those specifically targeted to cancer. More information can be found at <http://www.nihpromis.org/> (24). Additional useful resources for QoL measurement include <http://www.facit.org/>, <http://www.isoqol.org/>, <http://www.euroqol.org/>, <http://www.cancer.gov/>, and <http://www.ql-recorder.com/>.

QOL OUTCOMES AND CLINICAL TRIAL UPDATES FOR ENDOMETRIAL, CERVICAL, OVARIAN, AND VULVAR CANCER

Integrated multidisciplinary care has appropriately become the necessary standard of the complex care of patients frequently in specialist centers, with goals of care changing over the course of the disease (Fig. 33.3).

Endometrial Cancer

Literature has identified quality-of-life data that may inform therapeutic choices for women with endometrial cancer. In an advanced endometrial cancer study, patients were randomized to whole-abdominal irradiation (WAI) versus doxorubicin-cisplatin (AP) chemotherapy. Although overall QoL did not differ between the 2 treatment groups, there were symptom-related

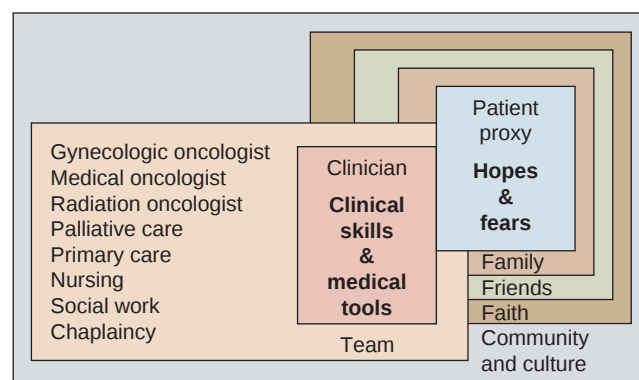


FIGURE 33.3. Holistic care.

differences (34). Specifically, WAI patients reported significantly higher fatigue than those who received AP chemotherapy for 7 cycles plus an additional cycle of cisplatin alone. Significant differences in functional alterations due to changes in bowel function were identified at the end of treatment ($p < 0.01$) and at 3 months ($p < 0.01$), with radiation associated with poorer scores. However, the AP group showed significantly higher peripheral neuropathy scores at the end of treatment and at 3 and 6 months posttreatment compared to the WAI group ($p < 0.01$). Therefore, although doxorubicin-cisplatin showed increased survival, the authors emphasized that the patients should be counseled regarding significant peripheral neuropathy that may have a significant impact on QoL.

Notably, QoL has also been evaluated in comparisons of laparoscopy versus laparotomy (35,36). In both studies, QoL was superior in the laparoscopy group. In the GOG LAP2 trial, which compared differences in QoL between those endometrial cancer patients who underwent comprehensive surgical staging via laparoscopic technique versus traditional laparotomy, patients treated by laparoscopy had a superior QoL through 6 weeks postsurgery compared to those treated by laparotomy, likely due to it being a less invasive procedure, resulting in less pain, faster recovery, and a small but significant reduced length of hospital stay. However, except for a significantly better body image in the laparoscopy than the laparotomy group, these differences were not sustained at 6 months.

Response patterns for the LAP2 QoL data were reexamined by conceptualizing patient reports by content domains and development of constructs (i.e., sexual function, quality of relationships, body image, and fear of sex). No differences were found between the surgical groups, but the quality of the relationship, younger age, and being married increased the likelihood of responding to the items and better sexual function. Factors such as age, relationship quality, body image, and pain may place women with endometrial cancer at risk for sexual difficulties.

Radiation therapy is recommended for patients with high-risk features or advanced disease and is commonly utilized to prevent recurrence (37). The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC-2) study examined the effects of high-dose intravaginal radiation therapy (HDIVRT) versus external beam radiation therapy (EBRT) (38). In the PORTEC-1 trial, it was observed that those women receiving EBRT versus observation had increased bowel and bladder symptoms in addition to QoL changes even 15 years out from treatment (39). With this information, the authors became skeptical of the actual benefit of EBRT in low to intermediate risk women. Then in PORTEC-2, the patients who received HDIVRT were found to have better QoL (38). Subsequently, HDIVRT has been gaining favor as a treatment modality, with supporting research demonstrating less morbidity (37,40–42) and excellent recurrence-free and overall survival rates (43) in comparison to EBRT (38,44). However, vaginal toxicities were noted with HDIVRT (dyspareunia, vaginal dryness, tightness, and shortening of the vagina), but further research is warranted to understand how these vaginal issues translate directly to sexual function for these women.

Finally, in the realm of endometrial cancer, obesity and its potential effect on QoL cannot be ignored. In fact, Fader et al. examined the association of obesity (BMI) and various QoL subscales (45). These authors highlighted the significant association of obesity with poor QoL in an otherwise highly curative cancer. Future research examining the role of diet and physical activity interventions is encouraged.

Cervical Cancer

In treatment of advanced cervical cancer, QoL considerations are primary. Several studies have demonstrated important QoL

results that have influenced clinical trial paradigms. For example, a randomized phase 3 trial demonstrated that although there was greater toxicity in the cisplatin/paclitaxel (CP) regimen, there was no statistically significant difference in overall QoL scores between this treatment arm and the cisplatin (C) single-agent regimen. This finding, combined with the improved response rate and progression-free survival in the CP arm and a higher dropout rate in the C arm, suggests a worse outcome for the single-agent regimen. In this case, QoL measurement contributed to the conclusion that CP is superior to C alone with respect to response rate, progression-free interval, and sustained or improved QoL for patients treated with cisplatin versus cisplatin plus paclitaxel (20,46).

Several other trials have reported QoL as a secondary endpoint to use in addition to survival data when choosing chemotherapeutic regimens to treat advanced cervical cancer (47,48). These authors effectively argue that when determining if certain chemotherapy combinations may improve survival, it is critical to consider QoL, as toxicity may worsen. One such study prospectively assessed the impact of treatment with cisplatin alone (C), versus C in combination with topotecan (C+T) on QoL in patients with advanced or recurrent cervical cancer, and explored the prognostic value of baseline QoL scores. Results from this study, employing the FACT-Cx measure, indicated there were no statistically significant differences in QoL up to 9 months postrandomization, despite more hematologic toxicity in the C+T arm. The baseline FACT-Cx was also associated with predicting survival (48). This was the first advanced cervical cancer study to note that patient-reported QoL measures may be an important prognostic tool in advanced cervical cancer. Finally, in an analysis of 3 phase 3 trials, the physical well-being subscale proved to be independently prognostic of survival even when controlling for known contributing factors (49). These phase 3 trials have challenged a traditional study design for chemotherapeutic agents by incorporating PROs into the interpretations and implications of the relative value of these regimens. Clearly, QoL is a critical factor in palliative chemotherapy for recurrent and/or persistent advanced cervical cancer, where life expectancy is likely to be brief. Pelvic exenteration is one of the most radical, but potentially curative, treatment strategies for advanced or recurrent cervical cancer. The procedure is an *en bloc* resection of the pelvic organs (i.e., uterus, cervix, vagina, ovaries, lower urinary tract, and/or rectosigmoid colon). This procedure requires a motivated patient, with a good support network to assist in the recovery period (50). Provision of information and presurgical preparation for potential changes to a woman's body (i.e., sexual function and ostomy care) are crucial for postoperative adjustment (50,51). Technological improvements in imaging have allowed for better selection of patients (no distant metastases) most likely to benefit from this extensive surgical procedure (52). The best candidates are those who are younger and have recurrent cervical cancer and pathologically negative surgical margins (52). This being said, the adjustment to life postexenteration is particularly challenging and requires intensive preoperative counseling.

Ovarian Cancer

Several phase 3 clinical trials have included longitudinal assessment of QoL as a secondary study endpoint. This information continues to influence a comprehensive interpretation of results, clinical trial design, and clinical decision making. For example, in a study of suboptimally debulked advanced ovarian cancer, although the addition of interval secondary cytoreduction to postoperative chemotherapy resulted in no notable long-term difference, a clinically significant QoL improvement was seen in both arms at 6 and 12 months after starting therapy. Fewer

complaints of neurotoxicity at 6 months were reported among patients who did versus did not undergo interval secondary cytoreduction, likely due to the break in chemotherapy (53). In this study, it was also shown for the first time in ovarian cancer that baseline QoL scores could predict survival, attributed primarily to the lowest scoring quartile on the FACT-O. This has been demonstrated in other trials as well. Carey et al. described the Canadian experience of QoL and performance status as they relate to progression-free survival and overall survival in a frontline chemotherapy trial for ovarian cancer (54). Both global QoL and PS were associated with progression-free survival and overall survival, thereby confirming the findings of Wenzel et al. in the United States in 2005. QoL has also predicted survival for patients participating in a phase 3 trial comparing gemcitabine with pegylated liposomal doxorubicin (55).

A controversial randomized phase 3 trial in optimal stage III epithelial ovarian cancer showed that intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel significantly lengthened PFS and OS compared to intravenous paclitaxel and cisplatin (56). During active treatment, patients on the intraperitoneal arm experienced more HRQoL disruption, abdominal discomfort, and neurotoxicity than those receiving conventional intravenous therapy. However, only neurotoxicity remained significantly greater for intraperitoneal patients 12 months post-treatment, and generally for both groups QoL improved over time (57). Given the continued controversy regarding intraperitoneal therapy, QoL information will continue to provide clinically meaningful information from which to guide treatment decisions. Studies are currently being conducted to mitigate the added burden associated with intraperitoneal therapy while hopefully maintaining survival benefit.

Several additional recent phase 3 trials have incorporated QoL endpoints into advanced ovarian cancer clinical trials (58–63). For example, du Bois et al. compared paclitaxel plus cisplatin (PT) with paclitaxel plus carboplatin (TC) in patients with advanced ovarian cancer, evaluating QoL utilizing the EORTC QLQ-C30 questionnaire (59). There were significant QoL differences in favor of the TC arm, therefore leading to the conclusion that paclitaxel plus carboplatin is a more reasonable and better-tolerated treatment overall. In a subsequent study, Greimel et al. (62) examined hematologic and nonhematologic toxicity of the TC versus PT regimens and the effects of toxicity on QoL. Again, QoL was better in the TC regimen, resulting in confirmation that where 2 regimens have equal progression-free and overall survival, paclitaxel/carboplatin is preferable. A similar recommendation can be made from QoL data where it was demonstrated that gemcitabine plus carboplatin significantly improved PFS and response rate without worsening QoL (58). The relationship between cancer treatment efficacy, benefit, and QoL for elderly patients is also being studied. In one phase 3 trial comparing cisplatin and paclitaxel to carboplatin and paclitaxel, although QoL scores did not differ between elderly and younger patients, the elderly patients showed a higher rate of early treatment discontinuation. The authors speculated that this may be due to provider and/or patient unwillingness to continue treatment in the setting of toxicities, which might otherwise be managed differently in a younger population (64).

Finally, in 2010, Vergote et al. reported the results of a Gynecologic Cancer Intergroup Collaboration trial, which compared upfront debulking followed by chemotherapy to neoadjuvant chemotherapy (65). As the standard approach to treatment has historically been surgical cytoreduction followed by chemotherapy, this was the first randomized phase III trial of this alternative strategy. In this trial, patients completed QoL assessments using EORTC-validated instruments. The authors reported similar survival outcomes in the 2 groups, with both perioperative and postoperative morbidity being higher in the upfront surgery group. However, the QLQ-C30 global health scores were

not significantly different between the 2 groups. The HRQoL measurement in this study did not seem to correlate with the “toxicity” (morbidity/mortality) demonstrated with upfront as compared to interval surgery. Future publications will hopefully elaborate on the QoL data to help explain this finding.

In the approach to recurrent ovarian cancer, tumor control without compromising HRQoL should be the goal of therapy (62). There have not been any phase III trials reported by the GOG that involve QoL assessments for recurrent ovarian cancer. There are, however, multiple international trials. The Gynecologic Cancer Intergroup used HRQoL measurements in their large trial of carboplatin and paclitaxel versus carboplatin and pegylated liposomal doxorubicin for recurrent platinum-sensitive ovarian cancer (CALYPSO) (66). QoL was measured every 3 months for 1 year from the date of enrollment. The doxorubicin arm was significantly less toxic. Patients treated with carboplatin and paclitaxel on this trial had longer-lasting and significant peripheral neuropathy, chemotherapy side effects in general, and worse body image. In addition, there were worse physical functioning and global QoL scores in these women at 3 months, although these were modest and did not persist at 6 months (67). This trial demonstrated the importance and utility of QoL data to challenge standard of care in large randomized phase III trials. Furthermore, in a German trial of nonplatinum doublets with topotecan versus topotecan alone, QoL measurements were also used (55). In this study, the doublet therapy neither provided survival advantage nor demonstrated differences in QoL scores. Combined therapy was associated in general with higher incidence of hematologic toxicity, yet this did not seem to be reflected in the QoL data. However, a detailed description of the data is lacking. In general, it appears that HRQoL data in the recurrent setting is deficient in terms of detailed descriptions of QoL disruptions and numbers of studies including QoL measurements.

Some may argue that QoL measurement in the recurrent setting is of particular importance being that therapy will often fail. This argument relates well to another sentinel paper published by Rustin et al. in 2010 (68). This study examined the impact of early versus delayed treatment of recurrent ovarian cancer based on CA-125 measurements exceeding twice the upper limit of normal. In patients in whom the CA-125 result was masked, treatment was initiated at clinical or symptomatic recurrence. The findings suggested that early treatment did not improve survival and, unfortunately, time to deterioration in QoL scores was shorter by several months in the early treatment group. This was seen across almost all QoL subscales. The QoL data here are noteworthy.

Unfortunately, effective screening programs and/or individual tests have yet to be clearly defined for ovarian cancer. Although QoL measurement in clinical trials evaluating therapeutic options for ovarian cancer is common, its use in the screening literature is limited. More commonly discussed is the impact of false-positive screening on QoL in cervical or breast cancer. Most QoL data in ovarian cancer screening lie in populations at high risk, such as those with genetic mutations undergoing risk-reducing salpingo-oophorectomy (RRSO). And, in the RRSO population, screening is more a process of early detection or diagnosis rather than a true screening test.

In general, the data are mixed regarding the negative impact of these screening tests on QoL (69). The U.S. National Cancer Institute’s Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was a large trial to determine whether annual screening tests could reduce disease-related mortality (69). For the ovarian cancer screening group, women underwent annual CA-125 blood tests and pelvic ultrasounds. QoL was also measured using the SF-12 Physical and Mental Component Scales at each assessment. A cancer-specific distress scale was also used to measure satisfaction with the decision to participate in the trial

as distress may indicate dissatisfaction and discomfort with the intervention of the trial. In this study, although not described as specific to ovarian cancer screening, participants with false-positive tests had higher levels of intrusive thoughts about cancer, yet this effect did not appear to be long-lasting. Women and participants with a first-degree relative with cancer were more likely to have these intrusive thoughts. The participants with false-negative tests were also less likely to comply with further testing. The authors concluded that in screening trials, it may be important to intervene on the part of the participants with false-negative results to decrease the potential stress involved in screening trials. Those assigned to the control group did not have statistically significant differences in HRQoL contrary to the belief that the mere ability to be involved in a cancer screening process alleviates stress associated with unknown risk for cancer.

There are several studies examining HRQoL in RRSO. In a cross-sectional study of 846 high-risk women, 44% had undergone RRSO instead of periodic gynecologic exams (70). Although “generic” QoL as measured by the SF-36 did not appear to differ between the groups, the RRSO group did report fewer concerns in general regarding their risk for cancer. Unfortunately, these women also had significantly more menopausal symptoms and worse sexual functioning relating to pleasure and discomfort than the women who underwent gynecologic exam alone. In 2009, Fang et al. described prospectively collected data on QoL, sexual functioning, body image, and depressive symptoms in 75 women undergoing either RRSO or serial screening (71). The women who underwent surgery reported poorer physical functioning, role limitations, pain, and social and sexual functioning at the 1-month assessment. Most deficits resolved by 6 months; however, the RRSO group had persistent menopausal complaints. Kahn et al. also published on the impact of ovarian cancer screening on QoL. In this study of 135 patients, abnormal ovarian cancer screening results was associated with a significant decrease in the Mental Component Summary form of the Short Form-36 (72). Finally, the GOG also published initial data regarding RRSO and CA-125 in women at risk for ovarian cancer (GOG 199) (73). The study included QoL measurement; however, the data have not been published. Future work should perhaps target the RRSO group in terms of pre-operative counseling, postoperative recovery, and treatment of menopausal symptoms.

Vulvar Cancer

Vulvar cancers are rarer than other gynecologic cancers and predominantly occur in older women (74). Radical vulvar excisions are associated with poorer QoL and lower sexual function (75). Surgical treatment of vulvar cancer requires inguinal lymph node dissection (unilateral or bilateral) to assess regional metastasis; and wound breakdown and other postoperative surgical complications can be high in these cases (76–78). The GOG conducted a small prospective trial to evaluate reduction of lymphedema with standard closure versus closure with a fibrin sealant (Tisseel®, Baxter Health Care, Deerfield, IL) sprayed into the inguinal lymphadenectomy wound during surgical treatment for vulvar cancer. In this study, 150 women newly diagnosed with vulvar cancer were enrolled and randomized to either the standard closure or the fibrin sealant closure arm of the study, with 137 evaluable cases. The incidence of lower extremity lymphedema (LLE) was not statistically significant between the 2 groups; however, LLE rates were found to be elevated (60%–67%) at 6 months’ postoperatively in both the intervention and control groups (79). This study challenged the validity of lymphedema rates cited in previous research using retrospective study designs (36%–51%

previously described in the literature) (80,81) and indicates that lymphedema rates may be greatly underestimated. Vulvar cancer set the groundwork for sentinel lymph node mapping, as lymphedema is a major issue among these patients. Nodal sampling seems to be a major contributory factor in lower extremity lymphedema (82).

CHALLENGES IN GYNECOLOGIC CANCER SURVIVORSHIP

Treatment side effects can influence short-term QoL for many women, and long-term QoL if sequelae persist or worsen over time. Recognition of and management for these issues can vary from simple strategies to improve QoL (i.e., managing nausea and vomiting) to complex psychosocial issues (e.g., reproductive concerns), for which clear guidelines may not exist. This section illustrates some of the current, potentially unique, and more complicated aspects of gynecologic cancer survivorship.

Pretreatment factors may influence a patient’s QoL both during and after treatment. Several authors have noted that QoL is affected by preoperative factors, such as education, lifestyle, general health, and obesity (83–85), all of which in turn may affect a patient’s ability to tolerate therapy. The interplay between cancer or cancer treatment symptoms and QoL is well documented in the gynecologic cancer literature (e.g., 86,87). Several prominent investigations deserve mention.

Cognitive issues—although there is a considerable and growing body of literature specific to cognitive impairment and fatigue during and after chemotherapy, only recently has this been considered within the gynecologic cancer cohort. For example, Hensley et al. were the first to study cognitive functioning prospectively in an ovarian cancer trial (88). Although they did not find significant decreases in cognitive functioning in women receiving paclitaxel, gemcitabine, and carboplatin in a phase II trial, they did note that highly educated women might suffer greater impairments, and thus, future trials should include cognitive functioning measures in their QoL assessments.

Fatigue—this occurs in 70% to 100% of patients with cancer, and is often underdiagnosed, inadequately treated, and hard to disentangle from other symptoms of physical compromise and psychological distress (89). Fatigue, during and subsequent to cancer treatment, is a related, prevalent, and understudied issue for gynecologic cancer patients. Treatable causes of fatigue include anemia, malnutrition, medications, infections, pain, depression, insomnia, muscle dysfunction, and anticancer therapy (90,91). In an important QoL investigation, in 2,370 anemic cancer patients undergoing chemotherapy, recombinant human erythropoietin significantly improved patient-reported functional capacity and QoL independent of tumor response (14). Many authorities also advocate either energy conservation or pushing apparent boundaries with graded exercise and cognitive-behavioral therapy (92). Psychostimulants, such as short- and long-acting methylphenidate, have been initially positive, but more rigorous studies have suggested that there is questionable benefit over placebo or daily telephone calls from a research nurse (93).

Neurotoxicity—an increasingly documented long-term problem that cause sensory loss, pain, loss of function, loss of mobility, and for some women, loss of professional and recreational activity. Platinum compounds, the mainstay of treatment for most gynecologic malignancies (94), are associated with cumulative myelosuppression (particularly thrombocytopenia), neurotoxicity, and nephrotoxicity, as well as severe nausea and vomiting (95,96). Neurotoxicity, anemia, and nausea/vomiting

all have well-known adverse effects on QoL. Paclitaxel in combination with a platinum compound is now considered the standard of care as first-line chemotherapy for advanced ovarian cancer (97,98). However, paclitaxel has a number of toxicities (e.g., granulocytopenia, neurotoxicity) that synergistically overlap those of the platins, and the coadministration of paclitaxel and a platinum compound can increase the frequency and/or severity of shared toxicities, especially neurotoxicity. Docetaxel is associated with significantly less neurotoxicity (99).

Administration of glutamine or the antidepressant venlafaxine may be helpful in cases of paclitaxel-induced neuropathy, and amifostine may provide protection from cisplatin-induced neuropathy (100,101). However, at present there appears to be no drug available to reliably prevent or treat chemotherapy-induced neuropathy (100,102). Therapeutic interventions for neurotoxicity remain controversial, with vitamins B₆ and E possibly reducing the efficacy of alkylator chemotherapy. Nonpharmacologic approaches to treatment of chemotherapy-induced neuropathy are based on patient education regarding potential neuropathic side effects, the impact of these side effects on performance of daily activities, and related safety issues (e.g., tripping in the dark, driving).

It is worth noting that a new, reliable, and valid patient-reported measure is now available to document symptoms of neurotoxicity. The FACT/GOG-NTX measure consists of 11 items assessing sensory, motor, and hearing symptoms as well as possible functional impact. It was administered to 263 advanced endometrial cancer patients prior to each of 7 cycles of chemotherapy. Results of this study indicated that the patient-reported sensory symptom scores (sum of 4 item scores) increased significantly over the treatment duration ($p < 0.001$) in the paclitaxel/doxorubicin/cisplatin (TAP) arm compared to the doxorubicin/cisplatin (AP) arm. It was also noted that as few as 4 sensory symptoms in the FACT/GOG-NTX subscale can be used to reliably and sensitively assess chemotherapy-induced neurologic symptoms in clinical oncology without compromising the psychometric properties of the overall scale (103).

Lymphedema—can be challenging for gynecologic cancer patients, with the highest rates occurring in women treated for vulvar cancer (104–106). It is a chronic, progressive condition (104). The specific incidence of lymphedema of the lower extremity (LLE) following treatment for gynecologic cancer, as well as risk factors for LLE development, are not well documented in the literature, in contrast to research on upper extremity lymphedema (105). Findings from a retrospective study demonstrated that women treated with radical hysterectomy for cervical cancer were at an eightfold increased risk of developing LLE (106). Lymphedema in patients undergoing lymphadenectomy for endometrial cancer has been reported in the 5% to 10% range (107,108), although prospective data are sparse. Nodal sampling has also been documented as a factor in the development of symptomatic lymphedema, with an increased risk after removal of 10 or more regional nodes during surgical staging (92).

The lack of incidence data, awareness of symptoms, and understanding of LLE has contributed to inadequate referrals and treatment delays (109). This can lead to women receiving treatment after lymphedema has progressed to a more chronic stage. Stages range from mild and reversible condition (stage 1) to chronic edema (stage 2), or a persistent condition with moderate to severe edema (stage 3) (104). A recent survey of lymphedema specialists found awareness of LLE and its symptoms among medical professionals and patients to be poor. LLE patients were less likely to be referred to or seen by a specialist within the first 3 months of experiencing symptoms in comparison to women with upper extremity lymphedema ($P < 0.01$) delays (109).

Studies examining the psychologic ramifications of lymphedema in other cohorts (i.e., breast cancer) note that signs and

symptoms may come as a shock if adequate information is not provided (110). Feelings of distress, anger, and helplessness emerge from limited and conflicting information (111,112). Many women are unaware of the risk factors, symptoms, and management of lymphedema (113). Furthermore, significant psychologic ramifications (i.e., anxiety, depression, and adjustment problems), as well as physical and sexual difficulties, have been described in the literature (114). Untreated cluster symptoms (i.e., heaviness, swelling, and numbness) of lymphedema may contribute to poorer QoL (115–117). Additional issues, including financial burdens (i.e., compression garments, medications, and bandages), limited clothing options, decreased activities due to restrictions from swollen legs, recurrent infection, and loss of work can also be problematic (118,119). Lymphedema can also be socially embarrassing or undermine confidence in appearance or body image (119). The chronicity of this condition also serves as a reminder of one's cancer history, possibly heightening fear of recurrence or advancing disease (120), and the required long-term management on a patient's QoL can be significant.

Mechanisms to identify these women (predictive risk factor model and symptom assessment) and educate the medical community (accurate incidence and risk factor data) are greatly needed to address this issue. A GOG trial will prospectively assess the prevalence of LLE following surgical staging and adjuvant therapy for gynecologic malignancy. This clinical trial will enhance our understanding not only of the risk factors for LLE, but also the implications of this chronic condition on the emotional well-being and overall QoL of cancer survivors, and will ultimately address this significant deficit in gynecologic oncology field.

Sexual dysfunction—various therapeutic procedures (i.e., surgery) for treatment of gynecologic malignancies can directly affect sexual functioning, depending on the anatomy involved (121), but treatment modalities have the potential to interfere with multiple aspects of sexuality, including body image, desire, frequency, satisfaction, vaginal dryness, dyspareunia, and a decrease in vaginal length. Dyspareunia, vaginal dryness, and loss of desire tend to be the most common sexual difficulties reported after cancer treatment (122–127).

For women surgically treated for gynecologic cancer, removal of the ovaries, uterus, cervix, vulva, and/or vagina may be necessary. These procedures can lead to damage to nerves and scarring or adhesions in the pelvic area as part of the healing process. When ovaries are removed, hormonal deprivation occurs, resulting in abrupt menopause and atrophy of the vagina for many women. Vaginal atrophy is associated with vaginal dryness, tightness, itching, burning, and pain during sexual activity or gynecologic examinations. Research on surgical treatment and sexual function demonstrates that hysterectomy for benign conditions does not appear to impair sexual function (128). Studies investigating sexual function after treatment for cervical cancer noted changes in lubrication, vaginal elasticity, pain, and arousal difficulties, much of which resolves by 1 year (129–131). However, vaginal dryness and decreased sexual satisfaction/interest have been shown to persist up to 2 years or more (130,131).

Many long-term survivors face the reality of surgical scarring and loss of body parts on a daily basis, resulting in abdominal and sexual sequelae (132–134). Individuals receiving treatment for advanced disease or bowel obstruction may require the placement of temporary or permanent ostomy(ies) for urine or stool. Management of these appliances requires practice and support from medical specialists and often other patients (135). Radiation therapy can also have long-term adverse effects on sexual functioning, including dyspareunia, vaginal stenosis, scarring, and fibrosis (136,137). These sexual consequences can have a negative impact on QoL and tend not to be uniformly discussed at follow-ups (138,139). This is particularly concerning since chronic fibrotic changes to the pelvis have been noted to worsen vaginal atrophy over time, in some cases up to 5 or more years post radiation therapy (140).

Sexual morbidity is associated with poor psychological adjustment and QoL in women treated for gynecologic cancer (141–143) both in the immediate post-treatment period (144–146) and in long-term survival (147,148). However, not all women are sexually active, with rates from 10%–50% in older ovarian cancer patients (116,138) compared to 77%–81% in younger patients (144–150). Many factors can influence sexuality, such as age, quality of relationship or health of partner (151,152). One study indicated that younger gynecologic cancer patients experienced greater difficulty with body image, resulting in impaired sexuality (153). Regardless of interest in future sexual activity, vaginal health concerns exist for all women and have the potential to interfere with comfort and compliance with gynecologic examinations if dryness is present. Research findings have noted that persistent, bothersome menopausal symptoms (i.e., vaginal dryness) place female cancer survivors at higher risk for distress and depression (125). Vasomotor symptoms can also be disruptive to QoL as well as sexuality by interfering with sleep and energy (154,155), and therefore require early assessment and management.

Simple strategies have been shown to be helpful in rehabilitating vaginal health and sexual function in cancer survivors by improving lubrication, moisture, and the pH of the vagina (156–158). Sexual/vaginal health promotion includes use of vaginal lubricants (usually water-based) and nonhormonal vaginal moisturizers. It is important to distinguish between vaginal moisturizers and vaginal lubricants, as patients and many health care providers are often confused about their respective uses and administration (124). Vaginal lubricants are used to aid in vaginal entry or penetration by decreasing dryness and friction, and thereby decreasing irritation and pain (124), whereas vaginal moisturizers (creams, gels, suppositories, or ovules) are not intended for sexual activity but to hydrate the vaginal tissues and improve pH (124,159). It is recommended that menopausal female cancer patients use a vaginal moisturizer at least 3 to 5 times per week to manage symptoms of vaginal atrophy, and to administer it prior to bedtime for optimal absorption. Lubricants should be used with all sexual activity (124).

For women with persistent vaginal dryness interfering with QoL, a low-dose vaginal estrogen may be considered, but many questions exist about hormone replacement in the setting of cancer. Low-dose vaginal estrogens may initially show a temporary increase in serum hormone levels, creating a complex and controversial issue for patients and medical professionals (160); however, these levels return to the normal postmenopausal range. This is not the case for systemic absorption of oral or transdermal administration of estrogen and testosterone (161,162). It is not unreasonable to discuss and consider hormonal supplemental options in select women within the gynecologic oncology setting that are suffering from unmanageable menopausal symptoms negatively impacting QoL (163,164). However, more safety data and long-term studies are greatly needed in cancer populations.

For treatment of dyspareunia, vaginal dilators can be beneficial in treating vaginal stenosis and adhesions (156,165). Dilator therapy has been recommended as the only modality meeting reasonable standards for evidence-based medicine in the treatment of pelvic radiation-induced sexual dysfunction (166). The theory behind vaginal dilator therapy is that it mechanically stretches the vaginal tissues, allowing for the secondary remodeling of fibrotic tissue, thus improving elasticity, but some have speculated that it may also cause improved blood flow through stimulation of the vaginal walls (158). The benefits of drawing blood flow to the pelvic floor were investigated in regards to the pelvic floor tone. Women with greater pelvic floor strength were found to have stronger arousal response (167). The belief is that the engorgement process needed for arousal is facilitated by increasing pelvic floor strength and drawing blood flow to the pelvic floor muscles (167,168). Pelvic floor exercises are also

recommended for awareness of how to maintain relaxation of these muscles during the dilator process or vaginal penetration, allowing for better control of these muscles, thereby decreasing pain associated with reflexively tightening (124). More research is warranted, but a combination of dilator therapy with pelvic floor exercises to get both potential benefits is a reasonable approach. One study evaluated the reliability of an instrument (the Vaginal Sound), which was designed to measure vaginal length. The Vaginal Sound is a simple, inexpensive, reproducible instrument that has demonstrated acceptable reliability and appears to be able to detect hypothesized changes in vaginal length (169). This instrument can be used to document the degree of vaginal stenosis associated with radical hysterectomy and radiation therapy plus or minus chemotherapy in women treated for cervical carcinoma. The ability to measure vaginal length and correlate vaginal stenosis with sexual function will provide a rationale for much needed interventional studies to maintain vaginal length and sexual function.

Embarrassment and fear have been shown to decrease compliance with dilator therapy, but in most cases, education and support can enhance compliance. Unfortunately, for many hospitals and office settings, it is not feasible or practical to have a sexual health program or professional on staff. Therefore, it is important to identify a referral network of local professionals with experience in treating sexual difficulties, which may include mental health professionals as well as gynecologists with expertise in treating patients with changes in sexual function (i.e., menopause) related to medical illness. Educational resources are also available to help patients achieve greater comfort with these issues.

It is important to note that limitations currently exist within the oncology field specific to accurate assessment and measurement of sexual/vaginal health issues in female cancer patients. Sexual dysfunction and symptoms in cancer survivors may differ from those experienced by women in the general population. Evidence-based research using validated empirical measures of sexual function is greatly needed in cancer populations. Many measures have been developed to measure sexual function (170), but the most frequently used measure in cancer cohorts has been the Female Sexual Function Index (FSFI). The Patient-Reported Outcomes Measurement Information System-Sexual Function (PROMIS-SF) has gained the attention of researchers. The FSFI has strong psychometric qualities but was only recently validated in a cancer cohort (171). However, scoring issues must be addressed to avoid reporting artificially low FSFI scores and estimates of female sexual dysfunction prevalence in those not sexually active (172). Short versions of the FSFI have also been developed in the general population (FSFI-6 SF) (173) and tested in the oncology setting (FSFI CA-6) (174) to facilitate screening for sexual dysfunction in busy clinical practices. The FSFI CA-6 results are very promising, with internal consistency reliability of 0.86 and Pearson correlation of 0.97 with the full FSFI (174).

The PROMIS-SF tool continues the work of the PROMIS network by providing a flexible and psychometrically robust measure of sexual function within oncology. Development procedures for the PROMIS-SF have included review of the sexual function measure literature, focus group methodology, and development of a conceptual model (175,176), with large-scale item testing, psychometric evaluation, validation, and translation underway (176). PROMIS-SF has been designed to be a brief assessment tool to reduce patient burden and allow for assessment of this important domain within future clinical trials.

Reproductive concerns—female cancer survivors coping with reproductive concerns have been shown to have poorer QoL (39). Gynecologic cancer can present before childbearing has been started or completed, during pregnancy, or can even arise out of pregnancy (gestational trophoblastic disease). Reproductive concerns can vary by site of disease, and some women

may have the option of conservative surgical management. For example, radical surgery was previously recommended for early-stage operable cervical cancer patients up to stage IIA. More recently, however, cone biopsy alone has become a therapeutic option for young patients with stage IA1 cervical cancer who wish to preserve fertility (177,178), and radical trachelectomy, initially received with skepticism because of the small but definite increase in risk of recurrence, is gradually gaining recognition and acceptance, performed both vaginally and abdominally (179,180). Some have also questioned whether the standard of care pelvic lymphadenectomy should be changed to sentinel lymph node biopsy (181).

However, many women will be medically unable to have fertility-preserving treatment, leaving the emotional ramifications of infertility to be dealt with as a cancer survivorship issue (182). Gynecologic cancer survivors have reported feelings of sadness and grief lasting more than 1 year posttreatment (125), with some feeling deprived of choices or misunderstood (183) in the setting of cancer-related infertility. Others have voiced feelings of stigma or being “less than a woman” due to loss of reproductive organs (184). A woman’s reaction will be contingent on her personal desire for a biologic child, the degree of fertility impairment, and the willingness to use reproductive assistance or family-building options. One study of women treated for malignant ovarian germ cell tumors found that reproductive and sexual functioning was encouraging, although emphasizing the importance of a stable relationship at the time of diagnosis (185).

One study investigating the emotional impact of fertility-preserving surgical treatment for early-stage cervical cancer (radical trachelectomy) found that reproductive concerns and anxiety persisted postoperatively over time for these women (144,186). Guidelines published by the American Society of Clinical Oncology highlighted the lack of research on the reproductive concerns of cancer survivors as well as the need for more information (187). In a cohort study of gynecologic cancer and BMT survivors, a large proportion (73%) indicated it would be helpful to speak with a reproductive specialist, but only one-third of the sample had done so (188). Gynecologic cancer survivors expressed a greater need for information about where to go or with whom to speak about these issues, which may have been connected with their perception of not having fertility options, despite the availability of reproductive alternatives (i.e., third-party reproductive options). Very little is known about whether patients are utilizing reproductive assistance or have knowledge about available resources or the emotional ramifications of seeking fertility/family building in cancer survivorship, but unmet informational needs about reproductive options have been associated with negative mood and increased distress (188).

Psychologic well-being—patients with gynecologic malignancies face an array of emotional challenges, many of which persist 5 to 10 years after diagnosis. Psychologic sequelae can include distress, depression, anxiety, fear, and social disruption. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fear to problems that can become disabling, such as depression, anxiety, panic, social isolation, and spiritual crisis. Recently the National Comprehensive Cancer Network (NCCN) advocated recording distress as the sixth vital sign using a simple thermometer (10 cm) VAS (189), given that 20% to 40% of patients have significant distress, and only 10% of them are identified and referred for psychosocial evaluation (190). Depression is the least recognized and least effectively treated psychologic problem in patients with cancer (191). In the context of life-threatening illness, diagnostic criteria for depression typically include a significant change in mood on most days for more than 2 weeks. Clinically significant levels of distress and depression, greater than what would be expected in the general population, have been documented in

gynecologic cancer patients. Specifically, higher levels of distress have been identified in the newly diagnosed, in those undergoing intracavitary brachytherapy (192), in patients with advanced or recurrent disease (6,193), and younger patients (193), perhaps due to the loss and adjustment many experience with sexuality, fertility, and premature menopause.

Psychologic shifts have also been observed in women following completion of cancer treatment. In a prospective study with ovarian cancer patients, depression levels were found to decrease 3 months after completion of chemotherapy; however, levels of anxiety were shown to increase (194), perhaps reflective of the uncertainty that many women face about possible recurrence and concerns of future prognosis. However, studies with long-term survivors (5 to 10 years) have shown that disease-free, early-stage survivors have resilience and adjustment over time, with an overall good QoL. Despite the identification of many psychologic difficulties within the gynecologic cancer experience, the literature reveals that many women are not using psychologic services (136), despite a need for cancer-specific support (195). It has been noted that patients may not be aware of or have access to supportive resources, but would utilize them if offered.

Psychologic care considerations—outcomes are improved by an integrative approach, only possible through a proactive collaboration with surgical, radiation, medical, and nurse oncologists working together with psychosocial support. Psychosocial support should include services such as emotional, spiritual, nutritional, genetic, and financial counseling, and general cancer information and support, as needed. At the core of a compassionate response there has to be both acknowledging and responding to physical, psychologic, and spiritual issues. An empathic response occurs when the clinician explicitly makes the connection between the clinical situation and how the patient is feeling. A compassionate response requires action, mobilizing the whole medical team to challenge fear and isolation (196). The medical interaction should be therapeutic on every level. Building a relationship takes more than asking questions. Courteous introductions and a genuine effort to establish rapport pay huge dividends. Consultations should have clear, explicit objectives. Avoid assumptions and be flexible, using focused but open-ended questions, frequently summarizing and screening for concerns. Find out how the illness affects the person. Information should be simple and clear and tailored to the patient’s understanding, with the goal of reinforcing realistic hopefulness and supporting shared decision making.

The very process of exploring a patient’s emotional symptoms can be therapeutic, but many patients may benefit from professional counseling, support groups, and/or medication. Meta-analyses indicate that preventive psychologic interventions in cancer patients may have a moderate clinical effect on anxiety but less on depression, and that group therapy is perhaps at least as effective as individual psychotherapy (197). Treatment of anxiety can include antidepressant and antianxiety medication (e.g., buspirone, clonazepam), counseling, and behavioral therapies (198). A wide variety of antidepressant medications with different mechanisms of action and adverse effects are available. Selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, sertraline, and citalopram) are usually well tolerated and can improve depression within 2 to 4 weeks in 60% of patients. The tricyclics (amitriptyline and nortriptyline) have a slightly longer onset of action but can be useful for patients with significant sleep disturbances. “Atypical antidepressants” (bupropion, venlafaxine, and mirtazapine) have a relatively rapid onset of action and paucity of adverse effects. Stimulants (methylphenidate and pemoline) provide the most rapid onset (hours to days). With respect to novel counseling methodologies, a recent psychosocial telephone counseling intervention was shown to improve QoL for cervical cancer survivors compared to controls (199). This type of intervention has promise for people unlikely

to access traditional services. However, counseling information and resources should be routinely provided to all patients.

CONCLUSION

QoL research activity in gynecologic cancer has increased substantially over the past decade. This has included key findings developed within and disseminated through national and international cooperative groups. These contributions have become more robust and influential as the study and science of QoL and other PROs have advanced. Consequently, future directions in gynecologic cancer QoL research are likely to include a continued focus on measurement science and trial interpretation to aid in treatment decision making, as well as provision of interventions to enhance QoL. For example, in endometrial cancer, we may see areas of active investigation that include the role of obesity as a comorbid factor in the development of this cancer, as well as the role of obesity on potential response

to treatment and survival. Cervical cancer investigations may emphasize identifying behavioral or social factors that influence uptake of the human papillomavirus (HPV) vaccine. With respect to this disease, additional QoL studies specific to outcomes and morbidity from multimodality therapy are anticipated. Areas of active investigation in ovarian cancer will continue to focus on evolving paradigms of care such as intraperitoneal therapy, treatment for an asymptomatic rising CA-125, and continual or intermittent therapy for recurrent disease versus therapy only for symptomatic progression. The QoL implications in each of these treatment considerations are paramount and should be systematically studied within well-designed trials. Further investigation is also needed in palliative care strategies for women with gynecologic cancer. This may include careful examination of the role of chemotherapy in the elderly, as well as interventions to reduce significant issues associated with advanced or advancing disease (e.g., bowel obstructions, neurotoxicities). In each case, evaluation of QoL and other PROs will serve a significant role in advancing gynecologic cancer care and survivorship.

REFERENCES

1. Cella D. What do global quality-of-life questions really measure? Insights from Hobday, et al. and the “do something” rule. *J Clin Oncol*. 2003;21(16): 3178–3179; author reply 3179.
2. WHO. Study protocol for the World Health Organization project to develop a quality of life assessment instrument (WHOQOL). *Qual Life Res*. 1993;2(2):153–159.
3. Cella DE. Measuring quality of life in palliative care. *Semin Oncol*. 1995;22(2 suppl. 3):73–81.
4. Bottomley A. The cancer patient and quality of life. *Oncologist*. 2002;7(2):120–125.
5. Velikova G, Stark D, Selby P. Quality of life instruments in oncology. *Eur J Cancer*. 1999;35(11):1571–1580.
6. Ferrell B, Smith SL, Cullinan CA, et al. Psychological well being and quality of life in ovarian cancer survivors. *Cancer*. 2003;98(5):1061–1071.
7. Gralla RJ. Silk purse in Atlanta: a commentary on SWOG 9509, an advanced non-small cell lung cancer trial. *Oncologist*. 1999;4(3):188–190.
8. Kornblith AB, Thaler HT, Wong G, et al. Quality of life of women with ovarian cancer. *Gynecol Oncol*. 1995;59(2):231–242.
9. Karnofsky D, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. *Evaluation of Chemotherapeutic Agents*. New York, NY: Columbia University Press; 1949:199–205.
10. Slevin ML, Plant H, Lynch D, et al. Who should measure quality of life, the doctor or the patient? *Br J Cancer*. 1988;57(1):109–112.
11. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403–2413.
12. Gelber RD, Goldhirsch A, Cavalli F. Quality-of-life-adjusted evaluation of adjuvant therapies for operable breast cancer. The International Breast Cancer Study Group. *Ann Intern Med*. 1991;114(8):621–628.
13. Kaye SB, Vasey PA. Docetaxel in ovarian cancer: Phase III perspectives and future development. *Semin Oncol*. 2002;29(3 suppl. 12):22–27.
14. Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. *J Clin Oncol*. 1998;16(10):3412–3425.
15. Groenvold M. Methodological issues in the assessment of health-related quality of life in palliative care trials. *Acta Anaesthesiol Scand*. 1999;43(9):948–953.
16. Cohen SR, Mount BM. Living with cancer: “good” days and “bad” days—what produces them? Can the McGill quality of life questionnaire distinguish between them? *Cancer*. 2000;89(8):1854–1865.
17. Coates A, Gebiski V, Signorini D, et al. Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. Australian New Zealand Breast Cancer Trials Group. *J Clin Oncol*. 1992;10(12):1833–1838.
18. Spiegel D. Mind matters—group therapy and survival in breast cancer. *N Engl J Med*. 2001;345(24):1767–1768.
19. Ruo B, Rumsfeld JS, Hlatky MA, et al. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA*. 2003;290(2):215–221.
20. McQuellon RP, Thaler HT, Cella D, et al. Quality of life (QOL) outcomes from a randomized trial of cisplatin versus cisplatin plus paclitaxel in advanced cervical cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2006;101(2):296–304.
21. Wenzel L, Monk B, Huang H, et al. Clinically meaningful quality-of-life changes in ovarian cancer: results from Gynecologic Oncology Group clinical trial 152. In: *Quality of Life III: Translating the Science of Quality-of-Life Assessment into Clinical Practice—An Example-Driven Approach for Practicing Clinicians and Clinical Researchers*. Scottsdale, AZ: Clinical Therapeutics: The International Peer-Reviewed Journal of Drug Therapy; 2003.
22. Hamidou Z, Dabakuyo TS, Bonnetain F. Impact of response shift on longitudinal quality-of-life assessment in cancer clinical trials. *Expert Rev Pharmacoeconomics Outcomes Res*. 2011;11(5):549–559.
23. Carr D, Goudas L, Lawrence D, et al. Management of cancer symptoms: pain, depression and fatigue: evidence report/technology assessment No. 61. AHRQ publication No. 02-E032. Rockville, MD: Agency for Healthcare Research and Quality; 2002.
24. Garcia S, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. *J Clin Oncol*. 2007;25(32): 5106–5112.
25. Cella DE, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570–579.
26. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5): 365–376.
27. Schulz MW, Chen J, Woo HH, et al. A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol*. 2002;168(1):155–159.
28. Levine MN, Ganz PA. Beyond the development of quality-of-life instruments: where do we go from here? *J Clin Oncol*. 2002;20(9): 2215–2216.
29. Browman GP. Science, language, intuition, and the many meanings of quality of life. *J Clin Oncol*. 1999;17(6):1651–1653.
30. Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet*. 2003;361(9375):2099–2106.
31. Efficace F, Bottomley A, Osoba D, et al. Beyond the development of health-related quality-of-life (HRQOL) measures: a checklist for evaluating HRQOL outcomes in cancer clinical trials—does HRQOL evaluation in prostate cancer research inform clinical decision making? *J Clin Oncol*. 2003;21(18):3502–3511.
32. Curran D, Molenberghs G, Aaronson NK, et al. Analysing longitudinal continuous quality of life data with dropout. *Stat Methods Med Res*. 2002;11(1):5–23.
33. Dalrymple JL, Levenback C, Wolf JK, et al. Trends among gynecologic oncology inpatient deaths: is end-of-life care improving? *Gynecol Oncol*. 2002;85(2):356–361.

34. Bruner DW, Barsevick A, Tian C, et al. Randomized trial results of quality of life comparing whole abdominal irradiation and combination chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Qual Life Res*. 2007;16(1):89–100.
35. Zullo F, Palomba S, Russo T, et al. A prospective randomized comparison between laparoscopic and laparotomic approaches in women with early stage endometrial cancer: a focus on the quality of life. *Am J Obstet Gynecol*. 2005;193(4):1344–1352.
36. Kornblith AW, J Huang H, Cella D. Quality of life of patients in a randomized clinical trial of laparoscopy (scope) vs. open laparotomy (open) for the surgical resection and staging of uterine cancer: a Gynecologic Oncology Group study GOG-2222. Chicago, IL: Society of Gynecologic Oncologists; 2006.
37. Alektiar KM, Venkatraman E, Chi DS, et al. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. *Int J Radiat Oncol Biol Phys*. 2005;62:111–117.
38. Nout RA, Putter H, Jürgenliemk-Schulz IM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. *J Clin Oncol*. 2009;27:3547–3556.
39. Nout RA, van de Poll-Franse IV, Lybeert ML, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the postoperative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. *J Clin Oncol*. 2011;29(13):1692–1700.
40. Peteret DG, Tannehill SP, Grosen EA, et al. Outpatient vaginal cuff brachytherapy for endometrial cancer. *Int J Gynecol Cancer*. 1999;9:456–462.
41. Anderson JM, Stea B, Hallum AV, et al. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. *Int J Radiat Oncol Biol Phys*. 2000;46:417–425.
42. MacLeod C, Fowler A, Duval P, et al. High-dose-rate brachytherapy alone post-hysterectomy for endometrial cancer. *Int J Radiat Oncol Biol Phys*. 1998;42:1033–1039.
43. Kumar VJ, Nin CY, Kuei LY, et al. Survival and disease relapse in surgical stage I endometrioid adenocarcinoma of the uterus after adjuvant vaginal vault brachytherapy. *Int J Gynecol Cancer*. 2010;20:564–569.
44. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomized trial. *Lancet*. 2010;375:816–823.
45. Fader AN, Frasure HE, Gil KM, et al. Quality of life in endometrial cancer survivors: what does obesity have to do with it? *Obstet Gynecol Int*. 2011;2011:308609.
46. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol*. 2004;22(15):3113–3119.
47. Long HJ 3rd, Monk BJ, Huang HQ, et al. Clinical results and quality of life analysis for the MVAC combination (methotrexate, vinblastine, doxorubicin, and cisplatin) in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2006;100(3):537–543.
48. Monk BJ, Huang HQ, Cella D, et al. Gynecologic Oncology Group. Quality of life outcomes from a randomized phase III trial of cisplatin with or without topotecan in advanced carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol*. 2005;23(21):4617–4625.
49. Chase DM, Huang HQ, Wenzel L, et al. Quality of life and survival in advanced cervical cancer: A Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;125(2):315–319.
50. Carter J, Chi DS, Abu-Rustum N, et al. Brief report: total pelvic exenteration—a retrospective clinical needs assessment. *Psycho-Oncol*. 2004;13(2):125–131.
51. Maggioni A, Roviglione G, Landoni F, et al. Pelvic exenteration: ten-year experience at the European Institute of Oncology in Milan. *Gynecol Oncol*. 2009;114(1):64–68.
52. Benn T, Brooks RA, Zhang Q, et al. Pelvic exenteration in gynecologic oncology: a single institution study over 20 years. *Gynecol Oncol*. 2011;122(1):14–18.
53. Wenzel L, Huang HQ, Monk BJ, et al. Quality-of-life comparisons in a randomized trial of interval secondary cytoreduction in advanced ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2005;23(24):5605–5612.
54. Carey MS, Bacon M, Tu D, et al. The prognostic effects of performance status and quality of life scores on progression-free survival and overall survival in advanced ovarian cancer. *Gynecol Oncol*. 2008;108(1):100–105.
55. Schouli J, Stengel D, Oskay-Oezcelik G, et al. Nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer: results of a phase III study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol*. 2008;26(19):3176–3182.
56. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354(1):34–43.
57. Wenzel LB, Huang HQ, Armstrong DK, et al. Gynecologic Oncology Group. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25(4):437–443.
58. Pfisterer J, Vergote I, Du Bois A, et al. Combination therapy with gem-citabine and carboplatin in recurrent ovarian cancer. *Int J Gynecol Cancer*. 2005;15(suppl. 1):36–41.
59. Pfisterer J, Weber B, Reuss A, et al. Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a Gynecologic Cancer Intergroup trial of the AGO-OVAR and GINECO. *J Natl Cancer Inst*. 2006;98(15):1036–1045.
60. du Bois A, Lück HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst*. 2003;95(17):1320–1329.
61. du Bois A, Weber B, Rochon J, et al. Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized Gynecologic Cancer Intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. *J Clin Oncol*. 2006;24(7):1127–1135.
62. Greimel ER, Bjelic-Radisic V, Pfisterer J, et al. Randomized study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group comparing quality of life in patients with ovarian cancer treated with cisplatin/paclitaxel versus carboplatin/paclitaxel. *J Clin Oncol*. 2006;24(4):579–586.
63. ten Bokkel Huinink W, Lane SR, Ross GA. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. *Ann Oncol*. 2004;15(1):100–103.
64. Hilpert F, du Bois A, Greimel ER, et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged >or = 70 years with advanced ovarian cancer—a study by the AGO OVAR Germany. *Ann Oncol*. 2007;18(2):282–287.
65. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med*. 2010;363(10):943–9.
66. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol*. 2010;28(20):3323–3329.
67. Brundage M, Gropp M, Mefti F, et al. Health-related quality of life in recurrent platinum-sensitive ovarian cancer—results from the CALYPSO trial. *Ann Oncol*. 2012 (ahead of print).
68. Rustin G, van der Burg M, Griffin C, et al. Early versus delayed treatment of relapsed ovarian cancer. *Lancet*. 2011;377(9763):380–381.
69. Taylor KL, Shelby R, Gelmann E, et al. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Natl Cancer Inst*. 2004;96(14):1083–1094.
70. Madalinska JB, Hollenstein J, Bleiker E, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. *J Clin Oncol*. 2005;23(28):6890–6898.
71. Fang CY, Cherry C, Devarajan K, et al. A prospective study of quality of life among women undergoing risk-reducing salpingo-oophorectomy versus gynecologic screening for ovarian cancer. *Gynecol Oncol*. 2009;112(3):594–600.
72. Kauff ND, Hurley KE, Hensley ML, et al. Ovarian carcinoma screening in women at intermediate risk: impact on quality of life and need for invasive follow-up. *Cancer*. 2005;104(2):314–320.
73. Greene MH, Piedmonte M, Alberts D, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev*. 2008;17(3):594–604.
74. Jemal A, Siegel R, Xu J, et al. Cancer statistics. *CA Cancer J Clin*. 2010;60:277–300.
75. Likes WM, Stegbauer C, Tillmanns T, et al. Correlates of sexual function following vulvar excision. *Gynecol Oncol*. 2007;105:600–603.
76. Burke TW, Stringer CA, Gershenson DM, et al. Radical wide excision and selective inguinal node dissection for squamous cell carcinoma of the vulva. *Gynecol Oncol*. 1990;38:328–332.
77. Berman ML, Soper JT, Creasman WT, et al. conservative surgical management of superficially invasive stage I vulvar carcinoma. *Gynecol Oncol*. 1989;35:352–357.
78. Hacker NF, Leuchter RS, Berek JS, et al. Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions. *Obstet Gynecol*. 1981;58:574–579.
79. Carlson JW, Kauderer J, Walker JL, et al. A randomized phase III trial of VH fibrin sealant to reduce lymphedema after inguinal lymph node dissection: A Gynecologic Oncology Group study. *Gynecol Oncol*. 2008;110(1):76–82.

80. Ryan M, Stainton C, Jaconelli C, et al. The experience of lower limb lymphedema for women after treatment for gynecologic cancer. *Oncol Nurs Forum*. 2003;30:417–423.
81. Judson PL, Jonson AL, Paley PJ, et al. A prospective, randomized study analyzing sartorius transposition following inguinal-femoral lymphadenectomy. *Gynecol Oncol*. 2004;95(1):226–230.
82. Abu-Rustum NR, Alektiar K, Iasonos A, et al. The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. *Gynecol Oncol*. 2006;103:714–718.
83. Gil KM, Gibbons HE, Jenison EL, et al. Baseline characteristics influencing quality of life in women undergoing gynecologic oncology surgery. *Health Qual Life Outcomes*. 2007;5:25.
84. Courneya KS, Karvinen KH, Campbell KL, et al. Associations among exercise, body weight, and quality of life in a population-based sample of endometrial cancer survivors. *Gynecol Oncol*. 2005;97(2):422–430.
85. von Gruenigen VE, Gil KM, Frasure HE, et al. The impact of obesity and age on quality of life in gynecologic surgery. *Am J Obstet Gynecol*. 2005;193(4):1369–1375.
86. Le T, Hopkins L, Kee Fung MF. Quality of life assessment during adjuvant and salvage chemotherapy for advanced stage epithelial ovarian cancer. *Gynecol Oncol*. 2005;98(1):39–44.
87. Vaz AF, Pinto-Neto AM, Conde DM, et al. Quality of life of women with gynecologic cancer: associated factors. *Arch Gynecol Obstet*. 2007;276(6):583–589.
88. Hensley ML, Correa DD, Thaler H, et al. Phase I/II study of weekly paclitaxel plus carboplatin and gemcitabine as first-line treatment of advanced-stage ovarian cancer: pathologic complete response and longitudinal assessment of impact on cognitive functioning. *Gynecol Oncol*. 2006;102(2):270–277.
89. Servaes P, Prins J, Verhagen S, et al. Fatigue after breast cancer and in chronic fatigue syndrome: similarities and differences. *J Psychosom Res*. 2002;52(6):453–459.
90. Cella D, Davis K, Breitbart W, et al. Fatigue Coalition. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol*. 2001;19(14):3385–3391.
91. Wilkinson PM, Antonopoulos M, Lahousen M, et al. EPO-INT-45 Study Group. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. *Br J Cancer*. 2006;94(7):947–954.
92. Gielissen MF, Verhagen S, Witjes F, et al. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*. 2006;24(30):4882–4887.
93. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol*. 2006;24(13):2073–2078.
94. Pignata S, De Placido S, Biamonte R, et al. Residual neurotoxicity in ovarian cancer patients in clinical remission after first-line chemotherapy with carboplatin and paclitaxel: the Multicenter Italian Trial in Ovarian Cancer (MITO-4) retrospective study. *BMC Cancer*. 2006;6:5.
95. Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. *Oncologist*. 2002;7(suppl. 5):20–28.
96. Dunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. *Oncologist*. 2002;7(suppl. 5):11–19.
97. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med*. 1996;334(1):1–6.
98. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21(17):3194–3200.
99. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004;96(22):1682–1691.
100. Hilpert F, Stähle A, Tomé O, et al. Neuroprotection with amifostine in the first-line treatment of advanced ovarian cancer with carboplatin/paclitaxel-based chemotherapy—a double-blind, placebo-controlled, randomized phase II study from the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group. *Support Care Cancer*. 2005;13(10):797–805.
101. Lorusso D, Ferrandina G, Greggi S, et al. Phase III multicenter randomized trial of amifostine as cytoprotectant in first-line chemotherapy in ovarian cancer patients. *Ann Oncol*. 2003;14(7):1086–1093.
102. Annas GJ. Informed consent, cancer, and truth in prognosis. *N Engl J Med*. 1994;330(3):223–225.
103. Huang HQ, Brady MF, Cella D, et al. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a Gynecologic Oncology Group study. *Int J Gynecol Cancer*. 2007;17(2):387–393.
104. Badger C, Preston N, Seers K, et al. Physical therapies for reducing and controlling lymphoedema of the limbs. *Cochrane Database Syst Rev*. 2004;(4):CD003141.
105. Petrek JA, Senie RT, Peters M, et al. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer*. 2001;92(6):1368–1377.
106. Bergmark K, Avall-Lundquist E, Dickman PW, et al. Lymphedema and bladder-emptying difficulties after radical hysterectomy for early stage cervical cancer and among population controls. *Int J Gyn Cancer*. 2006;16:1130–1139.
107. Nunns D, Williamson K, Swaney L, et al. The morbidity of surgery and adjuvant radiotherapy in the management of endometrial carcinoma. *Int J Gynecol Cancer*. 2000;10:233–238.
108. Fujiwara K, Kigawa J, Hasegawa K, et al. Effect of simple omentoplasty and omentopexy in the prevention of complications after pelvic lymphadenectomy. *Int J Gynecol Cancer*. 2003;13:61–66.
109. Langbecker D, Hayes SC, Newman B, et al. Treatment for upper limb and lower limb lymphedema by professionals specializing in lymphedema care. *Eur J Cancer Care*. 2008;17:557–564.
110. Woods M. Patients' perceptions of breast-cancer-related lymphoedema. *Eur J Cancer Care (Engl)*. 1993;2(3):125–128.
111. Carter BJ. Women's experiences of lymphedema. *Oncol Nurs Forum*. 1997;24(5):875–882.
112. Hare M. The lived experience of breast cancer-related lymphoedema. *Cancer Nurse Practice*. 2001:12–19.
113. Radina ME, Armer JM, Culbertson SD, et al. Post-breast cancer lymphedema: understanding women's knowledge of their condition. *Oncol Nurs Forum*. 2004;31(1):97–104.
114. Passik SD, McDonald MV. Psychosocial aspects of upper extremity lymphedema in women treated for breast carcinoma. *Cancer*. 1998;83(12 Suppl American):2817–2820.
115. Armer JM, Radina ME, Porock D, et al. Predicting breast cancer-related lymphedema using self-reported symptoms. *Nurs Res*. 2003;52(6):370–379.
116. Armer JM. The problem of post-breast cancer lymphedema: impact and measurement issues. *Cancer Invest*. 2005;23(1):76–83.
117. Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. *Support Care Cancer*. 2005;13(11):904–911.
118. Pereira de Godoy JM, Braile DM, de Fátima Godoy M, et al. Quality of life and peripheral lymphedema. *Lymphology*. 2002;35(2):72–75.
119. Janda M, Obermair A, Cella D, et al. Vulvar cancer patients' quality of life: a qualitative assessment. *Int J Gynecol Cancer*. 2004;14(5):875–881.
120. Frid M, Strang P, Friedrichsen MJ, et al. Lower limb lymphedema: experiences and perceptions of cancer patients in the late palliative stages. *J Palliat Care*. 2006;22:5–11.
121. Wilmoth MC, Spinelli A. Sexual implications of gynecologic cancer treatments. *J Obstet Gynecol Neonatal Nurs*. 2000;29(4):413–421.
122. Schover LR. Sexuality and fertility after cancer. *Hematol Am Soc Hematol Educ Program*. 2005;523–527.
123. Andersen BL, Woods XA, Copeland LJ. Sexual self-schema and sexual morbidity among gynecologic cancer survivors. *J Consult Clin Psychol*. 1997;65(2):221–229.
124. Carter J, Goldfrank D, Schover LR. Simple strategies for vaginal health promotion in cancer survivors. *J Sex Med*. 2011;8:549–559.
125. Carter J, Chi DS, Brown CL, et al. Cancer-related infertility in survivorship. *Int J Gynecol Cancer*. 2010;20(1):2–8.
126. Schover LR. Premature ovarian failure and its consequences: vasomotor symptoms, sexuality, and fertility. *J Clin Oncol*. 2008;26(5):753–758.
127. Matulonis UA, Kornblith A, Lee H, et al. Long-term adjustment of early-stage ovarian cancer survivors. *Int J Gynecol Cancer*. 2008;18(6):1183–1193.
128. Thakar R, Ayers S, Georgakapolou A, et al. Hysterectomy improves quality of life and decreases psychiatric symptoms: a prospective and randomised comparison of total versus subtotal hysterectomy. *BJOG*. 2004;111(10):1115–1120.
129. Grumann M, Robertson R, Hacker NF, et al. Sexual functioning in patients following radical hysterectomy for stage IB cancer of the cervix. *Int J Gynecol Cancer*. 2001;11(5):372–380.
130. Jensen PT, Groenvold M, Klee MC, et al. Early-stage cervical carcinoma, radical hysterectomy, and sexual function. A longitudinal study. *Cancer*. 2004;100(1):97–106.
131. Pieterse QD, Maas CP, ter Kuile MM, et al. An observational longitudinal study to evaluate micturition, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. *Int J Gynecol Cancer*. 2006;16(3):1119–1129.
132. Bodurka-Beyers D, Basen-Engquist K, Carmack CL, et al. Depression, anxiety, and quality of life in patients with epithelial ovarian cancer. *Gynecol Oncol*. 2000;78(3 Pt 1):302–308.

133. Stewart DE, Wong F, Duff S, et al. "What doesn't kill you makes you stronger": an ovarian cancer survivor survey. *Gynecol Oncol.* 2001;83(3): 537–542.
134. Wenzel LB, Donnelly JP, Fowler JM, et al. Resilience, reflection, and residual stress in ovarian cancer survivorship: a Gynecologic Oncology Group study. *Psychooncology.* 2002;11(2):142–153.
135. Schover LR. Counseling cancer patients about changes in sexual function. *Oncology (Williston Park).* 1999;13(11):1585–1591; discussion 1591–1592, 1595–1596.
136. Jensen PT, Groenvold M, Klee MC, et al. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2003;56(4):937–949.
137. Bergmark K, Avall-Lundqvist E, Dickman PW, et al. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med.* 1999;340(18):1383–1389.
138. Vaz AF, Ointo-Neto AM, Conde DM, et al. Quality of life and menopausal and sexual symptoms in gynecologic cancer survivors: a cohort study. *Menopause.* 2011;18(6):662–669.
139. White I, Allan H, Faithfull S. Assessment of treatment-induced female sexual morbidity in oncology: is this part of routine medical follow-up after pelvic radiotherapy. *Br J CA.* 2011;105:903–910.
140. Frumovitz M, Sun CC, Schover LR, et al. Quality of life and sexual functioning in cervical cancer survivors. *J Clin Oncol.* 2005;23(30):7428–7436.
141. Likes WM, Stegbauer C, Tillmanns T, et al. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med.* 2007;52(1):23–27.
142. Carpenter KM, Fowler JM, Maxwell GL, et al. Direct and buffering effects of social support among gynecologic cancer survivors. *Ann Behav Med.* 2010;39(1):79–90.
143. Levin AO, Carpenter KM, Fowler JM, et al. Sexual morbidity associated with Poorer psychological adjustment among gynecological cancer survivors. *Int J Gynecol Cancer.* 2010;20(3):461–470.
144. Carter J, Sonoda Y, Baser RE, et al. A two-year prospective study assessing the emotional, sexual and quality of life concerns of women undergoing radical trachelectomy versus radical hysterectomy for treatment of early-stage cervical cancer. *Gynecol Oncol.* 2010;119(2):358–365.
145. Le T, Menard C, Samant R, et al. Longitudinal assessments of quality of life in endometrial cancer patients: effect of surgical approach and adjuvant radiotherapy. *Int J Radiat Oncol.* 2009;75(3):795–802.
146. Kornblith AB, Huang HQ, Walker JL, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: A Gynecologic Oncology Group Study. *J Clin Oncol.* 2009;27(32):5337–5342.
147. Lindau ST, Gavrilova N, Anderson D. Sexual morbidity in very long term survivors of vaginal and cervical cancer: a comparison to national norms. *Gynecol Oncol.* 2007;106(2):413–418.
148. Canada AL, Schover LR. The psychosocial impact of interrupted childbearing in long-term female cancer survivors. *Psychooncology.* 2010.
149. Carmack Taylor CL, Basen-Engquist K, Shinn EH, et al. Predictors of sexual functioning in ovarian cancer patients. *J Clin Oncol.* 2004;22(5):881–889.
150. Greenwald HP, McCorkle R. Sexuality and sexual function in long-term survivors of cervical cancer. *J Womens Health.* 2008;17(6):955–963.
151. Greimel ER, Winter R, Kapp KS, et al. Quality of life and sexual functioning after cervical cancer treatment: a long-term follow-up study. *Psycho-Oncol.* 2009;18(5):476–482.
152. Stafford L, Judd F. Partners of long-term gynaecologic cancer survivors: psychiatric morbidity, psychosexual outcomes and supportive care needs. *Gynecol Oncol.* 2010;118(3): 268–273.
153. Bifulco G, De Rosa N, Tornesello ML, et al. Quality of life, lifestyle behavior and employment experience: a comparison between young and midlife survivors of gynecology early stage cancers. *Gynecol Oncol.* 2011. doi:10.1016/j.ygyno.2011.11.033.
154. Joffe H, Soares CN, Thurston RC, et al. Depression is associated with worse objectively and subjectively measured sleep, but not more frequent awakenings, in women with vasomotor symptoms. *Menopause.* 2009;16(4):671–679.
155. Williams RE, Levine KB, Kalilani L, et al. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas.* 2009;62(2):153–159.
156. Robinson JW, Faris PD, Scott CB. Psychoeducational group increases vaginal dilation for younger women and reduces sexual fears for women of all ages with gynecologic carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys.* 1999;44(3):497–506.
157. Ganz PA, Greendale GA, Petersen L, et al. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst.* 2000;92(13):1054–1064.
158. Schover LR, Jenkins R, Sui D, et al. Randomized trial of peer counseling on reproductive health in African American breast cancer survivors. *J Clin Oncol.* 2006;24(10):1620–1626.
159. van der Laak JA, de Bie LM, de Leeuw H, et al. The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerized cytometry. *J Clin Pathol.* 2002;55:446–451.
160. Kendall A, Dowsett M, Folkard E, et al. Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. *Ann Oncol.* 2006;17(4):584–587.
161. Schover LR. Premature ovarian failure and its consequences: vasomotor symptoms, sexuality and fertility. *J Clin Oncol.* 2008;26(5):753–758.
162. Cardozo L, Bachmann G, McClish D, et al. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol.* 1998;92(4 Pt. 2):722–727.
163. Ilbeanu O, Modesitt SC, Ducie J, et al. Hormone replacement therapy in gynecologic cancer survivors: why not? *Gynecol Oncol.* 2011;122:447–454.
164. King J, Wynne CH, Assersohn L, et al. Hormone replacement therapy and women with premature menopause—A cancer survivorship issue. *Eur J CA.* 2011;47:1623–1632.
165. Juraskova I, Butow P, Robertson R, et al. Post-treatment sexual adjustment following cervical and endometrial cancer: a qualitative insight. *Psychooncology.* 2003;12(3):267–279.
166. Denton AS, Maher EJ. Interventions for the physical aspects of sexual dysfunction in women following pelvic radiotherapy. *Cochrane Database Syst Rev.* 2003;(1):CD003750.
167. Lowenstein L, Gruenewald I, Gartman I, et al. Can stronger pelvic muscle floor improve sexual function? *Int Urogynecol J Pelvic Floor Dysfunct.* 2010;21:553–556.
168. Schroder M, Mell LK, Hurteau JA, et al. Clitoral therapy device for treatment of sexual dysfunction in irradiated cervical cancer patients. *Int J Radiat Oncol Biol Phys.* 2005;61:1078–1086.
169. Bruner DW, Nolte SA, Shahin MS, et al. Measurement of vaginal length: reliability of the vaginal sound—a Gynecologic Oncology Group study. *Int J Gynecol Cancer.* 2006;16:1749–1755.
170. Jeffery DD, Tzeng JP, Keefe FJ, et al. Initial report of the cancer patient-reported outcomes measurement information system (PROMIS) sexual function committee review of sexual function measures and domains used in oncology. *Cancer.* 2009;115(6):1142–1153.
171. Baser RE, Li Y, Carter J. Psychometric validation of the female sexual function index (FSFI) in cancer survivors. *Cancer.* 2012;Feb 22 e-pub.
172. Meyer-Bahlburg HFL, Curtis D. The female sexual function index: a methodological critique and suggestions for improvement. *J Sex Marital Therapy.* 2003;33:217–224.
173. Isidori AM, Pozza C, Esposito K, et al. Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction. *J Sex Med.* 2010;7(3):1139–1146.
174. Baser RE, Carter J, Li Y. *Psychometric Evaluation of a 6-Item Short Form of the Female Sexual Function Index (FSFI) in a sample of Cancer Survivors.* ISOQOL 2010 London UK 2010; poster (Translating Quality of Life Measurement into Decision Making).
175. Flynn KE, Jeffery DD, Keefe FJ, et al. Sexual functioning along the cancer continuum: focus group results from the Patient-Reported Outcomes Measurement Information System (PROMIS (R)). *Psycho-Oncol.* 2011;20(4): 378–386.
176. Flynn KE, Reese JB, Jeffery D. Patient experiences with communication about sex during and after treatment for cancer. *Psycho-Oncol.* 2012;21(6):594–601.
177. Morris M. Management of stage IA cervical carcinoma. *J Natl Cancer Inst Monogr.* 1996;(21):47–52.
178. Rose PG. Type II radical hysterectomy: evaluating its role in cervical cancer. *Gynecol Oncol.* 2001;80(1):1–2.
179. Roy M, Plante M. Radical vaginal trachelectomy for invasive cervical cancer. *J Gynecol Obstet Biol Reprod (Paris).* 2000;29(3):279–281.
180. Abu-Rustum NR, Neubauer N, Sonoda Y, et al. Surgical and pathologic outcomes of fertility-sparing radical abdominal trachelectomy for FIGO stage IB1 cervical cancer. *Gynecol Oncol.* 2008;111(2):261–264.
181. Gortzak-Uzan L, Jimenez W, Nofech-Mozes S, et al. Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: Is it time to change the gold standard? *Gynecol Oncol.* 2010;116(1):28–32.
182. Wenzel L, Dogan-Ates A, Habbal R, et al. Defining and measuring reproductive concerns of female cancer survivors. *J Natl Cancer Inst Monogr.* 2005;(34):94–98.
183. Corney R, Everett H, Howells A, et al. The care of patients undergoing surgery for gynaecological cancer: the need for information, emotional support and counselling. *J Adv Nurs.* 1992;17(6):667–671.

184. Schover L. *Sexuality and Fertility after Cancer*. New York, NY: John Wiley & Sons; 1997.
185. Gershenson DM, Miller AM, Champion VL, et al. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25(19):2792–2797.
186. Carter J, Sonoda Y, Abu-Rustum NR. Reproductive concerns of women treated with radical trachelectomy for cervical cancer. *Gynecol Oncol*. 2007;105(1):13–16.
187. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol*. 2006;24(18):2917–2931.
188. Carter J, Raviv L, Applegarth L, et al. A cross-sectional study of the psychosexual impact of cancer-related infertility in women: third-party reproductive assistance. *J Cancer Surv*. 2010;4(3):236–246.
189. Holland JC, Bultz BD. The NCCN guideline for distress management: a case for making distress the sixth vital sign. *J Natl Compr Canc Netw*. 2007;5(1):3–7.
190. Kadan-Lottick NS, Vanderwerker LC, Block SD, et al. Psychiatric disorders and mental health service use in patients with advanced cancer: a report from the coping with cancer study. *Cancer*. 2005;104(12):2872–2881.
191. Pirl WF. Evidence report on the occurrence, assessment, and treatment of depression in cancer patients. *J Natl Cancer Inst Monogr*. 2004;(32):32–39.
192. Kamer S, Ozsaran Z, Celik O, et al. Evaluation of anxiety levels during intracavitary brachytherapy applications in women with gynecologic malignancies. *Eur J Gynaecol Oncol*. 2007;28(2):121–124.
193. Norton TR, Manne SL, Rubin S, et al. Prevalence and predictors of psychological distress among women with ovarian cancer. *J Clin Oncol*. 2004;22(5):919–926.
194. Hipkins J, Whitworth M, Tarrier N, et al. Social support, anxiety and depression after chemotherapy for ovarian cancer: a prospective study. *Br J Health Psychol*. 2004;9(Pt 4):569–581.
195. Ferrell BR, Smith SL, Ervin KS, et al. A qualitative analysis of social concerns of women with ovarian cancer. *Psychooncology*;2003;12(7):647–663.
196. Baile WF, Buckman R, Lenzi R, et al. SPIKES—a six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist*. 2000;5(4):302–311.
197. Sheard T, Maguire P. The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. *Br J Cancer*. 1999;80(11):1770–1780.
198. Fricchione G. Clinical practice. Generalized anxiety disorder. *N Engl J Med*. 2004;351(7):675–682.
199. Wenzel L. *Psychological, Social, and Employment Impacts on Breast and Cervical Cancer Survivors: Biobehavioral Outcomes of a Telephone Counseling Intervention for Cervical Cancer Survivors*. London, England: International PsychoOncology Society; 2007.

34

End-of-Life Care

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The goal of end-of-life care is to provide maximal palliation of symptoms and maximal psychological support at the end of life, as part of the continuum of oncology care. Ensuring that our patients get the best care as the goal of medicine shifts from curing disease to relief of suffering is one of the obligations of health professionals. To do so effectively requires engaging not only the physicians and nurses who have been part of the oncology treatment, but also the skilled assistance of palliative care and hospice professionals with the patient and their caregiving network of family and friends. It is a particular challenge in low-resource settings, where many of the medications and support structures are limited or absent, making reliance on family and friends with guidance from mid-level or trained health assistants who may not have participated in whatever level of prior cancer care the woman received the best path to palliative care.

THE END-OF-LIFE TRANSITION

Discussions about the nature of disease, the status of treatment, and the expectation and side effects of treatment are an ongoing conversation in oncology care. With the lengthening of survival for even the most deadly gynecologic cancer, ovarian cancer, and the multiplicity of options for ongoing chemotherapy, the decision to limit chemotherapy or other interventions involves multiple conversations over time aimed at balancing the potential side effects of new chemotherapies or other treatments against the expected benefit and impact on quality of life for the patient. In the setting of continuing conversation between the health care team and the patient, with or without her significant support individuals, there is often a point at which the ongoing therapy aimed at disease control or cure has a harm to quality of life that is greater than any benefit—a point at which the transition to comfort-focused end-of-life care is more clear, although palliative care may well have been initiated for some symptoms prior to this point (Table 34.1).

The balance can be difficult, as Callahan points out: “The most fundamental problem with technological medicine is twofold: that it can give us a longer life and a slower dying and that it can keep us alive when we might be better off dead” (1). Patient perspectives on what constitutes high-quality end-of-life care reinforces the importance of interactions most physicians would identify, such as communication, accessibility, continuity, and emotional support, but surprisingly, oncology patients compared to terminal patients with other diagnoses more often hold on to a desire to maintain hope (2). As a health professional, keeping this door open while realistically portraying prognosis and options and pursuing palliative care can be the hardest balance of all.

The timing and expectation of death for cancer patients continues to change. Thirty years ago, survival from advanced stage ovarian cancer of more than 2 years was very unlikely, and now is routine. As a backdrop to this advance, the age of death in the developed world has steadily increased, as the major cause of death has changed over the past hundred years from sudden death from infection, trauma, and childbirth in the young to a slower decline from chronic illnesses, usually in advanced age. Cancers that previously caused a rapid death now follow a more chronic recurring course, which changes not only patient and family perceptions about the length of time until they need to deal with the issue of death, but offers a longer time to work through the phases of dying and the opportunity to bring to closure key goals for an individual. Even the gender and role of caregivers at the end of life are changing, and the role of men as caregivers for women with gynecologic cancers deserves special attention (3). The development of palliative care teams, usually in hospital settings, has added significant expertise to symptom management, discharge planning, and accomplishing improved end-of-life care (4). Engagement of gynecologic oncologists into these teams further improves the breadth of knowledge and team perspective as end-of-life plans are made. Given the prolonged course of many of these cancers, the advance planning for end-of-life care has both more time for consideration and can evolve as the patient’s prognosis changes. The frequency and timing of hospice referral has been studied in older women with ovarian cancer, and significant disparities in care have been identified. Although more older women received hospice care during the time period studied, the proportion of late referrals to hospice stayed the same. Similar to other studies, significant disparities in the use of hospice were seen depending on race and socioeconomic status. Timely hospice referral was identified as a significant area for improvement in the care of older women dying of ovarian cancer (5). A recent study showed that even in the absence of a prolonged course of illness, the treating health care team can significantly improve end-of-life care by informing the patient of imminent death, thereby increasing the likelihood of patients and families getting the resources needed at the time of death, with no increase in anxiety seen (6).

ADVANCE PLANNING FOR END-OF-LIFE CARE: REDUCING THE EMOTIONAL BURDEN ON SURROGATE DECISION MAKERS

Along with improved symptom management at end of life have come improved vehicles for ensuring that patients have their wishes represented in their care, in terms of legal documents, but

Table 34.1 Key Issues to Address When the Therapeutic Focus Shifts from Cure to Care

Issue	Examples
Communication about terminal nature of cancer should occur in the course of ONGOING communication	“We are not achieving the goals we set together with this chemotherapy” “The cancer is continuing to grow despite our efforts with this new agent”
Assess what the patient WANTS to know	“I would not continue any further chemotherapy at this point, but feel we should focus on relieving your symptoms. What do you think?” “Do you have questions about what we just discussed?”
Identify that, in fact, the patient’s condition is terminal, and particularly if asked directly	“Am I going to die of this?” “Yes, but our attention now needs to be focused on making whatever time you have as pain-free and active as it possibly can be”
Identify the goals that the patient wants to achieve	“Are there any special events or things that are on your agenda that we need to know about as we plan your treatment?”
Identify what resources the patient is planning to access (e.g., support systems as well as insurance coverage/hospice coverage)	“Have you talked to your spouse/partner/children/friends about your plans to be at home, and do they have ideas about how that will work?”
Make sure that the priority items for the patient are dealt with immediately	“What is the number one issue for you right now?”

also ensuring that surrogate decision makers adequately represent patient wishes.

Serving as a surrogate for a woman with advanced cancer who can no longer make her own treatment decisions places a profound burden on the surrogate. Advance planning can make the burden lighter. Both the public and health care professionals often underestimate the burden of serving as a decision maker. Formal measures of stress document that months after serving as a surrogate in a decision to withdraw life-sustaining treatment, the surrogate’s emotional stress levels remain remarkably high. One study found that the stress of serving as a health care decision maker was twice as high as the stress levels on households who had lost their homes to fire in the Berkeley-Oakland firestorm (7). Decision makers commonly report waking up at two in the morning and wondering if they made the right decision. They make statements such as, “It was the hardest thing I have ever done in my life.”

When patients have not previously documented their wishes about life-sustaining treatment, the stress levels of their surrogate decision makers tend to be even higher. When surrogates are guided by the patient’s written advance directive, their stress levels are about 30% lower when measured 2 months after a decision to stop life support (7). Surrogates who “stand by” and affirm the patient’s prior written instructions worry less about whether they made the right decision. Those who had never talked with the patient ahead of time felt the anguish of “deciding for” a woman they love. An important message to women with cancer who are reluctant to engage in advance care planning is that they are continuing to take care of the ones they love by completing an advance directive and lessening their burden.

THE ROLE OF TRADITIONAL ADVANCE DIRECTIVES

Advance directives provide a woman with a means to legally document her preferences about medical treatments in the event she is no longer able to make her own decisions. The legal details and breadth of clinical context vary substantially by state within the United States, and by country of the world, with some legal systems not supporting this type of advance direction for their health care (8). In many jurisdictions, these

documents allow the formal appointment of a surrogate who becomes the woman’s legally authorized medical decision maker in the event of future incapacity. Being asked to document one’s preferences for treatment in conditions like “imminent death regardless of treatment” and “persistent vegetative state” can be anxiety provoking for anyone. The context of a new diagnosis of cancer often makes completing an advance directive a statement of prognosis rather than planning for something that may or may not be needed, and perhaps overwhelming. It is difficult to combine conversations about advance care planning with initial discussions of curative treatment and creates a temptation to put off these discussions until they have no further treatment options to offer or the patient declines further curative treatment.

Waiting until the patient is gravely ill or near death to have these important conversations risks that the patient may become too ill to be able to make her wishes known. Without prior planning, the patient will not have appointed the surrogate of her choice. Without her guidance, family and friends may disagree on treatment decisions, which add further to family distress. In addition, patients and their loved ones often benefit from having advance planning be more of a process than an event. Having discussions with the patient about who should and should not be given medical information can naturally lead into who would be the most appropriate decision maker should the patient temporarily be unable to make decisions for herself. When the patient reveals strongly held value differences within her social network, or when she indicates that her most trusted surrogate is not her legal next of kin, the patient should be strongly encouraged to complete a written advance directive if that legal construct is available.

Advance directives are remarkably effective in allowing the patient to designate her choice of a surrogate decision maker. These legal instruments are also effective in silencing those whose wishes and values diverge from the patient’s. Advance directives are also helpful to focus end-of-life treatment decisions on what the patient would have wanted. Advance directives are effective in designating a surrogate, but are less effective in turning values into action, which require medical orders.

Advance directives alone may not be enough to ensure that patients’ wishes regarding life-sustaining treatment will be followed (9). In technologically developed countries, decisions about whether to use cardiopulmonary resuscitation, ventilators, antibiotics, and feeding tubes are an integral part of the care of

women with advanced gynecologic cancers. Most persons with advanced stages of cancer and other chronic diseases ultimately make a decision to forego some or all forms of life-sustaining treatment (10).

When a thoughtful decision has been made to forego attempts at resuscitation, it is most distressing to family members to have the patient receive unwanted cardiopulmonary resuscitation (CPR). Emergency medical personnel who might inadvertently be called need written medical orders indicating not to provide specific treatments like CPR. Without such medical orders, emergency medical services (EMS) in most circumstances must attempt all possible life-sustaining treatments. As patients move from one place to another, a uniform set of medical orders is needed to ensure the patient's wishes will be followed no matter what their setting of care.

One of the best-studied systems of medical orders to document advance care planning is the Physician Orders for Life-Sustaining Treatment (POLST) paradigm. The POLST document converts patient treatment preferences into written medical orders based on a conversation among health care professionals, the patient, and/or surrogates about treatment goals. The form transfers with the patient across care settings to ensure that her wishes are honored no matter whether she is cared for at home, in an ambulance, in a nursing home, or in an acute care hospital. A 1-year prospective study of nursing home residents with advanced chronic illness followed residents whose POLST forms included a Do Not Resuscitate (DNR) order and an order for comfort measures only. None of these patients received unwanted intensive care, ventilator support, or CPR (11). If such laws do not exist, health professionals taking care of women at the end of life should make sure that a patient's wishes, and the support needed through orders, are present to avoid the harm that unwanted resuscitation and increased pain can have not only for the woman but for her family. In some legal systems, assuring that a DNR order is in place is solely the responsibility of health care professionals (9).

In summary, women beginning cancer treatment often benefit from the first stage of advance care planning, which is formally appointing a surrogate decision maker who shares their wishes and values. Women with advanced cancer who wish to forego one or more forms of life-sustaining treatment need to have carefully constructed guidance to all other health care personnel who currently are, or in the future may, provide care in life's last chapter.

ROLE OF FAMILY IN DECISION MAKING

Given the sequential and repetitive conversations described above, the inclusion of family and other support persons is almost universal and clearly preferable. They are the ones with whom they have shared their lives and their dearest and deepest emotions. They are also the ones by whom the patient wants to be surrounded during the last phase of life. However, patients have the right to exclude or include whomever they wish in conversations. Also, medical events can be so acute that they trigger discussions with family members who struggle to consider what the patient might have wanted in that circumstance and are not clear about who should be the surrogate decision maker. Expert communication with the family then becomes the most critical means of ensuring that the patient's best interests are served and there is a broad understanding of issues. Unfortunately, research suggests that communication is not as effective as it needs to be in these circumstances. Fifty-four percent of families did not understand basic information (diagnosis, prognosis, treatments) after physician–family meetings in an intensive care setting (12). Well-structured discussions that focus

on the disease process, the goals of palliative therapy, and understanding the concerns of family members may help the family formulate decisions that support the dignity and choices that the patient herself would have chosen rather than create conflict that might impede an appropriate transition to a palliative care setting.

To prevent problems, it is wise to respect several rules:

- Always ask the patient if she has preferences in her contacts with friends and relatives. Often, she wants some to be more involved than others.
- Ask the patient for one or two contact persons to organize the communication with family and friends. Communicate essential information always in the presence of them or of other relatives or friends chosen by the patient. In this way, the family and friends are well informed and they share the same information with the patient. They can also help the patient with the evaluation of the information afterward.
- Never talk about the patient “behind her back.” If the physician does, and the patient finds out, the relationship of trust may be damaged. This also prevents the patient from thinking that the family knows more than she does, which can also strain family relationships.
- In countries where health care is a financial burden to the family, it is the responsibility of the physician to ensure that decision making concerning continuation of treatment or starting a treatment is based on the ethical principles of autonomy, beneficence, and nonmaleficence. This decision making cannot be driven by financial pressures alone.

At the end of life, we should expect emotional reactions by patients and their significant others, including family, to the inevitable lifestyle changes and impending death. It is the task of the physician to try to understand the thoughts and behavior of the patient regarding death and dying as well as her worries and unfinished emotional and personal business. Information on the patient's values and beliefs should be sought—even information about very personal matters like relationships and sexuality might be needed for a proper assessment of her situation. The patient has to know that she has the choice to what extent she wants to participate in this assessment and what information she is comfortable to share both with the physician or care team and with her family and friends. In normal life, family and friends often meet the spiritual and emotional needs of a patient, and the role of the health team is to support these relationships, not replace them.

UNIQUE CIRCUMSTANCES FOR DECISION MAKING: PREGNANT PATIENTS

A rare but particularly poignant context of end-of-life decision making is that of the pregnant woman with terminal, metastatic cancer in whom survival even to the end of a normal pregnancy is unlikely. The choices for palliative therapy (e.g., pelvic radiation for control of local bleeding and pressure) may directly impact the likelihood of fetal survival. The possibility of delivery of a newborn—particularly prematurely, with all the known consequences—without surviving to mother the child make the choices even more complex for the woman and for her family. The primary objective of care for the mother is alleviation of symptoms, and choices to decrease the level of palliative care in order to facilitate fetal development are considered only if strongly desired and pursued by the patient herself. Maternal autonomy in making such decisions has been supported by both ethical and legal reviews, and these confirm that the patient's wishes must guide decisions regarding fetal well-being, including accepting or not accepting caesarian section in the terminal phase

of disease (13). There is no role for withholding appropriate and maximal pain and symptom management simply because the woman has a concurrent pregnancy (14). The health care team carries a special burden in this circumstance to ensure that the patient has all relevant and unbiased information regarding harms and benefits of all potential options for her and for her pregnancy to maximize her ability to make choices.

In the absence of the ability of the patient to speak for herself, the surrogate decision makers must weigh not only her wishes regarding a premature timing of delivery of the child and invasion with a surgical procedure such as a caesarian section, but also the likelihood of viability of the fetus and the supporting family's ability and choices about caring for a significantly premature child. End-of-life directives for pregnant patients that specifically address these issues may be helpful in discussion and documentation of patient wishes (15). Some states and countries have special restrictions regarding decision making about limiting life-sustaining treatment in terminally ill pregnant women. In fact, 27 states have statutes that prohibit an out-of-hospital DNR order being written on a pregnant woman or otherwise have a "pregnancy limitation." The role of the woman in fixing the parameters for balancing fetal well-being against her own needs for alleviation of pain and suffering is central, both if she can speak for herself or in representing those wishes by surrogate decision makers, and it is her health care team's obligation to make sure that these are well defined and described, and that the patient's wishes about her health care (autonomy) are respected in the terminal phase of her disease.

MAXIMIZING PALLIATION: MANAGING SYMPTOMS AT THE END OF LIFE

Pain Control

The mainstay of pain management at any time, and even more critically at the end of life, is a careful assessment of the type of pain (nociceptive [somatic or visceral] or neuropathic), the level of pain, the location and referral of pain, and the actions that increase or decrease the pain. This assessment will need multiple repetitions, as the kind of pain and level are likely to shift with disease progression. The management strategy is to focus on not only the type and level of pain but also the level of consciousness and the level of activity that a woman would like to achieve, and to vary the strategies accordingly (16).

The World Health Organization's three-tier pain ladder starts with low to increasing levels of pain and increasing strategies from acetaminophen and nonsteroidal anti-inflammatory drugs to opioid analgesics for more severe pain. Usually using a 1 to 10 (10 being the worst) pain scale with patients fixes their position on the tier and suggests management strategy, although combinations from other levels or even within a level may be required for maximal comfort. Given that many gynecologic oncology patients are in the severe category (7 to 10) at the end of life, this might even include combining two opioids, particularly during pain syndrome escalation, to control the pain (17). In the course of adequate pain or symptom management, the anticipated side effects may shorten the time to death (principle of double effect), which is a well-recognized consequence of ensuring maximal palliative care. The ethical obligation is to alleviate the pain and suffering first and foremost, and the side effects that cannot be avoided (which rarely impact time to death simply because most patients already have substantial tolerance for narcotic pain medications) are accepted in this setting.

Pharmacologic measures to address severe nociceptive pain usually require narcotic medications. The options for administration are broad and can be tailored to the patient's circumstances.

As a principle that supports patient and family control, a means such as dermal, oral (pill, sublingual, and liquid), buccal, or rectal can make administration easier. With long-term sustained-release formulations, the goal is to establish adequate base pain coverage with every 8- to 12-hour dosing and adequate breakthrough pain coverage with an immediate-release form of the agents. Having the patient or caregiver track the amount and timing of breakthrough dosing can help adjust both the base and rescue dosing and timing. Sustained-release formulations are available for morphine, oxycodone, and hydromorphone (18). Drug dose escalation may be necessary to provide adequate pain relief. A modified release narcotic may take 2 to 3 days to reach a therapeutic level, whereas a transdermal patch may take 3 to 6 days, and a long acting medicine, like methadone, may take 5 to 6 days or longer (19). While titrating a long-acting narcotic, an intravenous (IV) formulation may be required to control pain. Once a patient's pain is more adequately controlled with a sustained-release formulation, the short-acting agent should account for only 5% to 15% of the total drug dose.

Methadone is another option that has been utilized and can be particularly helpful when morphine is not adequate or is problematic for individual patients. It has a variable conversion ratio and pharmacokinetics in individuals and is much more difficult to titrate and manage with other medications. Methadone may be particularly helpful in patients in whom neuropathic pain resistant to opioids is a significant part of the pain complex. The final option to avoid IV pain management is the transdermal fentanyl patch. This is particularly helpful, when stabilized dosing is reached, for individuals who require continuous baseline coverage, and it is useful in patients who are unable to tolerate oral medications. The downside is the long time to peak concentrations, which renders initial evaluation and titration of dosages difficult and requires significant use of short-term release opioids to cover (20).

The use of IV forms of opioids with patient-controlled analgesia pumps can be accomplished in the home setting if needed. The use of a basal IV infusion with patient-controlled boluses is the preferred method. Subcutaneous infusion of opioids can also be used, with near equivalent efficacy, and it can be more easily managed in some home settings (21). For all methods, titration to comfort is the goal, with management of secondary symptoms such as nausea or sleepiness as needed by the patient and within the context of her goals. The last few hours of life can be marked by both increased or decreased pain, and a strategy to address this needs to be in place as part of the pain control program.

The multiplicity of tumor-related and therapy-related pain syndromes that result in neuropathies from invasion, radiation, or other therapy often require additional therapies (21). Anticonvulsants are helpful adjuncts. The most commonly used would be gabapentin, which is routinely used for postherpetic, chemotherapy-related, and diabetic neuropathies. Clonazepam and lamotrigine also may be effective. Additionally, tricyclic antidepressants (e.g., amitriptyline, desipramine, nortriptyline) may be helpful for neuropathic pain as they also treat underlying depression, have their own direct analgesic effect, and potentiate opioid analgesia (23). α 2-Adrenergic agonists, usually clonidine, have also been effective adjuvant analgesics for neuropathic pain as they work through a different receptor from opioids and decrease sympathetic outflow related to neuropathic pain. Corticosteroids such as dexamethasone can provide additional relief, particularly for inflammation irritating nerve endings. For the extensive pelvic tumor invading the nerves in the pelvic floor, the use of sacral or regional nerve blocks, epidural pumps, or ablation of nerve roots may play an important role (24). Implanted programmable pumps for neuroaxial infusion have been shown to increase analgesia and decrease the side effects that systemic opioids cause (43, 44). Topical lidocaine patches may also provide local relief.

Mind-body and psychological approaches, such as guided imagery, have been explored for dealing with cancer pain. These have been shown to decrease pain and positively affect symptoms (25,26).

Pain control in some settings, usually low-resource settings, may be restricted because of laws that do not allow patients access to adequate narcotic pain medicine at home or lack of access throughout the country. For these settings, use of any available pain medications along with local therapy (heat, cold, massage) may help add comfort. The fact that many women globally still die in severe pain argues for significant advocacy by the gynecologic oncology community, both in the U.S. and globally, with ministries of health and other relevant settings to address end-of-life pain control.

Nausea, Vomiting, and Bowel Obstruction

The etiology of nausea and vomiting at the end of life can be related to medications, constipation, or brain metastases, but more often for gynecologic cancer patients, it is related to malignant bowel obstruction. Ovarian and endometrial cancers have a higher likelihood of developing obstruction with disease progression, and therefore for effective symptoms management, it is critical to distinguish the obstructed bowel from constipation/obstipation.

Since the majority of patients are already at risk for constipation from medications (opioids, serotonin antagonist antiemetics) as well as low motility of the bowel, initiation and continued reevaluation of a bowel regimen is an important part of effective palliation. If patients can achieve adequate oral intake, the addition of fiber in the diet and fluid intake can assist in management. Patients maintained on an opiate regimen should take a baseline bowel regimen including a stimulant, such as senna, with or without a stool softener (27,28). If constipation persists, rectal laxatives or osmotic agents such as the polyphenolic compounds can be added as needed, and higher doses of these may be required to resolve constipation (29). There is insufficient evidence to recommend one laxative over another, and therefore, choice of laxative must be based on interpretation of individual contributing factors and side effect profiles. Metoclopramide is FDA-approved for treatment of cancer-related and opioid-induced constipation and may be helpful as a prokinetic agent in patients with gastroparesis or carcinomatous ileus. Other strategies that have been investigated with varying success include opioid rotation and administration of naloxone (30,31).

If obstruction is diagnosed, the consideration for surgery should be limited to women in good overall condition with a single site of obstruction. Various studies have shown that advanced age, poor general health or nutritional status, diffuse peritoneal carcinomatosis, ascites, palpable masses, prior radiation, and multiple obstructed sites carry a higher mortality and morbidity (32,33). Careful selection of patients has been shown to not only achieve symptom relief but also extend survival. Preoperative evaluation to ascertain the likelihood of benefit for individual patients should include imaging procedures (Gastrografin enemas, carefully chosen use of computed tomograph, and limited upper gastrointestinal evaluations) that target the identification of multiple sites of obstruction. Failure to identify the presence of multiple sites of obstruction can lead to a failed procedure, with consequent increase in the pain and discomfort of the patient during the dying phase.

Symptom management is usually the path taken in the treatment of bowel obstruction at the end of life. Nasogastric tubes provide quick relief, but are uncomfortable, and some reports suggest that they are ineffective in longer-term management of symptoms. Gastrostomy tubes are generally more comfortable, but require surgical or radiology intervention that may not be desired by patients. For individuals with partial and complete bowel

obstruction and carcinomatous ileus, gastrostomy tubes can provide significant symptom management with just dependent drainage or suction (34). Left-sided omental caking may present an obstacle to successful percutaneous gastrostomy tube placement, and intraluminal stenting for relief of gastroduodenal obstruction can be useful in advanced ovarian cancer patients with significant upper abdominal disease (35). Distal rectal obstruction can sometimes be relieved through the use of stent placement (36,37), which is worth consideration. At the end of life, when the major objectives of treatment are quality of life and relief from the symptoms of obstruction, successful stent placement can avoid the need for laparotomy, with the associated significant morbidity and mortality that is seen in this group of patients. Stents are easiest to use in left-sided colon lesions and should be placed proximal to the dentate line for comfort (38). For many patients at the end of life, pharmacologic agents will be the mainstay of treatment for nausea and vomiting associated with bowel obstruction and carcinomatous ileus. Dopamine antagonists such as haloperidol are the drugs of choice for antiemetics in the setting of bowel obstruction (39). These agents can be associated with significant extrapyramidal side effects, which can be lessened or prevented with antihistamines, such as diphenhydramine, which also has antiemetic effects in patients with bowel obstruction. Additionally, hysocine hydrobromide and hysocine butyl bromide are helpful with patients experiencing colicky pain and nausea. Somatostatin analogues such as octreotide are well tolerated and can limit the secretions and motility and diminish the symptoms of bowel obstruction overall (40,41). Octreotide has the option of a long-acting formulation, which only requires monthly injections, and has been shown to assist in the setting of advanced ovarian cancer (42). Hospice Pharmacia formulates a suppository with Lorazepam, diphenhydramine, and Haloperidol that can be inserted rectally for easy drug delivery in outpatients with vomiting (43).

Finally, corticosteroids have been used to reduce inflammation, and potentially reduce the obstruction in some patients, and are worth a trial as part of conservative management. Dexamethasone in a dose of 4 to 8 mg per day for 3 to 5 days is generally used for this and additionally can potentiate the effect of pain medications and antiemetics (44). Improvement should be noted within 3 to 5 days if these agents are effective.

Several alternative treatments are worthy of mention, although not much data on their use exist in palliative care. Acupuncture, which has been found to be helpful in alleviating chemotherapy-related nausea, was associated only with transient improvement in symptoms of nausea in a small pilot of patients receiving palliative care for cancer (45). Medicinal cannabis has also been found to help with chemotherapy-related nausea. Dronabinol is a purified synthetic cannabinoid (delta 9 tetrahydrocannabinol) that is approved for use in the treatment of nausea and vomiting associated with chemotherapy; however, its side effect profile, including vertigo, xerostomia, dysphoria, and hypotension, is unacceptable to many patients (46).

Nutritional Management at End of Life

The value of end-of-life nutritional maintenance must be firmly set in the context of what the goal of the intervention is. Giving artificial nutrition in the dying phase of life has generally not been shown to prolong survival, adds risk, and may not enhance comfort (47). Families and patients can have cultural- and religious-based concerns about not providing “nutrition” in the dying phase, often framed as “starving” the patient, which need to be addressed. It is very important to explain to patients and families that hunger and thirst are symptoms that are experienced differently in healthy people from those who are seriously ill. Those who are near death are often comfortable even though they are no longer eating.

At times, earlier in the trajectory of the patient's illness, management of nutrition as a trial to achieve another palliative or quality of life goal, for example to maximize stamina for a special event with a limited time line for treatment, may be an appropriate strategy. In this context, nutritional support might be started as a trial to evaluate whether this can achieve greater palliation of symptoms or to reach a clearly defined goal of the patient, such as attending a specific event, and defined time lines need to be discussed with patients ahead of time to assess the efficacy of this strategy in meeting these goals. In a sense, it allows patients to try to meet the energy needs for the energy expenditure they have set as a goal that they are otherwise unable to accomplish.

The options for artificial nutrition are enteral if feasible and parenteral if not. Most patients at the end of life have tried increased oral feeding, but owing to low transit times with associated nausea and lack of appetite, have ceased trying to eat. If a time-limited option to increase appetite is desired, then corticosteroids such as dexamethasone can be considered, although their efficacy is limited. Additional appetite stimulants include progesterones such as Megace. Both can have a limited impact on oral intake. Diet supplements then form the basis for increasing nutritional input, including simple formulations such as instant breakfast or intact protein formulations with low lactose.

Other enteral feeding approaches generally focus on feeding tubes either placed under fluoroscopy via a nasogastric approach or surgically placed in the jejunum or the stomach. These use protein hydrolysates with timed feedings or continuous infusions (48,49). The discomfort of nasogastric feeding tubes sometimes prevents this means of enteral feeding from being effective, but does allow for easy removal. J tubes require surgical intervention in the abdomen, in which landmarks are possibly obscured by tumor, and placement must be evaluated in light of the potential issues with the type of tumor and the likelihood of surgical difficulty. In patients with low motility and partial obstruction, the use of enteral feeding formulations may allow the patient to meet her goals without requiring the cumbersome and more difficult to adjust total parenteral nutrition (TPN).

TPN remains the final option for attempting to improve nutritional status transiently in end-of-life care. TPN ties a patient to an intravenous line, costs more, and is associated with increased morbidity that can add to the burden of symptoms such as dyspnea at the end of life. It is often more than a support person can manage at home, and may obligate the individual to undesired nursing home or hospital care settings. Furthermore, IV access with ports in the face of terminal disease and often-compromised immune surveillance can result in infections that diminish access not only for TPN but also for needed pain control or other IV medications (50). This, therefore, must be understood in a framework that defines clear stopping parameters (failure to meet goals of symptom relief or improved stamina for an event) and a clear overall time line. In general, TPN is not of benefit in the end of life for patients with cachexia from metastatic cancer.

Ascites Management

For women with ovarian cancer, ascites (and associated pleural effusions) create continual pressure, pain, and diminished pulmonary capacity that significantly impact activities of daily life and quality of life in the dying process. Management relies on elements of constriction of influx and increasing efflux. The pathophysiology of malignant ascites is not only obstructed efflux through lymphatics in the diaphragm (51), but also increased production of fluid. The fact that the protein content of ascites fluid is high (85% of plasma levels versus 25% of plasma levels for transudates) suggests that the vessel walls are compromised. An emerging culprit is vascular endothelial growth factor (VEGF), which enhances vascular permeability (52). This

suggests that VEGF receptor inhibitors might have a role in the palliative management of this problem. VEGF inhibitors have been used intravenously and intraperitoneally to palliate symptomatic ascites in ovarian cancer, with some success (53,54).

The mainstay of ascites management, however, remains paracentesis, and its application has been improved through ultrasound guidance. The use of pleuracentesis kits and vacuum bottles allows this to be done in outpatient settings or even at the bedside at home with ease, and many patients are managed simply with once or twice weekly removal of 1 to 4 L in an office setting, often without fluid replacement (55). Use of the closed drainage system developed for pleural drainage (Pleur-X; Denver Biomedical, Golden, Colorado, USA) has been successful with malignant ascites as well and offers a method that can be managed by the patient and family (56). Large volumes of fluid (10 L) can be removed (57), but this must be balanced with colloid infusions and risks further diminishing of the intravascular albumin and protein concentrations (58), leading to worsening anasarca and associated symptoms.

Another common strategy in the management of ascites is the use of diuretics to diminish vascular volume and loss through the vascular tree. Spironolactone is the mainstay of managing ascites associated with cirrhosis and is worth considering for malignant ascites (59,60). Other diuretics can be considered as well, particularly furosemide, but their primary benefit may be the peripheral edema associated with hypoproteinemia. There have been no clear head-to-head studies of diuretics versus paracentesis and quality of life outcomes in these patients to guide therapy.

In the presence of a slow-growing refractory malignancy that requires frequent paracentesis for symptomatic relief, peritoneovenous shunts as well as the tunneled catheter described above can be considered. A retrospective study of Denver shunts in malignant ascites reported a complication rate of 38%, including occlusion and disseminated intravascular coagulation (61). More radical means, such as laparoscopically guided intraperitoneal hyperthermic chemotherapy, have a role in earlier palliative care but would rarely be applicable in the end-of-life setting (62).

Pulmonary Management

Among the most frightening symptoms for women and their families at the end of life are the symptoms of dyspnea and chest pain. Three etiologies stand out in metastatic gynecologic cancers: malignant pleural effusions, parenchymal metastases, and nodal/mediastinal metastases with airway compromise. Although quite different in etiology, some basic principles form the basis of symptom management. These include the use of oxygen, relief of bronchospasm, control of secretions, and measures to promote relaxation, which are helpful with all these etiologies.

Probably the most difficult issue to treat is pleural effusions, particularly as they compound the pulmonary constriction caused by ascites in ovarian cancer patients. Thoracentesis (with ultrasound guidance) gives immediate relief, but reaccumulations are common. Repeated thoracentesis may be a strategy appropriate to short-term management or if only needed every few weeks, with the 4% or greater risk of pneumothorax with each procedure as well as the concurrent discomfort (63). Alternatives are restricted to those who have recurrent symptomatic pleural fluid, in whom this is the primary source of symptomatology and survival is expected to be more than a few weeks. One option is a tunneled closed system pleural catheter, which can provide considerable relief without requiring more major surgery and is successful in greater than 80% of patients (64). Another option for these patients is chemical pleurodesis, now virtually always done with talc by direct application with video-assisted thoracoscopic surgery (VATS) or through a chest tube (65,66). Success is more limited in the setting of repeated prior thoracentesis,

with scarring that can make the procedure less effective. Any suggestion of a trapped lung or an endobronchial obstruction further diminishes success to the point that pleurodesis would not be a useful choice (67). Most individuals will have a fever and moderate to severe pain around the time of instillation, and complications include arrhythmias, pneumonitis, empyema, and respiratory failure. Such a procedure requires the patient to be in the hospital for several days with a chest tube and occasionally in the intensive care unit for observation overnight if a VATS plus talc procedure is done. This creates costs and side effects that must be weighed carefully against the benefits. Pleurodesis should be restricted to individuals in whom this intervention has a significant chance of alleviating the primary symptoms to avoid exposing women unnecessarily to pain and side effects that further burden their dying phase of life (68).

Management of pulmonary metastases in the end-of-life setting, even if solitary, is focused on symptom relief. Many parenchymal lesions are asymptomatic, but pleural irritation can be problematic with coughing as well as hypoxemia. Lymphangitic carcinomatosis is less common in gynecologic malignancies than in others, such as breast or lung cancer, but dyspnea and hypoxemia with the thickened septa and interstitial edema are the primary symptoms to be managed. The dyspnea associated with lymphangitic spread is often symptomatically greater than the actual pulmonary disease present (69). Strategies to treat these symptoms are attention to environment, and diminishing walking or activity requires doing simple activities of daily living by changing the environment. The use of a handheld fan for air circulation, nasal oxygen (with portable units), and trials of pursed lip breathing may all help. Certainly, consideration should be given to diuretic therapy if there is any component of fluid overload, and opiates, particularly morphine, are helpful (70).

Morphine, whether or not it is in use for pain control, has an important role in decreasing air hunger and dyspnea and has improved efficacy when combined with midazolam (71). Concerns regarding iatrogenic respiratory failure are common amongst caregivers when medicating patients for air hunger. Clemens et al evaluated respiratory parameters in palliative care patients with shortness of breath and found that titration of opioids alleviated symptoms and decreased respiratory rates without causing hypoxia (72).

Anxiolytics, although helpful for the anxiety component and commonly used as an adjuvant, can occasionally worsen symptoms by causing respiratory depression and a resultant increase in air hunger and should be used judiciously in addressing pulmonary symptoms. Acupuncture has been shown to improve symptoms of dyspnea in patients receiving palliative care for cancer when given for 4 weeks, with sustained benefit seen after treatment (45,70).

Airway obstruction and cough have similar symptoms, and some of the therapy is similar. Cough may be due to multiple issues, including conditions unrelated to malignancy such as asthma or sinusitis, and from gastroesophageal reflux, which is more common with ascites. Therapies tailored specifically to these issues, such as the use of inhaled or intranasal steroids, antihistamines, and proton pump inhibitors for reflux, are appropriate. Cough due to airway obstruction responds to narcotic suppression with morphine or codeine. Occasionally, steroid inhalers add additional relief from bronchial irritation induced by metastatic disease. Even humidifiers may be helpful for some patients, particularly for coughs from irritated mucosal linings from prior mediastinal chest radiation. Inhaled furosemide may be helpful in reducing dyspnea and inhibiting the cough reflex as well as preventing bronchoconstriction in asthma. In some cases, radiation therapy targeted to specific areas of obstructing disease in the mediastinum, with an obviously longer survival estimate, may be of value in managing symptoms. In summary, the therapies for pulmonary symptoms rely on supplemental oxygen, local suppression of inflammation, suppression of cough and air hunger through opiates, and removal of fluid compression as needed.

Central Nervous System Involvement: Management of Seizures, Brain Metastases, and Mental Status Changes

Mental status changes are usually present at the end of life, and management of these symptoms are often the key toward patients achieving their personal goals at the end of life, many of which center around being awake and conversant to bring closure with family and friends. Delirium is particularly distressing to family members who also are seeking closure with the dying patient. For both, the decline in function from a prior baseline heralds more losses to come and creates even greater anxiety. Etiologies can be metabolic abnormalities (sepsis, renal failure), innumerable drugs, and structural brain lesions, with obvious differences in approach to treatment. There are clear predisposing factors, including age, multisensory impairment, medical illness, depression, dehydration, and abnormal serum electrolyte levels, pertinent to the end stage of malignancies (73–75).

Understanding the nature of the delirium is important in addressing what may be more than one contributing factor. Assessing alertness, distractibility, the patient's ability to concentrate and talk easily, and simple cognitive disturbances of memory, reasoning, or perception all contribute to the delirium, along with specific neurologic deficits or neuromuscular activity that can point to central nervous system metastases. Laboratory and physical evaluation with infection, hypercalcemia, renal failure, hypoglycemia, hypomagnesemia, and hypoxemia being key conditions to look for (75–78). Tuma and DeAngelis (79) noted that with appropriate workup, a significant number of patients can improve their symptoms (68%), even when terminal.

Addressing electrolytic abnormalities and treating infection have value when the goal of a clearer sensorium at the end of life can be achieved. Drug-induced delirium may be caused by opioids, corticosteroids, benzodiazepines, or anticholinergic medicines. Opioid-induced neurotoxicity may present as sedation, hallucinations, cognitive impairment, delirium, or even as a seizure. If opioid-induced delirium is the diagnosis, then rotation of types of opioids used can be helpful in restoring function (80). If there are hallucinations and agitation, particularly in elderly dying patients, the use of antipsychotics may alleviate symptoms (81,82). Haloperidol, risperidone, and olanzapine were found to be equally effective in a Cochrane review. Typical doses include haloperidol 1.25 to 2.5 mg/day, risperidone 0.25 to 1 mg given twice a day, and olanzapine 4.5 to 8.2 mg a day (83). Given intravenously, haloperidol can be effective within 30 minutes and generally lasts for at least 4 hours. Given by mouth, the half-life of haloperidol is considerably longer and can be used in mild delirium states. The starting dose is 0.5 mg twice a day, which can be increased up to 3.5 mg a day and can be given as often as every 8 hours. It is important to remember that these drugs have the potential of lowering the seizure threshold, as the more common electrolytic abnormalities associated with prior chemotherapy such as magnesium deficiency also may be present and compound the risk. They can also prolong the QT interval and may lead to cardiac arrhythmia. Finally, some patients may benefit from combining drugs and including a benzodiazepine to decrease associated agitation. Some studies have noted that delirium in patients with advanced cancer more commonly requires more than one medication (84). The most commonly used are Lorazepam (up to 2 mg) or midazolam, which is preferred if a subcutaneous route is to be used (85).

Another source of delirium or abnormalities in central nervous system function is brain metastasis. Initial therapy after diagnosis is the immediate use of corticosteroids to decrease local edema and also headache associated with this. This may, in fact, be all that is needed if the patient has a very short time to live, as median survival with brain metastasis with steroids

alone is about 2 months. However, if a patient is otherwise functional and treatment could improve her overall quality of life, then targeted radiation therapy should be considered. For this use, generally 300 Gy total dose given in 30-Gy fractions is administered (86). For care at the end of life, more aggressive resection and radiation is generally not appropriate.

Control of seizures depends on the etiology of the seizures. The more common causes in gynecologic oncology patients are electrolyte induced, often hypomagnesemia or hyponatremia. Primary brain etiologies range from brain metastases to brain hemorrhage and stroke. Virtually all will be able to be controlled initially with Lorazepam, either intravenously or by mouth. Electrolyte repletion should be undertaken (87). Seizures associated with brain metastasis may be controlled with simply the decrease in inflammation with corticosteroids.

Local Comfort Measures

Many of the measures for comfort at the end of life are related to simple things that can escape notice but create comfort for the dying woman (88). The environment itself gives comfort if familiar things are around, including sounds, smells, and pictures that hold meaning for the woman. Smells themselves may provide comfort, such as aromasticks, which have been shown to have some benefit in a noncontrolled setting for nausea and sleep disturbance (89). Music has been found to strengthen the “living human document” that there is a musical memory and energy from hearing it and sharing it at the end of life that gives comfort (90). Assuring that the issues of access and fall prevention are addressed by a care team is important to the success of home care. Skin protection through rotation if the patient is bed bound and early identification and treatment of skin breakdown prevents unnecessary sources of pain and infection. Many patients derive great comfort from gentle massage, and virtually all benefit from human touch and presence. Developing a plan for passive (or active) movement during the day alleviates pain and discomfort from decreased mobility. Eye care with artificial tears or even hydrogel eye patches may be needed. Perineal care and the use of urinary catheters to eliminate skin breakdown in the perineum are commonly used when the patient is no longer mobile. Prevention of pressure ulcers prevents unneeded pain and suffering so an integrated skin protection plan is of value (91). Families and patients sometimes need “permission” from their health care team to make the environment home rather than a hospital at home. Yet it is the breeze from the window, the smells of home, the sights of loved ones rocking in a chair beside them that bring the most comfort—and the physician must actively support choices that make this possible at the end of life.

Management of Fistulas in the Terminal Care Setting

The fistulas encountered at the end of life from both the urinary system and the gastrointestinal system are often the most difficult for family and caregivers to deal with. The principles of management are simple but difficult to achieve. The options are diversion, containment, and closure, regardless of the site of the fistula.

Enterocutaneous fistulae can occur from every part of the bowel, but those from the small bowel have high output and are irritating to the skin. Diversion is rarely an option in the setting of terminal cancer, primarily because the intra-abdominal spread of disease is frequently the etiology of the fistula itself in association with prior therapies, such as radiation. Surgical diversion, if the patient is medically stable and surgery could be limited, has benefits solely to provide better control and better fit of pouches over the ostomy site than over a fistula site. As noted

by Marsden et al., this does not remove the problem, as there may still be a discharge from the site of tumor-related necrotic material that must be managed (92). If this is not possible, the only recourse—similar to bowel obstruction—is to attempt to diminish flow through the gastrointestinal tract with octreotide and then to minimize and manage skin irritation actively. Small bowel fistulae can be associated with significant skin irritation due to autolysis of the skin from digestive enzymes. If a post-operative fistula location is not amenable to coverage with a pouch, wound vacuum-assisted closure (VAC) devices may be of short-term benefit (93).

Large bowel fistulae, most commonly to the vagina, can be more easily diverted, and this is the first choice if the patient is medically stable. Even a simple loop colostomy can provide relief from the volume of vaginal discharge. However, some discharge usually remains. The use of metronidazole for tumor necrosis and discharge in the vaginal area relieves some of the anaerobic odors, and sitz baths and douches as needed to control odor are also helpful.

Vesicovaginal and ureterovaginal fistulae are primarily handled by diversion, if appropriate. The primary problem with diversion is the discomfort and management of new percutaneous nephrostomies, and for some patients there may be a component of renal failure that there is no desire to reverse. Additionally, nephrostomies alone may not be adequate for resolution, and the use of ureteral occlusion with coils and sponge pledgets may also be helpful (94). Local measures, including scrupulous management of pelvic and perineal hygiene, the use of adult diapers, and the use of creams such as 1% silver sulfasalazine or skin barriers, are primary measures. There are no effective vaginal means to control or contain the output. Various measures, such as the use of diaphragms glued to catheters or local tissue glues, have generally been ineffective in this setting.

Bleeding related to the pelvic/vaginal fistula or to vaginal recurrence can potentially be controlled by single fraction pelvic radiation (95), or if severe and causing significant distress with radiologic embolization. Local measures, such as Monsel's solution, have only limited efficacy and packing can add considerably to patient discomfort. So, try to pick an approach that fits both the overall status of the patient (if only a few days are likely, then the value of any intervention would be negligible) and the comfort and decrease in anxiety she might gain from addressing the bleeding.

Management of Bone Metastases

Bone metastases are rare in terminal gynecologic cancers, being primarily confined to unusually high-grade cell types, such as glassy cell malignancies, neuroendocrine tumors, melanomas, small cell malignancies, or clear cell malignancies. When they occur, however, the pain associated with bone metastases can be the most excruciating of all the symptoms to be managed at the end of life. Corticosteroids and nonsteroidal anti-inflammatory drugs may have a significant role in managing the inflammatory pain from bone metastases and should be considered as part of initial management. If the metastases are localized, radiation therapy on a palliative basis may supply additional pain relief, with a success rate of 24% to 50% total pain relief and 80% to 90% of patients noting relief of pain (96,97). Relief of pain may be immediate or it may require several months, which may make it less helpful at the extreme ends of life, and the use of anti-inflammatory pain medications during treatment may aid in symptom relief until the effects of radiation become evident.

Key aspects of treatment include ensuring that radiation fields encompass the entire area of bone involvement (98) and also the prevention of overlap with prior radiation fields. One of the key areas for treatment is the periosteum, in which the

pain fibers are particularly abundant. Multiple schemes have been used depending on the urgency, the general condition, and the overall expected survival time of the patient. There does not seem to be a difference between single-fraction versus multiple-fraction approaches, except for the need for retreatment with single fraction (99) if survival is prolonged. Also, if there is a longer life expectancy, consideration should be given to prophylactic surgical fixation of weight-bearing bones with greater than 50% cortical destruction or size greater than 2.5 cm prior to radiation therapy (100,101). Newer interventions, such as flexible nails and cement, may allow stabilization even in medically fragile patients (102). Another option for consideration is the use of osteoblast-affinic agents, such as strontium 89 or samarium 153, which deliver localized radiation to osteoblastic bony metastases. The primary problem in their use is bone marrow suppression, which often limits their use in patients with ongoing residual suppression from their prior therapies. These agents are not appropriate for use in hypercalcemic patients, and the pain relief is slower in onset, with duration of about 12 weeks. This option may require multiple doses to increase efficacy (103,104). Research with radiofrequency and combined techniques is rapidly accumulating, which may be of particular assistance with pelvic metastases and those for whom radiotherapy is not appropriate or has failed (104,105). New approaches with embolization and ultrasound strategies are also being researched, providing broader options for the future (106,107).

Psychologic Needs in Terminally Ill Cancer Patients

An important aspect of palliative care in terminally ill cancer patients is the recognition and treatment of psychologic symptoms to improve quality of life at the end of life. The understanding of suffering requires not just addressing physical needs, but also distress, existential concerns, and social relational worries, which contribute to overall suffering in terminal cancer patients (108). Health care professionals often ignore the role that religion and spirituality play in coping with terminal illness. Most patients consider religion or spiritual aspects to be at least some what important, and the majority report that their spiritual needs were supported minimally or not at all by the medical system (109). Referral to chaplaincy services or other integrative medicine services is deemed valuable by our patients, and assessing their desire for this should be part of psychologic assessment and treatment (110). This is an area in which little training and modeling exist, and the ability to address spirituality comfortably with patients is limited but it is important for health professionals to improve in discussing and addressing these issues (111,112).

Depression and anxiety occur in a high percentage of cancer patients, particularly as disease advances and curative cancer treatment fails (113). The prevalence of depression in cancer patients has been the subject of numerous studies, and the reported rates have ranged from as high as 58.0% to as low as 4.5%, with age, lower performance status, smaller social networks, and less participation in organized religious services all significant in predicting depression and anxiety (114).

Anxiety in terminally ill cancer patients has received less attention than depression. Anxiety commonly increases as patients become aware of both the relative ineffectiveness of medical treatments in halting the progress of their disease and, consequently, their limited life expectancy (115). The awareness of the inevitable death is likely to cause anxiety in terminally ill cancer patients. Breitbart et al. suggest that the incidence of both anxiety and depression in cancer patients increases with higher levels of disability, advanced illness, and pain (116). The closer the patient is to dying, the higher the score on depression and the lower the score on physical performance.

Although depression and anxiety are important to continually assess in terminally ill patients prior to death, data show that a relatively high percentage of terminally ill cancer patients suffer from psychologic distress a few weeks before death, which appears to be related to physical symptoms. Treating the physical symptoms maximally is the first task in addressing depression and anxiety. Standard treatment for depression and anxiety is effective in this population, and tricyclic antidepressants that additionally address neuropathic pain are reasonable choices. Lorazepam is often used for assisting in managing other symptoms but also provides relief for anxiety. Some integrative medicine solutions, such as aromatherapy massage, have been shown to assist in decreasing anxiety and depression (117). In summary, psychologic symptoms in terminally ill cancer patients need to be systematically assessed and considered by the care team in the overall decision making and treatment plan at the end of life. Treatment of anxiety and depression clearly also improves overall management of pain, as well as making the process of closure more possible for dying women. If patients can reconcile their concerns with psychologic and pharmacologic support, this will substantially remove the suffering from emotional distress for the patient and her family.

REQUESTS FOR HELP IN DYING

Sometimes patients ask to end their life because of fear of an inability to control suffering at the end of life or inadequately managed pain or suffering. In most countries in the world, the law forbids assisted suicide. In the Netherlands, Belgium, and the United States (State of Oregon), individuals have access to laws that make assisted suicide available for those experiencing unbearable suffering, and this access is highly regulated. Data from the Oregon experience (118) as well as the Netherlands (119) show that most patients do not follow through even with an expressed intent for assisted suicide.

Regardless of where health providers are in the world, this is a question that will come up directly or indirectly if actively caring for dying patients—and challenges our communication skills as few have been educated specifically for end-of-life discussions (120). Additionally, having such a discussion requires physicians to address for themselves their own understanding and barriers to discussing dying, futility, and assisted suicide (121,122). Dying patients expect and need at least a minimal level of emotional support, defined by them as compassion and treating the whole person and not just the disease (123). Set in this context, this conversation is an opportunity to embrace the compassion and acknowledgment of the whole person that is expected by the patient and to enhance understanding of the fears and the needs of the patient in the present. Patients who state that they would like “extra” prescriptions for pain medicine or anxiolytics, or who blatantly state that they are thinking of ending it all themselves or would like help in doing so, are usually asking for an exploratory conversation about how “unbearable” dying will be.

Even in the middle of a busy clinic, time has to be made for this discussion. Confirming that the patient’s request has been heard and confirming the patient’s importance to her health professionals is part of the therapeutic relationship. A consult room with the inclusion of whomever the patient wants to include (or not) is a better setting than an examination room, if available. Exploration with more open-ended questions, such as “Why do you feel you need this extra prescription right now?” “What do you think will happen that might make you think of (whatever phrasing the patient used)?” is a way to begin the dialog. Remembering that suffering is not only physical but also psychologic and spiritual is important to ensure that all dimensions of fear and questions are answered, or if unanswerable,

acknowledged as important. Follow-up questions that explore the patient's motivation are outlined in Bascom and Tolle's article (119). Exploring each fear and, more importantly, assuring that with maximal effort at palliative care this can be addressed (and how), and that the patient is not viewed as a burden and is valued, will open critical communication and provides an opportunity to address the underlying concern of the patient. In addition, this is an optimal time to introduce or reintroduce the importance of advance directives and to implement specific written orders regarding life-sustaining treatments if these are available to the patient (124). If this is an area of communication that is uncomfortable to the physician, then having another member of the team lead this discussion with the patient would be valuable, but with the specific assurance that respecting her wishes and continuing to care for the patient are still of importance to the physician who has been a critical member of that patient's care.

BEREAVED FAMILY AND FRIENDS

Medicine focuses on the individual care of patients, and the needs and issues of the social network that supports patients are often ignored. End-of-life care, however, engages that entire social network of family, friends, and often spiritual advisors and requires understanding their needs and roles as the patient nears the end of life. Families define high-quality end-of-life care as first achieving good control of symptoms for the patient, but they also weigh quality on how well the dying person was able to control decisions and whether the family members felt that they had to be constant advocates for the needs and wishes of the dying person. In addition, education and emotional support for the family and friends caring for the patient were seen as important (125). **Caregivers of cancer patients may neglect their own health and emotional well-being to care for their loved ones. This may manifest as greater levels of depression and anxiety.** All the members of this network of care for the patient experience high levels of stress, burden, and diminished quality of life, which can be helped with specific coping skills training (126). Caregivers who are able to accept and reframe the patient's illness feel less strain and feel more capable of solving illness-related problems, all of which will directly improve the care of the dying woman (127). **Since those caring for dying cancer patients may not make time to seek care for themselves, it has been suggested that oncology practices assess for caregiver distress. This can be done by any member of the care team, including a social worker, and referrals to caregiver resources may be beneficial (128).**

While the care and comfort of the families and friends of dying patients are not a direct responsibility of the oncologic physician, advocating for the development of support for this network for patients and providing access to such support are. In addition, regardless of whether the physician and primary oncology team are directly involved in the end-of-life care of the patient, acknowledging the patient's death and the team's concern for her family with a card or phone call to the family is important in closing the circle for the family as well as the primary oncology team.

CARE FOR THE CAREGIVERS

Within palliative care in general and end-of-life care in particular, there is a tendency for patients and relatives to demand and benefit from a more personal approach to their care. The model of complete cancer care in gynecologic oncology provides a great

deal of satisfaction and reward and naturally leads to satisfying and potentially longstanding doctor-patient relationships. The personal distress physicians and nurses may experience as patients die coupled with the intensity of contact in end-of-life care can lead to serious risk of depletion of the team's emotional resources and to resultant burnout. Physicians and nurses should be aware of the risk factors for burnout in order to prevent this serious threat to their health and to their work performance. In oncology, and especially in end-of-life care, the stressors appear to be strongly related to the social and interpersonal aspects of the job, including relationships with patients and coworkers on the team (129–130). Self-care and development of self-awareness have both been identified as vital tools for the oncology physician in the avoidance of burnout and should be considered a fundamental part of a physician's approach to the dying patient. Improvement in self-awareness facilitates self-care of the caregiver (131).

One of the best ways to understand and prevent emotional exhaustion and burnout is for physicians and nurses to be able to share their responses and feelings with others at work. This can be done by the organization of support groups at work where they can discuss what moved them and how they dealt with the situation (135–137). Improvement in physician communication skills regarding these stressful issues actually diminishes physician stress since the doctor-patient relationship plays an important role in this regard (138–139).

The participants get the opportunity to discuss the emotional aspects of the care of the terminal patient. This can include revisiting conversations that were held about death with patients and their families. The team listens and discusses how these emotional events affected the person involved. Especially for younger and inexperienced personnel, this type of guidance by "peers" is very important. For the more experienced members, the team meetings can establish a framework for junior members to learn from and emulate. Physician experience can result in diminished emotional involvement and appropriate distancing of relationships, thereby allowing the treating physician to appreciate the satisfaction associated with caring for patients at the end of life. Comments, advice, and help of colleagues are important factors in staying mentally fit—again, a message for all health professionals for all aspects of end-of-life care.

CONCLUSIONS

End-of-life care is a very important part of caring for women with cancer. It requires the total commitment of the entire health care team. It includes medical interventions to relieve suffering, but also psychosocial care. Communication skills are very important to ensure optimal end-of-life care, and also to relieve the stress on the caregivers (139). In this communication, the autonomy of the patient has to be respected. The caregivers must respect the delicate balance between professional and personal involvement. Communication not only involves the patient but also her relatives and friends. It is important that this communication take place in the presence of the patient as much as possible to avoid misunderstandings. Psychologic symptoms need to be routinely assessed and considered by physicians in the overall decision making concerning the end of life. Special attention must focus on anxiety and depression to ensure all domains of suffering are addressed.

End-of-life care in oncology does not mean that the physician has to postpone the inevitable as long as possible. The goal is quite simply to continue the expert and compassionate care the patient has received throughout her treatment into the maximal alleviation of symptoms and suffering at the end of life.

REFERENCES

- Callahan D. Living and dying with medical technology. *Crit Care Med*. 2003;31:S344–S346.
- Curtis JR, Wenrich MD, Carline JD, et al. Patients' perspectives on physician skill in end-of-life care: differences between patients with COPD, cancer, and AIDS. *Chest*. 2002;122:356–362.
- Fromme EK, Drach LL, Tolle SW, et al. Men as caregivers at the end of life. *J Pall Med*. 2005;8:1167–1175.
- Fromme EK, Bascom PB, Mith MD, et al. Survival, mortality and location of death for patients seen by a hospital-based palliative care team. *J Pall Med*. 2006;9:903–911.
- Fairfield K, Murray K, Wierman H, et al. Disparities in hospice care among older women dying with ovarian cancer. *Gyn Oncol*. 2012;125:14–18.
- Lundquists G, Rasmussen B, Axelsson B. Information of imminent death or not: does it make a difference? *J Clin Oncol*. 2011;29:3927–3930.
- Tilden VP, Tolle SW, Nelson CA, et al. Family decision-making to withdraw life-sustaining treatments from hospitalized patients. *Nurs Res*. 2001;50(2):105–115.
- Hickman SE, Hammes BJ, Moss AH, et al. Hope for the future: achieving the original intent of advance directives. *Hastings Cent Special Rep*. 2005;35(6):S26–S30.
- Tilden VP, Tolle SW, Drach LL, et al. Out-of-hospital death: advance care planning, decedent symptoms, and caregiver burden. *JAGS*. 2004;52:532–539.
- Babgi A. Legal issues in end of life care: Perspectives from Saudi Arabia and United States. *Am J Hospice Palliative Med*. 2009;2:119–127.
- Tolle SW, Tilden VP, Dunn P, et al. A prospective study of the efficacy of the physician orders for life sustaining treatment. *JAGS*. 1998;46(9):1097–1102.
- Evans N, Walsh H. The organization of death and dying in today's society. *Nurs Stand*. 2002;16:33–38.
- Finnerty JJ, Chisholm CA. Patient refusal of treatment in obstetrics. *Semin Perinatol*. 2003;27:435–445.
- Milliez J, Veronique C. Palliative care with pregnant women. *Best Pract Res Clin Obstet Gynecol*. 2001;15:323–331.
- Finnerty JF, Fuerst CW, Karns LB, et al. End-of-life discussions for the primary care obstetrician/gynecologist. *Am J Obstet Gynecol*. 2002;187:296–301.
- Thomas JR, vonGunten CF. Pain in terminally ill patients: guidelines for pharmacologic management. *CNS Drugs*. 2003;17:621–631.
- Mercadante S, Villari P, Ferrera P, et al. Addition of a second opioid may improve opioid response in cancer pain: preliminary data. *Support Care Cancer*. 2004;12:762–766.
- Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. *J Pain Pall Care Pharm*. 2006;20:33–39.
- Portenoy RK. Treatment of cancer pain. *Lancet*. 2011;377(9784):2236–2247.
- Ellershaw JE, Kinder C, Aldridge J, et al. Care of the dying: is pain control compromised or enhanced by continuation of the fentanyl transdermal patch in the dying phase? *J Pain Symptom Manage*. 2003;26:589–590.
- Anderson SL, Shreve ST. Continuous subcutaneous infusion of opiates at end of life. *Ann Pharmacother*. 2004;38:1015–1023.
- Gordin V, Weaver MA, Hahn MB. Acute and chronic pain management in palliative care. *Best Pract Res Clin Obstet Gynecol*. 2001;15:203–234.
- Hammond DL. Pharmacology of central pain-modulating networks (biogenic amines and non-opioid analgesics). *Adv Pain Res Ther*. 1985;9:499–512.
- Harrison GR. The use of epidural ropivacaine in high doses for the management of pain from invasive carcinoma of the cervix. *Anesthesia*. 1999;54:459–465.
- Kwekkeboom KL, Cherwin CH, Lee JW, et al. Mind-body treatments for the pain-fatigue-sleep disturbance cluster in persons with cancer. *J Pain Symptom Man*. 2010;39:126–138.
- Bardia A, Barton DL, Prokop LJ, et al. Efficacy of complementary and alternative medicine therapies in relieving cancer pain: a systematic review. *J Clin Oncol*. 2006;24(34):5457–5464.
- Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *J Palliat Med*. 2008;11(4):575–581.
- Reville B, Axelrod D, Maury R. Palliative care for the cancer patient. *Prim Care Clin Office Pract*. 2009;36:781–810.
- Solomon R, Cherny NI. Constipation and diarrhea in patients with cancer. *Cancer J*. 2006;12:355–364.
- Thomas J, Karver S, Cooney GA, et al. Methylal-trexone for opioid induced constipation in advanced illness. *N Engl J Med*. 2008;358:2332–2343.
- Candy B, Jones L, Goodman ML, et al. Laxatives or methylal-trexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev*. 2011;1.
- Kolomainen DE, Daponte A, Barton DP, et al. Outcomes of surgical management of bowel obstruction in relapsed epithelial ovarian cancer (EOC). *Gynecol Oncol*. 2011;11:1106–1111.
- Pothuri B, Vaidya A, Aghajanian C, et al. Palliative surgery for bowel obstruction in recurrent ovarian cancer: an updated series. *Gynecol Oncol*. 2003;89:306–313.
- Meyer L, Pothuri B. Decompressive percutaneous gastrostomy tube use in gynecologic malignancies. *Curr Treat Options Oncol*. 2006;7:111–120.
- Rao A, Land R, Carter J. Management of upper gastrointestinal obstruction in advanced ovarian cancer with intraluminal stents. *Gynecol Oncol*. 2004;95:739–741.
- Diaz PL, Pinto PI, Fernandez LR, et al. Palliative treatment of malignant colorectal strictures with metallic stents. *Cardiovasc Intervent Radiol*. 1999;22:29–36.
- Tack J, Gevener AM, Rutgeerts P. Self-expandable metallic stents in the palliation of rectosigmoid carcinoma: a follow up study. *Gastrointest Endosc*. 1998;48:267–271.
- Pothuri B, Guirguis A, Gerdes H, et al. The use of colorectal stents for palliation of large-bowel obstruction due to recurrent gynecologic cancer. *Gynecol Oncol*. 2004;95:513–517.
- Dalal S, DelFabbro E, Bruera E. Symptom control in palliative care – part I: oncology as a paradigmatic example. *J Palliat Med*. 2006;9:391–407.
- Mangili G, Franchi M, Mariani A, et al. Octreotide in the management of bowel obstruction in terminal ovarian cancer. *Gynecol Oncol*. 1996;61:345–348.
- Mercadante S, Casuccio A, Mangione S. Medical treatment for inoperable malignant bowel obstruction: a qualitative systematic review. *J Pain Symptom Manage*. 2007;33:217–223.
- Matulonis UA, Seiden MV, Roche M, et al. Long acting octreotide for the treatment and symptomatic relief of bowel obstruction in advanced ovarian cancer. *J Pain Symptom Manage*. 2005;30:563–569.
- Hospice Pharmacia Medication use Guidelines, Nausea and Vomiting protocol, 2005. 7th ed. www.hospicepharmacia.com/docs/pdfs/sample MUGs.pdf.
- Phillip J, Lickiss N, Grant PT, et al. Corticosteroids in the management of bowel obstruction in advanced ovarian cancer. *Gynecol Oncol*. 1999;74:68–73.
- Lim JT, Wong ET, Aung SK. Is there a role for acupuncture in the symptom management of patients receiving palliative care for cancer? A Pilot study of 20 patients comparing acupuncture with nurse-led supportive care. *Acupunct Med*. 2011;29:173–179.
- deJong F, Engels F, Mathijssen R, van Zuylen L, Verweij J, Peters R, Sparreboom A. Medicinal cannabis in Oncology Practice: Still a bridge too far? *J Clin Oncol*. 2005;23:2886–2891.
- Casarett D, Kapo J, Caplan A. Appropriate use of artificial nutrition and hydration—fundamental principles and recommendations. *N Engl J Med*. 2005;353:2607–2611.
- Gore DC, DeLegge M, Gervin A, et al. Surgically placed gastrojejunostomy tubes have fewer complications compared to feeding jejunostomy tubes. *J Am C Nutr*. 1996;15:144–146.
- Jabbar A, McClave SA. Prepyloric versus post pyloric feeding. *Clin Nutr*. 2005;24:719–726.
- Chang L, Tsai JS, Huang SJ, et al. Evaluation of infectious complications of the implantable venous access system in a general oncologic population. *Am J Infect Control*. 2003;31:34–39.
- Nagy JA, Herzberg KT, Dvorak JM, et al. Pathogenesis of malignant ascites formation: initiating events that lead to fluid accumulation. *Cancer Res*. 1993;53:2631–2643.
- Kraft A, Weindel K, Ochs A, et al. Vascular endothelial growth factor in the sera and effusions of patients with malignant and nonmalignant disease. *Cancer*. 1999;85:178–187.
- Masoumi Moghaddam S, Aminii A, Morris DL, et al. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. *Cancer Metastasis Rev*. 2011. 20 epub ahead of print.
- Hamilton C, Maxwell LG, Chernofsky M, et al. Intraperitoneal bevacizumab for the palliation of malignant ascites in refractory ovarian cancer. *Gynecol Oncol*. 2008;111:530–532.
- Numnum TM, Rocconi RP, Whitworth J, et al. The use of bevacizumab to palliate symptomatic ascites in patients with refractory ovarian carcinoma. *Gynecol Oncol*. 2006;103:425–428.
- Macdonald R, Kirwan J, Roberts S, et al. Ovarian cancer and ascites: a questionnaire on current management in the United Kingdom. *J Pall Med*. 2006;9:1264–1270.
- Richard HM 3rd, Coldwell DM, Boyd-Kranis RL, et al. Pleurx tunneled catheter in the management of malignant ascites. *J Vasc Interv Radiol*. 2001;12:373–375.
- Gough IR, Balderson GA. Malignant ascites: a comparison of peritoneovenous shunting and nonoperative management. *Cancer*. 1993;71:2377–2382.
- Arroyo V, Gines P, Planas R. Treatment of ascites in cirrhosis. Diuretics, peritoneovenous shunt, and large-volume paracentesis. *Gastroenterol Clin North Am*. 1992;21:237–256.
- Greenway B, Johnson PJ, William R. Control of malignant ascites with spironolactone. *Br J Surg*. 1982;69:441–442.

61. White MA, Agle SC, Padia RK, et al. Denver peritoneovenous shunts for the management of malignant ascites: a review of the literature in the post LaVeen era. *Am Surg*. 2011;77:1070–1075.
62. Garafalo A, Valle M, Garcia J, et al. Laparoscopic intraperitoneal hyperthermic chemotherapy for palliation of debilitating malignant ascites. *EJSO*. 2006;32:682–685.
63. Bartter T, Mayo PD, Pratter MR, et al. Lower risk and higher yield for thoracentesis when performed by experienced operators. *Chest*. 1993;103:1873–1876.
64. Karnal A, Maguire J, Wheeler J, et al. Dyspnea review for the palliative care professional: treatment goals and therapeutic options. *J Palliat Care Med*. 2012;15:106–114.
65. Luh SP, Chen CY, Tzao CY. Malignant pleural effusion treatment outcomes: pleurodesis via video assisted thoracic surgery (VATS) versus tube thoracostomy. *Thorac Cardiovasc Surg*. 2006;54:332–336.
66. Arapis K, Caliendo R, Stern JB, et al. Thorascopic palliative treatment of malignant pleural effusions: results in 273 patients. *Surg Endosc*. 2006;20:919–923.
67. Sahn SA. Malignancy metastatic to the pleura. *Clin Chest Med*. 1998;19:351–356.
68. Barbetakis N, Asteriou C, Papadopoulou F, et al. Early and late morbidity and mortality and life expectancy following thorascopic talc insufflations for control of malignant pleural effusions: a review of 400 cases. *J Cardiothoracic Surg*. 2010;19:27.
69. Tucakovic M, Bascom R, Bascom PB. Pulmonary medicine and palliative care. *Best Pract Res Clin Obstet Gynecol*. 2001;15:291–304.
70. Karnal A, Maguire J, Wheeler J, et al. Dyspnea review for the palliative care professional: treatment goals and therapeutic options. *J Palliat Care Med*. 2012;15:106–114.
71. Ben-Aharon I, Gafer-Gvili A, Paul M. Interventions for alleviating cancer-related dyspnea: a systematic review. *J Clin Oncol*. 2008;26:2396–2404.
72. Clemens KE, Klaschik E. Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. *J Pain Symptom Manage*. 2007;33:473–481.
73. Schor JD, Levkoff SE, Lipsitz LA, et al. Risk factors for delirium in hospitalized elderly. *JAMA*. 1992;267:827–831.
74. Bruera E, Miller L, McCallion J, et al. Cognitive failure in patients with terminal cancer: a prospective study. *J Pain Symptom Manage*. 1992;7:192–195.
75. Minagawa H, Yosuke U, Yamawaki S, et al. Psychiatric morbidity in terminally ill cancer patients: a prospective study. *Cancer*. 1996;78:1131–1137.
76. deStoutz ND, Tapper M, Faisinger RL. Reversible delirium in terminally ill patients. *J Pain Symptom Manage*. 1995;10:249–253.
77. Seymour DG, Henschke PJ, Cape RDT, et al. Acute confusional states and dementia in the elderly: the role of dehydration volume depletion, physical illness and age. *Age Ageing*. 1980;9:137–146.
78. Bruera E. Severe organic brain syndrome. *J Palliat Care*. 1991;7:36–38.
79. Tuma R, DeAngelis L. Altered mental status in patients with cancer. *Arch Neurol*. 2000;57:1727–1731.
80. Morita T, Takigawa C, Hideki O, et al. Opioid rotation from morphine to fentanyl in delirious cancer patients: an open label trial. *J Pain Symptom Manage*. 2005;30:96–103.
81. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam—the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry*. 1996;153:231–237.
82. Resnick M, Burton B. Droperidol vs. haloperidol in the initial management of acutely agitated patients. *J Clin Psychiatry*. 1984;45:298–299.
83. Caraceni A, Simonetti F. Palliating delirium in patients with cancer. *Lancet Oncol*. 2000;10:64–72.
84. Stiefel F, Fainsinger R, Bruera E. Acute confusional states in patients with advanced cancer. *J Pain Symptom Manage*. 1992;7:94–98.
85. Bottomley D, Hanks G. Subcutaneous midazolam infusion in palliative care. *J Pain Symptom Manage*. 1990;5:259–261.
86. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37:745–751.
87. Singh G, Rees JH, Sander JW. Seizures and epilepsy in oncological practice: causes, course, mechanisms, and treatment. *J Neurol Neurosurg Psychiatry*. 2007;78:342–349.
88. Cain JM. Practical aspects of hospice care at home. *Best Pract Res Clin Obstet Gynecol*. 2001;15:305–311.
89. Stringer J, Donald G. Aromasticks in cancer care: an innovation not to be sniffed at. *Complement Therapies Clin Pract*. 2011;17:116–121.
90. Tees B, Budd J. The sound of spiritual care: music interventions in a palliative care setting. *J Pastoral Care Counsel*. 2011;65(1–2):5:1–10.
91. Nenna M. Pressure Ulcers at end of life: an overview for home care and hospice clinicians. *Home Healthcare Nurse*. 2011;29:350–365.
92. Marsden DE, Lickiss JN, Hacker NF. Gastrointestinal problems in patients with advanced gynecologic malignancy. *Best Pract Res Clin Obstet Gynecol*. 2001;15:253–263.
93. Heller L, Levein SL, Butler CE. Management of abdominal wound dehiscence using vacuum assisted closure in patients with compromised healing. *Am J Surg*. 2006;191:165–172.
94. Farrell T, Wallace M, Hichs M. Long term results of transrenal occlusion with use of gianturco coils and gelatin sponge pledgets. *J Vasc Interv Radiol*. 1997;24:449–452.
95. Onsrud M, Hagen B, Stickert T. 10 Gy single fraction pelvic irradiation for palliation and life prolongation in patients with cancer of the cervix and corpus uteri. *Gynecol Oncol*. 2001;82:167–171.
96. Carstens D. Palliative radiation therapy in female genital cancers. In: Vahrson HW, Brady LW, Heilmann HP, eds. *Radiation Oncology of Gynecologic Cancers*. New York, NY: Springer; 1997:55–65.
97. Meeuse JJ, van der Linden YM, et al. Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Duth bone Metastasis Study. *Cancer*. 2010;116:2716–2725.
98. Smith SC, Koh W. Palliative radiation therapy for gynecologic malignancies. *Best Pract Res Clin Obstet Gynecol*. 2001;15:265–278.
99. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol*. 2007;25:1423–1436.
100. Fidler M. Incidence of fracture through metastasis in long bones. *Acta Orthop Scand*. 1981;52:623–627.
101. Townsend PW, Smalley SR, Cozad SC, et al. Role of postoperative radiation therapy after stabilization of fractures caused by metastatic disease. *Int J Radiat Oncol Biol Phys*. 1995;31:43–49.
102. Kim JH, Kang HG, Kim JR, et al. Minimally invasive surgery of humeral metastasis using flexible nails and cement in high risk patients with advanced cancer. *Surg Onc*. 2011;20:e32–e37.
103. Lin A, Ray ME. Targeted and systemic radiotherapy in the treatment of bone metastasis. *Cancer Metastasis Rev*. 2006;25:669–675.
104. Bauman G, Charette M, Reid R, et al. Radio-pharmaceuticals for the palliation of painful bone metastasis: a systemic review. *Radiother Oncol*. 2005;75:258–270.
105. Lane MD, Le HBQ, Lee S, et al. Combination radiofrequency ablation and cementoplasty for palliative treatment of painful neoplastic bone metastases: experience with 53 treated lesions in 36 patients. *Skeletal Radiol*. 2011;40:25–32.
106. Tacker PG, Callstrom MR, Curry TB, et al. Palliation of painful metastatic disease involving bone with imaging-guided treatment: comparison of patients' immediate response to radiofrequency ablation and cryoablation. *AJR*. 2011;197:510–515.
107. Koike Y, Takizawa K, et al. Transcatheter arterial chemoembolization (TACE) or embolization (TAE) for symptomatic bone metastases as a palliative treatment. *Cardiovasc Intervent Radiol*. 2011;34:7930–7801.
108. Avedian RS, Gold G, Ghanouni P, et al. Magnetic resonance guided high intensity focused ultrasound ablation of musculoskeletal tumors. *Curr Orthopaedic Pract*. 2011;22:303–308.
109. Wilson KG, Chochinov M, McPherson CJ, et al. Suffering with advanced cancer. *J Clin Oncol*. 2007;25:1691–1697.
110. Balboni TA, Vanderwerker LC, Block SD, et al. Religiousness and spiritual support among advanced cancer patients and associations with end of life treatment preferences and quality of life. *J Clin Oncol*. 2007;25:467–468.
111. Skalla K, McCoy JP. Spiritual assessment of patients with cancer: the moral authority, vocational, aesthetic, social and transcendent model. *Oncol Nurs Forum*. 2006;33:745–751.
112. Daaleman TP, VandeCreek L. Placing religion and spirituality in end of life care. *JAMA*. 2000;284:2514–2517.
113. McCord G, Ghilchrist VJ, Grossman SD, et al. Discussing spirituality with patients: a rational and ethical approach. *Ann Fam Med*. 2004;2:356–361.
114. Breitbart W. Identifying patients at risk for, and treatment of major psychiatric complications of cancer. *Support Care Cancer*. 1995;3:45–60.
115. Wilson KG, Chochinov HM, Skirko MG, et al. Depression and anxiety disorders in palliative cancer care. *J Pain Symptom Manage*. 2007;33:118–129, 67, 68.
116. Shuster JL, Jones GR. Approach to the patient receiving palliative care. In: Stem TA, Herman JB, Slavin PL, eds. *The MGH Guide to Psychiatry in Primary Care*. New York, NY: McGraw-Hill; 1998:147–165.
117. Breitbart W, Bruera E, Chochinov HM, et al. Neuropsychiatric syndromes and psychological symptoms in patients with advanced cancer. *J Pain Symptom Manage*. 1995;9:412–415.
118. Wilkinson SM, Love SB, Westcombe AM, et al. Effectiveness of aromatherapy massage in the management of anxiety and depression in patients with cancer: a multicenter randomized controlled trial. *J Clin Oncol*. 2007;25:532–539.
119. Bascom PB, Tolle SW. Responding to requests for physician-assisted suicide: "These are uncharted waters for both of us." *JAMA*. 2002;288(1):91–98.
120. Norwood F, Kimsma G, Battin MP. Vulnerability and the "slippery slope" at the end of life: a qualitative study of euthanasia, general practice and home death in the Netherlands. *Fam Pract*. 2009;26:472–480.

121. Ramondetta LM, Tortolero-Luna G, Bodurka DC, et al. Approaches for end of life care in the field of gynecologic oncology: an exploratory study. *Int J Gynecol Cancer*. 2004;14:5380–5388.
122. von Gruenigen VE, Daly BJ. Futility: clinical decisions at the end of life in women with ovarian cancer. *Gynecol Oncol*. 2005;97:638–644.
123. Randall F, Downie R. Assisted suicide and voluntary euthanasia: role contradictions for physicians. *Clin Med*. 2010;10:323–325.
124. Wenrich MD, Curtis JR, Amrozy DA, et al. Dying patients' need for emotional support and personalized care from physicians: perspectives of patients with terminal illness, families, and health care providers. *J Pain Symptom Manage*. 2003;25:236–246.
125. Teno JM, Bruneir A, Schwartz Z, et al. Association between advance directives and quality of end of life care: a national study. *J Am Gerontol Soc*. 2007;55:189–194.
126. Teno JM, Casey VA, Welch LC, et al. Patient focused, family centered end of life medical care: views of the guidelines and bereaved family members. *J Pain Symptom Manage*. 2001;22:738–751.
127. McMillian SC, Small BJ, Weitzner M, et al. Impact of coping skills intervention with family caregivers of hospice patients with cancer: a randomized clinical trial. *Cancer*. 2006;106:214–222.
128. Redinbaugh EM, Baum A, Tarbell S, et al. End of life caregiving: what helps family caregivers cope? *J Palliat Med*. 2003;6:901–909.
129. Bevans M, Sternberg EM. Caregiving burden, stress and health effects among family caregivers of adult cancer patients. *JAMA*. 2012;307:398–403.
130. Physician stress and burnout course. Texas Medical Association; 1999.
131. Penson RT, Dignan FC, Canellos GP, et al. Burnout: caring for the caregivers. *Oncologist*. 2000;5:425–434.
132. Whippen D, Canellos GP. Burnout syndrome in the practice of oncology: results of a random survey of 1000 oncologists. *J Clin Oncol*. 1991;9:1916–1920.
133. Halperin JD, Zabora JR, Brintzenhofe S. The emotional health of oncologists. *Oncol Issues*. 1997;21:20–22.
134. Kearney M, Weininger R, Vachon M, et al. Self-care of physicians caring for patients at the end of life "Being connected...A key to my survival". *JAMA*. 2009;301:1155–1164.
135. Ramirez A, Graham J, Richards M, et al. Mental health of hospital consultants: the effects of stress and satisfaction at work. *Lancet*. 1996;347:724–728.
136. Ramirez A, Graham J, Richards M, et al. Burnout and psychiatric disorder among cancer clinicians. *Br J Cancer*. 1995;71:1263–1269.
137. Creagan ET. Stress among medical oncologists: the phenomenon of burnout and a call to action. *Mayo Clin Proc*. 1993;68:614–615.
138. Armstrong J, Holland J. Surviving the stresses of clinical oncology by improving communication. *Oncology*. 2004;18:363–368.
139. Jackson VA, Mack J, Matsuyama R. A qualitative study of oncologist's approaches to end of life care. *J Palliat Med*. 2008;11:893–903.

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